ISOCOUMARINS. DEVELOPMENTS SINCE 1950

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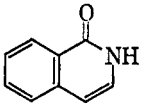
I. INTRODUCTION

A. THE SCOPE OF THE REVIEW

As in many areas of science, the past decennium has seen great strides made toward increasing our understanding in the various fields of chemistry. In many instances, borderlines between the various areas of science are very difficult to define. Chemistry, too, is becoming more diffuse, and whereas this review was originally intended to cover the chemistry of isocoumarin and its derivatives, it soon became apparent that biogenesis and biological activity of isocoumarins would also need to be included. The additional material required working with taxonomists as well as zoologists in order to adequately cover the topic.

This review covers the literature 1950–1963 and some of the literature pertaining to isocoumarins before 1950 when not included in the last review (191). In order to keep this survey as up-to-date as possible, recent copies of the more common journals were scanned up until the completed manuscript was typed. Therefore, a number of current publications relating to isocoumarins are included in this review. Further, some workers in this area kindly described their most recent investigations which were published recently or in press during the preparation of the manuscript. The author is particularly grateful to Drs. G. Berti and D. N. Chaudhury for this help.



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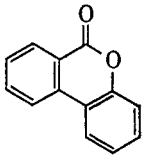
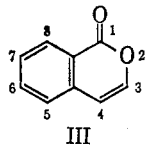


II

The lactam analogs of isocoumarins (called isocarbostyrils) (I) will not be covered in this review, and a complete survey of compounds of type II, which could be described under benzocoumarins or benzoisocoumarins, has not been attempted.

B. NOMENCLATURE

The nomenclature followed in this review is mainly from *Chemical Abstracts*. Isocoumarin (1H-2-benzopyran-1-one) (III) is numbered as shown, and the 3,4-dihydro analog (IV) will be called 3,4-dihydroisocoumarin, rather than isochroman-1-one. In *Chemical Abstracts* isocoumarincarboxylic acids are indexed as 1-oxo-1H-2-benzopyrancarboxylic acid, and 3,4-dihydroisocoumarincarboxylic acids are found under 1-oxoisochromancarboxylic acid. The former naming of the acids will be used in this review. Another exception to the use of the *Chemical Abstracts* nomenclature will be brevifolin for V, rather than 1,2-dihydro-7,8,9-trihydroxycyclopenta[*c*][2]benzopyran-3,5-dione, and similar complex compounds will be called by their common names unless there is an advantage to using the more complicated but accurate nomenclature.



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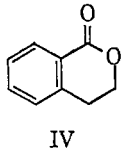

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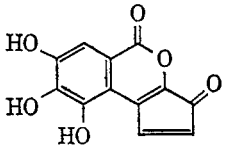
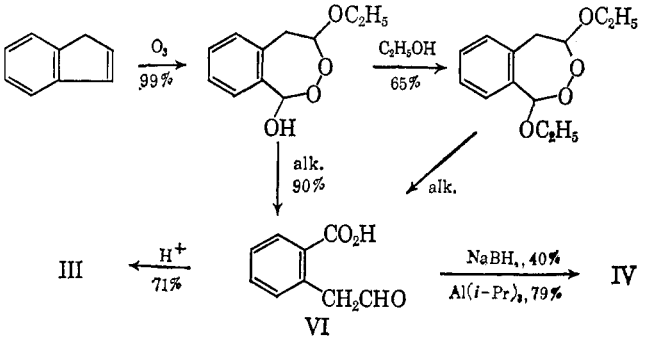


V

II. SYNTHESIS OF ISOCOUMARINS

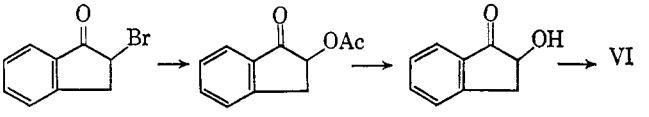
A. OXIDATION OF INDENES, INDANONES, AND INDONES

Isocoumarin has been prepared in high yield by ozonization of indene in ethyl alcohol, followed by decomposition of the intermediate cyclic perester (190). Treatment of 2-carboxyphenylacetaldehyde (VI) with mineral acid (or copper powder, although the yield is not so high) (166) leads to isocoumarin, and reduction



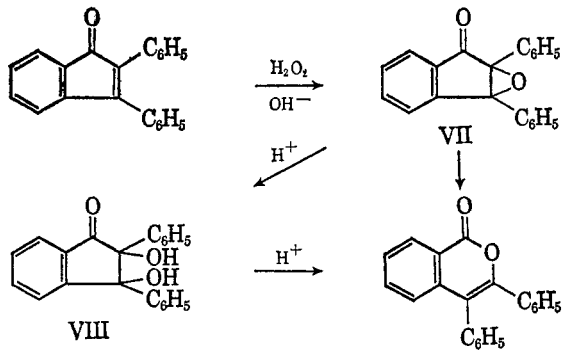
of the aldehyde produces 3,4-dihydroisocoumarin. This is one of the most convenient methods for synthesizing isocoumarin and 3,4-dihydroisocoumarin. The ozonization technique should also prove useful for preparing substituted isocoumarins, pending the availability of starting materials—the appropriate indenes.

Periodate oxidation of 2-hydroxyindanone, obtained from 2-bromoindanone, as shown, furnishes a quantita-

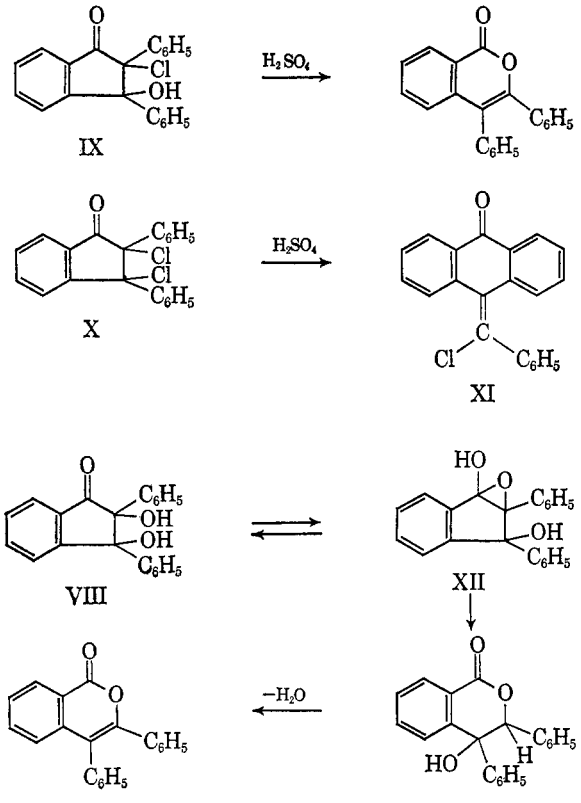


tive yield of 2-carboxyphenylacetaldehyde (VI), which can be cyclized to isocoumarin as described previously, providing another potential route to isocoumarins (166).

Alkaline hydrogen peroxide oxidizes 2,3-diphenylindone to 2,3-diphenyl-2,3-oxidoindanone (VII), which can be rearranged in the presence of acids to 3,4-diphenylisocoumarin (3, 4, 16, 97, 131, 188). Thus, treatment of VII with an acetic acid–hydrogen chloride mixture gives 2,3-diphenyl-2,3-dihydroxyindanone (VIII), which rearranges to 3,4-diphenylisocoumarin in the presence of mineral acids (3). This sequence also has been applied to convert 2,3-diphenyl-5,6-di-



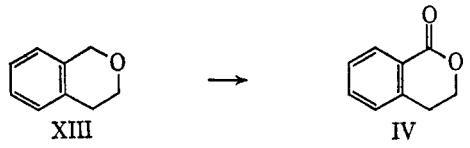
methylindone, 2,3-diphenyl-5,6-dibromoindone, and 2,3,5,6-tetraphenylindone to the corresponding isocoumarins (3, 16). The oxido ketones such as VIII can be converted to isocoumarins in one step using acetic acid–mineral acid mixtures or boron trifluoride etherate (16, 97, 188, 193). Further, hydrogen peroxide and acetic acid–mineral acid mixtures have been used to transform 2-methyl-3-phenylindone, 2-ethyl-3-phenylindone, and 2-cyano-3-phenylindone in high yields to 3-methyl-4-phenylisocoumarin, 3-ethyl-4-phenylisocoumarin, and 3-cyano-4-phenylisocoumarin, respectively, without the necessity of isolating the intermediate oxido ketones. In this case the reaction is of the Baeyer–Villiger type (131). In a similar reaction, 2,3-diphenyl-2-chloro-3-hydroxyindanone (IX) yielded mainly 3,4-diphenylisocoumarin when treated with sulfuric acid, but 2,3-diphenyl-2,3-dichloroindanone (X) yielded mainly 9-(α-chlorobenzylindene)anthrone (XI) (16).

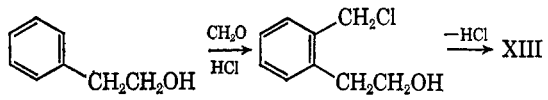


The conversion of 2,3-diphenyl-2,3-dihydroxyindanone (VIII) to 3,4-diphenylisocoumarin has been explained in terms of the α-oxanol intermediate (XII), which could break down to give either the original diol (VIII) or 3,4-diphenyl-4-hydroxy-3,4-dihydroisocoumarin, followed by dehydration to 3,4-diphenylisocoumarin (3).

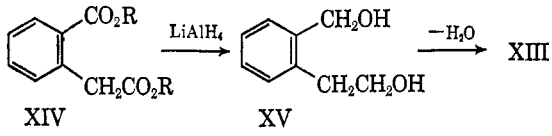
B. OXIDATION OF ISOCHROMANS

Oxidation of isochromans (XIII) with a variety of agents furnishes a good route to 3,4-dihydroisocoumarins. Isochromans are available through chloromethylation of β-aryl ethyl alcohols, followed by cyclization of the intermediate β-(2-chloromethylphenyl)ethyl alcohols. In some cases cyclization to the isochroman occurs spontaneously, otherwise heat or aluminum chloride treatment is necessary (62, 63).





Another route to isochromans is through lithium aluminum hydride reduction of homophthalic acid esters (XIV) and cyclization of the β-(2-hydroxymethylphenyl)ethyl alcohols XV (133, 144, 179, 186).



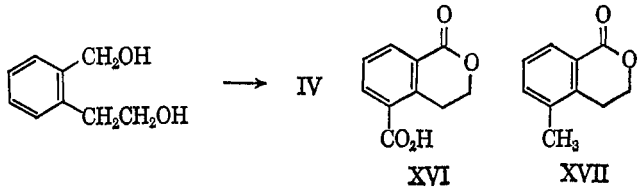
High yields of 3,4-dihydroisocoumarins are obtained through oxidation of isochroman with selenium dioxide in xylene or without a solvent (62, 63, 127, 129). Table I shows the yield of 3,4-dihydroisocoumarins from selenium dioxide oxidation of the corresponding isochromans (62, 63).

TABLE I

	Yield, %
3,4-Dihydroisocoumarin	65–85
7-Methyl-3,4-dihydroisocoumarin	50
5,8-Dimethyl-3,4-dihydroisocoumarin	59
3-Methyl-3,4-dihydroisocoumarin	50
5,6-Benzo-3,4-dihydroisocoumarin	43

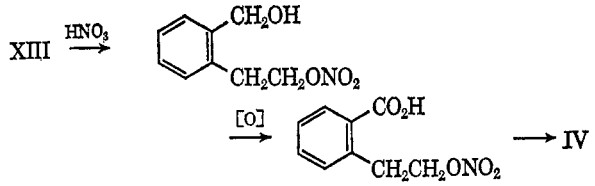
Chromium trioxide in acetic acid oxidizes isochromans to 3,4-dihydroisocoumarins (49, 133, 144, 179) and is reported to be better than selenium dioxide (133, 179). The following 3,4-dihydroisocoumarins have been prepared by this procedure: 6-methoxy-, 6,7-dimethoxy-, 5,6-dimethoxy-, 5-methoxy-7-methyl-, 6,7-

methylenedioxy-, 6-methoxy-7-benzyloxy-, 3,4,5-trimethyl-6,7,8-trimethoxy-. Some reports describe the direct oxidation of β-(2-hydroxymethylphenyl)ethyl alcohols to 3,4-dihydroisocoumarins with chromium trioxide. Thus, 3,4-dihydroisocoumarin-5-carboxylic



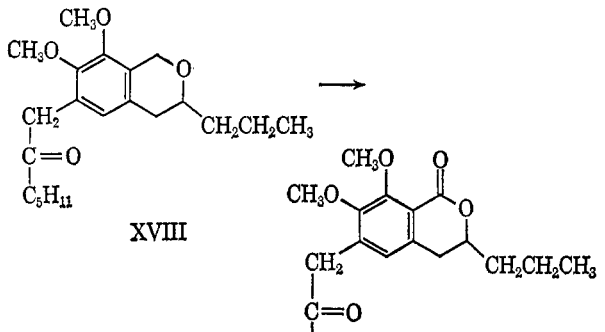
XVI XVII

acid (XVI) (122, 186) and 5-methyl-3,4-dihydroisocoumarin (XVII) (122) have been made by this method. This reaction probably occurs through initial con-



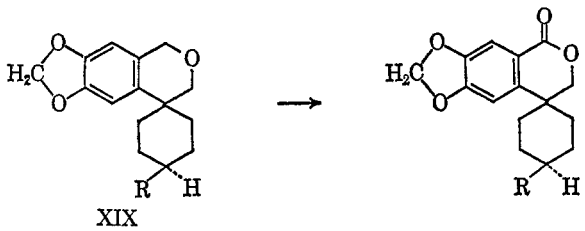
version to the isochroman, followed by oxidation to the 3,4-dihydroisocoumarin, since the ethyl alcohol group is not oxidized.

Nitric acid has been found to oxidize isochromans to 3,4-dihydroisocoumarins, presumably through intermediate nitrates (128).



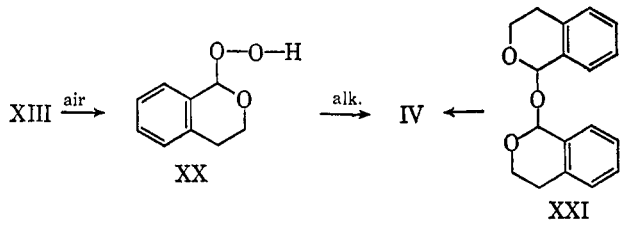
XVIII

Another useful reagent for the oxidation of isochromans is potassium permanganate in acetone. Hexahydro-O-methylaporubropunctatin (XVIII) (88) has been oxidized in this manner, as has the spiroisochroman (XIX, R = H or CH_3) (103).



XIX

Air oxidation of isochromans produces hydroperoxides (XX) which can be converted to 3,4-dihydroisocoumarins by treatment with alkali (151) (66% yield for isochroman hydroperoxide), or by acids to the corresponding peroxide, followed by heating in a carbon

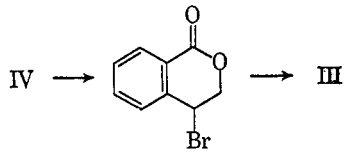


XX XXI

dioxide atmosphere to give the 3,4-dihydroisocoumarin (152).

Diisochromanyl ether (XXI) can be converted to 3,4-dihydroisocoumarin in 41% yield by treatment with aqueous sulfuric acid, 9.5% yield with hydrobromic acid, and 12.7% yield with hydrochloric acid (150).

Isocoumarins can be prepared from 3,4-dihydroisocoumarins through bromination with N-bromosuccinimide, followed by dehydrohalogenation with triethylamine. This sequence has been carried out for several

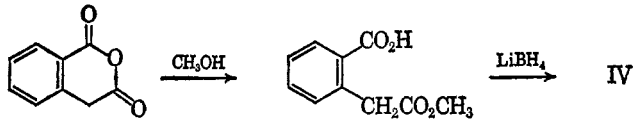


3,4-dihydroisocoumarins and is a good method for obtaining the isocoumarins (17, 133, 178, 179).

In summary, oxidation of isochromans using selenium dioxide, chromium trioxide, potassium permanganate, nitric acid, or air yields 3,4-dihydroisocoumarins. In turn, the 3,4-dihydroisocoumarins can be converted to isocoumarins through bromination and dehydrobromination. The usefulness of these procedures depends largely on the availability of the isochromans, and, based on the literature reports, chromium trioxide or potassium permanganate in acetone are the best reagents for carrying out the oxidation.

C. REDUCTION OF 2-CARBOXYPHENYLACETATES

Methyl 2-carboxyphenylacetates are obtained by methanolysis of homophthalic anhydrides. Lithium borohydride reduction of these half-esters yields 3,4-dihydroisocoumarins. This method has been used to

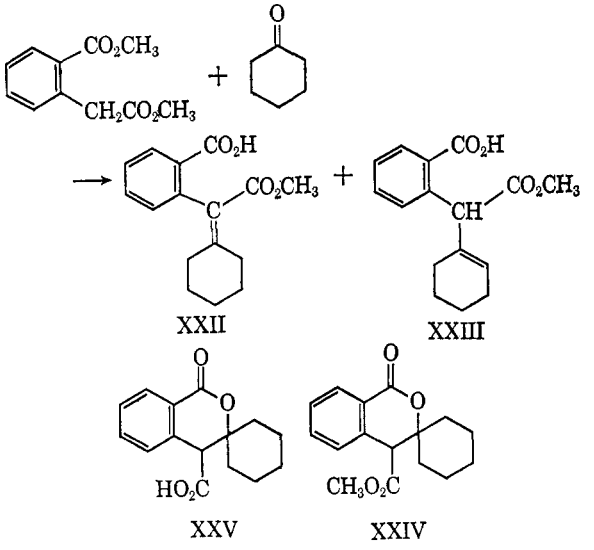


prepare 4,5-, 4,6-, and 5,6-dimethoxy-3,4-dihydroisocoumarins (48). As discussed in section IIB, the 3,4-dihydroisocoumarins can be easily converted to isocoumarins *via* bromination and dehydrobromination.

D. ALDOL-TYPE CONDENSATIONS BETWEEN HOMOPHTHALIC ACIDS, ESTERS, OR ANHYDRIDES, AND CARBONYL COMPOUNDS

1. Stobbe Condensations of Homophthalates with Aldehydes and Ketones

Dimethyl homophthalate condenses with cyclohexanone in the presence of sodium hydride yielding a mixture of methyl α-cyclohexylidene-α-(2-carboxyphenyl)acetate (XXII) and methyl α-(1-cyclohexenyl)-α-(2-carboxyphenyl)acetate (XXIII). Acetic anhydride, acetic acid, and sodium acetate produce the spiroisocoumarincarboxylate (XXIV) from either of

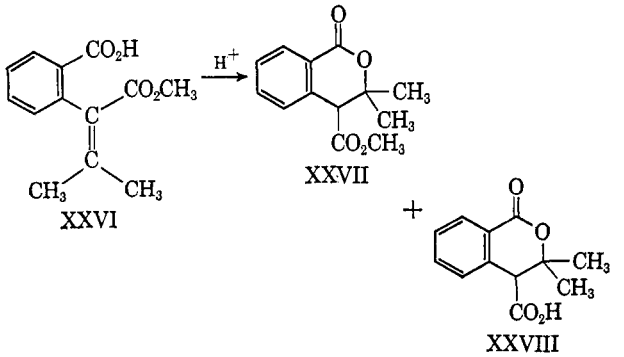


XXII XXIII

XXV XXIV

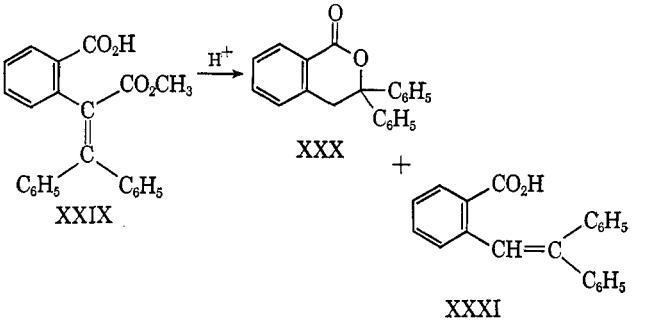
the half-esters, whereas hydrobromic acid in acetic acid converts the half-esters to the spiroisocoumarincarboxylic acid (XXV). Alcoholic alkali regenerates the half-esters XXII and XXIII from the spiro ester XXIV. The intermediate leading to formation of the half-esters during the Stobbe condensation is probably the spiro ester XXIV, which could explain the occurrence of the half-esters.

Dimethyl homophthalate and acetone in the presence of sodium hydride similarly gives the half-ester XXVI which can be converted to methyl 3,3-dimethyl-3,4-dihydroisocoumarin-4-carboxylate (XXVII) and 3,3-dimethyl-3,4-dihydroisocoumarin-4-carboxylic acid (XXVIII) in the same manner as for the cyclohexanone



XXVI XXVII XXVIII

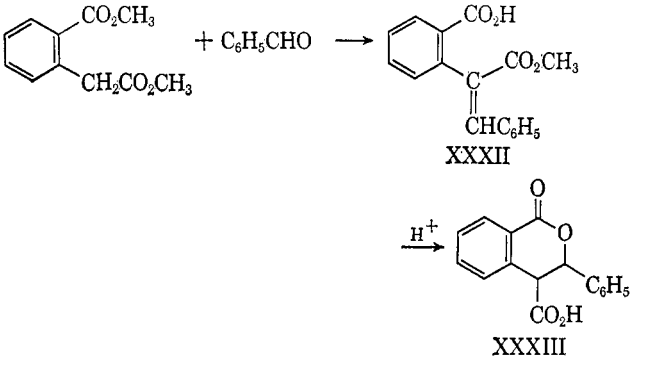
product. Benzophenone also follows this sequence, but treatment of the half-ester XXIX with strong acid leads to decarboxylation producing 3,3-diphenyl-



XXIX XXX XXXI

3,4-dihydroisocoumarin (XXX) and β-phenylstilbene-2-carboxylic acid (XXXI).

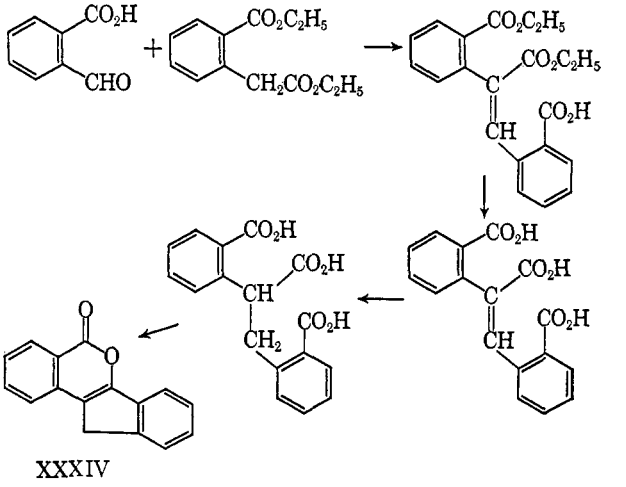
Benzaldehyde can be condensed with dimethyl homophthalate in the presence of sodium hydride or sodium methoxide in methanol yielding methyl α-benzylidene-α-(2-carboxyphenyl)acetate (XXXII), which is con-



XXXII XXXIII

verted to 3-phenyl-3,4-dihydroisocoumarin-4-carboxylic acid (XXXIII) with strong acids (125).

A moderate yield of indeno[3′,2′:3,4]isocoumarin (XXXIV) has been obtained from the condensation of

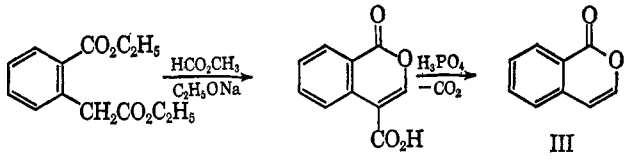


XXXIV

phthaldehydic acid with diethyl homophthalate (56–58).

2. *Claisen Condensations of Homophthalates with Formates*

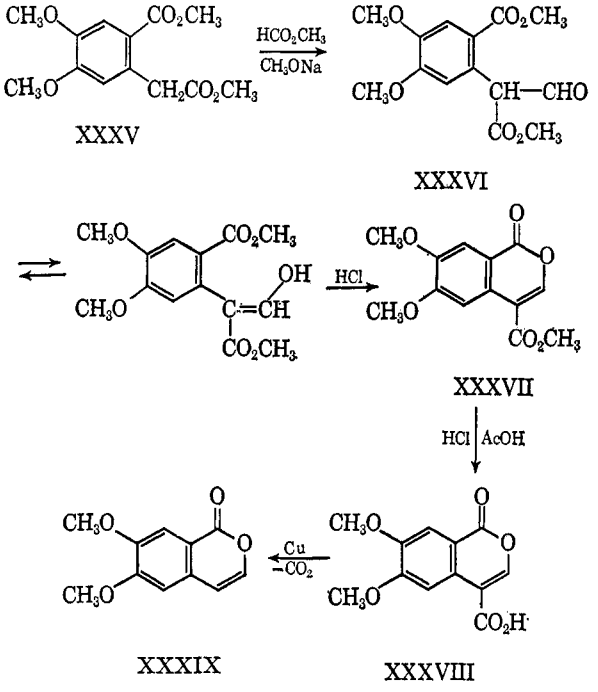
Diethyl homophthalate condenses with methyl formate in the presence of sodium ethoxide imparting a 66% yield of isocoumarin-4-carboxylic acid. Decarboxylation with phosphoric acid furnishes isocoumarin



III

(109).

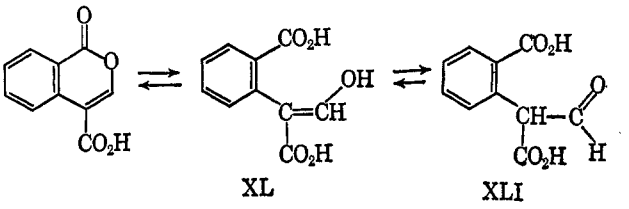
Dimethyl 4,5-dimethoxyhomophthalate (XXXV) condenses with methyl formate in the presence of sodium methoxide in ether forming dimethyl α-formyl-4,5-dimethoxyhomophthalate (XXXVI) which yields methyl 6,7-dimethoxyisocoumarin-4-carboxylate (XXXVII) when warmed with hydrochloric acid (yield



XXXV XXXVI XXXVII XXXIX XXXVIII

76–82%). A mixture of acetic acid and hydrochloric acid converts XXXVII into 6,7-dimethoxyisocoumarin-4-carboxylic acid (XXXVIII) (88% yield), and decarboxylation with copper bronze gives 6,7-dimethoxyisocoumarin (XXXIX) (87).

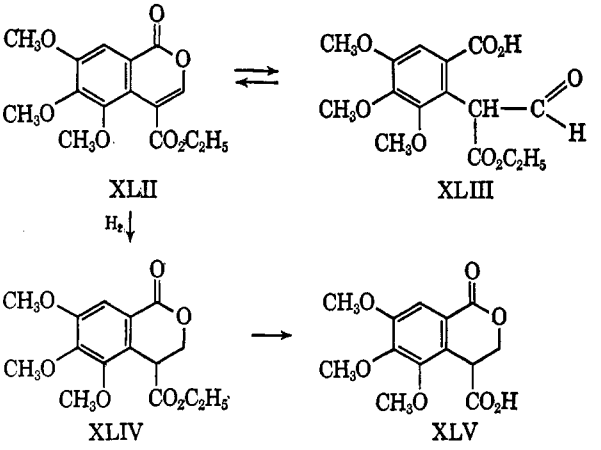
Methyl 6,7-dimethoxyisocoumarin-4-carboxylate (containing the 6,7-dimethoxy group) is readily converted into 6,7-dimethoxyisocoumarin-4-carboxylic acid with acetic acid and hydrochloric acid. However, for the case of 5,7-dimethoxy- or 6,8-dimethoxyisocoumarin-4-carboxylic acid esters, poor yields of the corresponding acids were obtained using the acetic acid and hydrochloric acid mixture. This is attributed to the equilibrium between α-hydroxymethylenehomophthalic acid (XL), α-formylhomophthalic acid (XLI) (tautomer of XL), and the isocoumarin-4-carboxylic acid, in which case acid catalysts could cause several



XL XLI

side reactions. Attempts to effect hydrolysis of the esters by treatment with acetic acid–hydriodic acid mixtures resulted in loss of the ester group together with cleavage of the methoxy groups. Alkaline hydrolytic conditions similarly gave poor yields. Best results were obtained using a mixture of boron trifluoride and acetic acid, although in some cases simultaneous decarboxylation occurred.

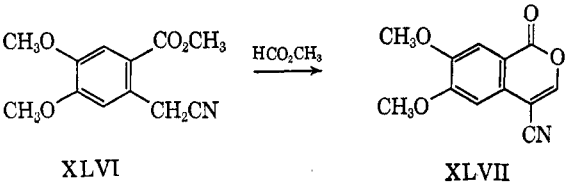
Ethyl 5,6,7-trimethoxyisocoumarin-4-carboxylate (XLII), prepared from the corresponding homophthalate and ethyl formate in the presence of potassium ethoxide, was unreactive toward acetic acid–hydrochloric acid, boron trifluoride–acetic acid, and alkalies, presumably due to formation of the stable α-aldehydic ester intermediate (XLIII). However, catalytic reduction of XLII to ethyl 5,6,7-trimethoxy-3,4-dihydroisocoumarin-4-carboxylate (XLIV) using palladium



XLII XLIII XLIV XLV

on charcoal, followed by treatment with acid in boiling water, resulted in easy hydrolysis to 5,6,7-trimethoxy-3,4-dihydroisocoumarin-4-carboxylic acid (XLV) (87).

Another useful reaction in this series involves the condensation between 2-carbomethoxy-4,5-dimethoxy-

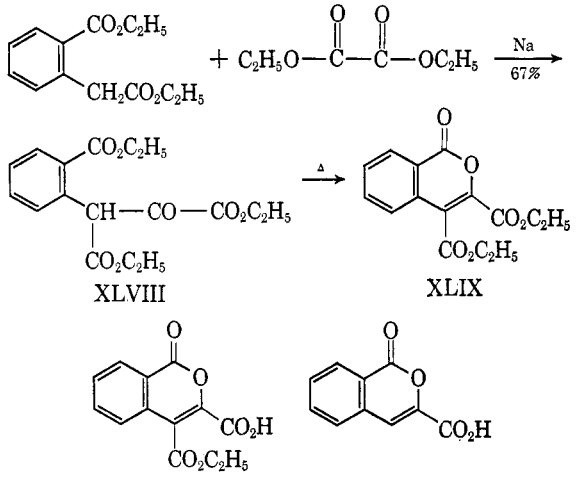


XLVI XLVII

phenylacetonitrile (XLVI) and methyl formate yielding 4-cyano-6,7-dimethoxyisocoumarin (XLVII) (55).

3. Claisen Condensations of Homophthalates with Oxalates

Metallic sodium in ether, or better without a solvent, effects ready condensation between diethyl homophthalate and diethyl oxalate, giving a 67% yield of triester XLVIII. The triester loses ethanol when heated yielding diethyl isocoumarin-3,4-dicarboxylate (XLIX). Depending on the hydrolysis conditions,



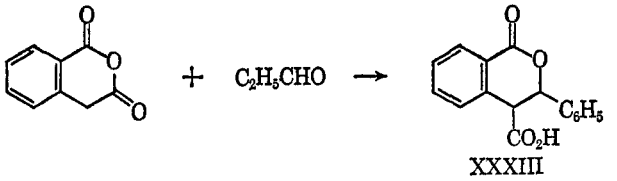
XLVIII XLIX

isocoumarin-3-carboxylic acid or ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate is formed. Thus, heating XLIX at 68–72° for 3 hr. gives ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate, and prolonged heating yields isocoumarin-3-carboxylic acid. Boiling hydrochloric acid or heating in a sealed tube at 180–190° converts XLIX to isocoumarin-3-carboxylic acid in 84% yield (189). Treatment of diethyl 5,6,7-trimethoxyisocoumarin-3,4-dicarboxylate, obtained from the diethyl oxalate method using potassium ethoxide and heating at 140° for 3 hr., with dilute sulfuric acid gives 5,6,7-trimethoxyisocoumarin-3-(carboxylic acid)-4-carboxylate (87).

These results indicate that the 3-ester is hydrolyzed first, but that the 4-acid is more easily decarboxylated.

4. Perkin Condensations of Homophthalic Anhydrides with Aromatic Aldehydes

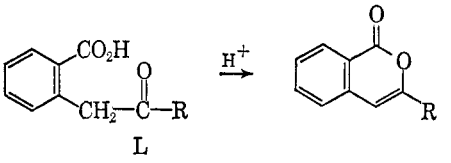
Homophthalic anhydrides condense with aromatic aldehydes in the presence of bases such as triphenylmethylsodium to yield 3-phenyl-3,4-dihydroisocoumarin-4-carboxylic acids, important intermediates in certain alkaloid syntheses (108, 134, 136).



XXXIII

E. CYCLIZATION OF 2-CARBOXYBENZYL KETONES AND RELATED COMPOUNDS

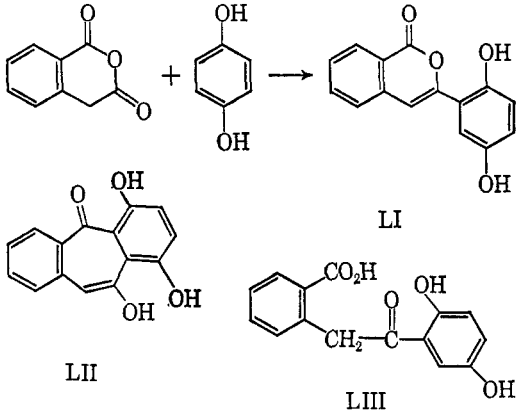
Isocoumarins can be derived from the cyclization of 2-carboxybenzyl ketones (L) by a variety of reagents. In some cases cyclization occurs spontaneously, and the free acids cannot be obtained in the free state. In



L

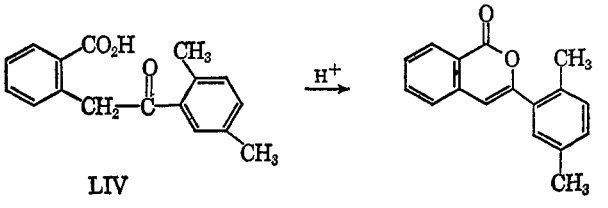
other cases cyclization must be induced by treatment under various conditions. Usually, boiling the ketone with traces of mineral acid will bring about lactone formation. Thionyl chloride has been used as an agent for cyclization of 2-carboxybenzyl phenyl ketone giving 3-phenylisocoumarin (172).

The Friedel–Crafts acylation between homophthalic anhydride and benzene in the presence of aluminum chloride gives both 2-carboxylbenzyl phenyl ketone and 3-phenylisocoumarin, but when the reaction mixture is heated the only product is 3-phenylisocoumarin. Thus, Lewis acids can effect cyclization of compounds of type L (171). Cyclization can also be effected with a mixture of aluminum chloride and sodium chloride, with stannic chloride, or with concentrated hydrochloric acid. Condensation of homophthalic anhydride with hydroquinone in the presence of stannic chloride yields 2-(2,5-dihydroxyphenyl)isocoumarin (LI), also formed by heating or by hydrochloric acid treatment of 2-carboxybenzyl 2,5-dihydroxyphenyl



LII LIII

ketone (LIII). Fusion with aluminum chloride and sodium chloride in this instance produces 1,4,11-tri-



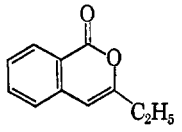
LIV

hydroxy-5H-dibenzo[*a*,*d*]cyclohepten-5-one (LII) (176).

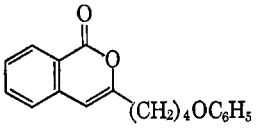
Mineral acid in ethanol has been used to cyclize 2-carboxybenzyl 2,5-dimethylphenyl ketone (LIV) to 3-(2,5-dimethylphenyl)isocoumarin, and 2-methyl-4-hydroxyphenylisocoumarin is produced directly from homophthalic anhydride and *m*-methylphenol in the presence of aluminum chloride (99).

Formic acid is another useful reagent for cyclizing 2-carboxybenzyl ketones, examples being 2-carboxy-3-hydroxybenzyl methyl ketone to 3-methyl-8-hydroxyisocoumarin (21) and 2-carboxy-3,5-dimethoxybenzyl propyl ketone to 3-propyl-6,8-dimethoxyisocoumarin (132, 139).

Addition of dialkylcadmium to acid chlorides is a good method for preparing 2-carboxylbenzyl ketones, which can then be cyclized to isocoumarins. This procedure has been used to prepare 3-ethylisocoumarin



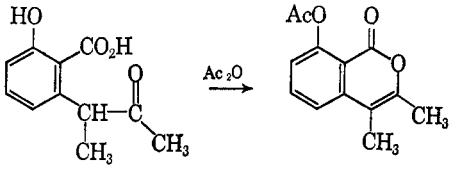
LV



LVI

(LV) and 3-(4-phenoxybutyl)isocoumarin (LVI) (100).

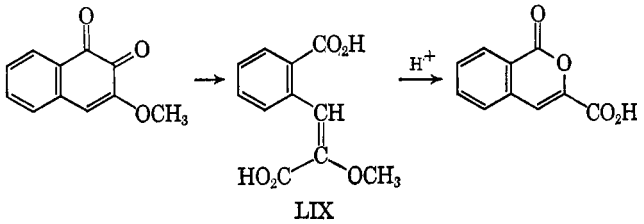
Acetic anhydride and sodium acetate has been used to cyclize 2-carboxy-3-hydroxy-α-methylbenzyl methyl



LVII LVIII

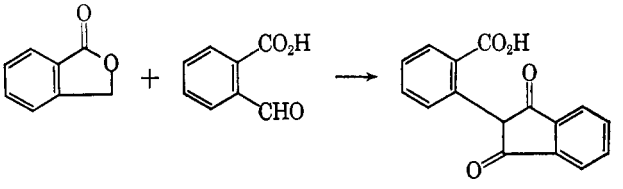
ketone (LVII) to 3,4-dimethyl-8-acetoxyisocoumarin (LVIII) (203).

Sodium periodate oxidation of 3-methoxynaphthalene-1,2-quinone produces 2-carboxy-α-methoxycinnamic acid (LIX), which is converted to isocoumarin-3-carboxylic acid with warm acid (1).

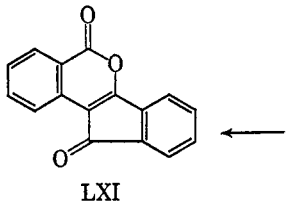


LIX

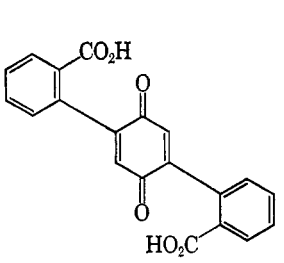
The aldol condensation between phthalide and *o*-phthaldehydic acid in the presence of methanolic sodium methoxide yields 2-(2-carboxyphenyl)-1,3-indanedione (LX), which cyclizes with heat, acetic anhydride, or merely by dissolving in benzene, to isocoumarin (LXI) (140). Cyclization of 2,5-bis(2-carboxyphenyl)benzoquinone (LXII) occurs easily to give benzoisocoumarin (LXIII) (141).



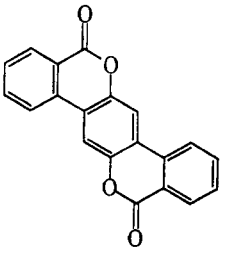
LX



LXI

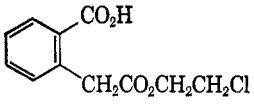


LXII

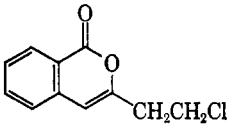


LXIII

Homophthalic anhydride can be esterified with β-chloroethyl alcohol, and the resulting half-ester, β-chloroethyl 2-carboxyphenylacetate (LXIV), cyclized to 3-(β-chloroethyl)isocoumarin (LXV) with phos-



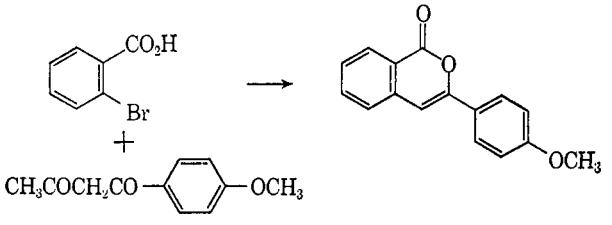
LXIV



LXV

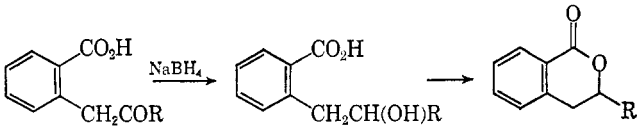
phorus pentachloride (154).

Another method involving a 2-carboxylbenzyl ketone intermediate is the sodium ethoxide effected coupling



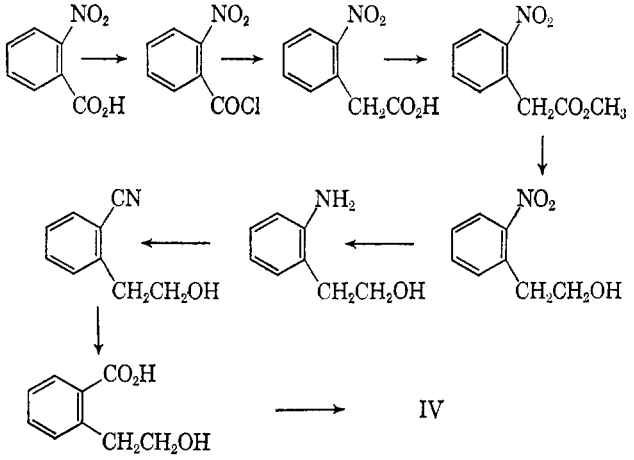
of 2-bromobenzoic acid and 1-(4-methoxyphenyl)-1,3-butanedione, followed by cyclization with mineral acid to give 3-(4-methoxyphenyl)isocoumarin (96).

Reduction of 2-carboxybenzyl ketones with sodium borohydride furnishes a route to 3,4-dihydroisocou-

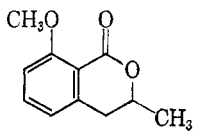


marins. This method has been used to prepare 3-methyl-3,4-dihydroisocoumarins, as well as other 3-substituted isocoumarins (21, 33, 126).

Another useful method for preparing 3,4-dihydroisocoumarins from 2-nitrobenzoic acids has recently been described. In this instance 2-nitrobenzoic acids are converted to 2-nitrophenylacetic acids by the Arndt–Eistert synthesis. Successive reduction of 2-nitro-



phenylacetic acid, by way of the methyl ester, with lithium aluminum hydride and sodium dithionite furnishes β-(2-aminophenyl)ethyl alcohol. Alternately, the 2-nitrophenylacetic acid can be converted to the acid chloride and reduced with sodium borohydride to β-(2-nitrophenyl)ethyl alcohol. Use of the Sandmeyer procedure replaces the amino group giving β-(2-cyanophenyl)ethyl alcohol, and hydrolysis of the nitrile furnishes β-(2-carboxylphenyl)ethyl alcohol. The alcohol can be cyclized by heat to 3,4-dihydroisocoumarin. This procedure has been used to prepare several methoxy-3,4-dihydroisocoumarins, among them 5,8-, 6,7-, and 7,8-dimethoxy-3,4-dihydroisocoumarin (18, 19, 177). As discussed in section IIB, the N-bromosuccinimide procedure can be used to make isocoumarins from the corresponding 3,4-dihydroisocoumarins. By means of the ethoxymagnesiomalonate method, 2-nitrophenylacetic acid can be converted to the acid chloride and 2-nitrobenzyl ketones prepared. This sequence

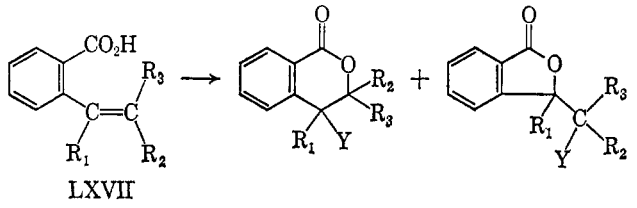


LXVI

has been used to prepare racemic mellein methyl ether (3-methyl-8-methoxy-3,4-dihydroisocoumarin) (LXVI) (41, 42) (see section IVM).

F. CYCLIZATION OF 2-VINYLBENZOIC ACIDS AND RELATED REACTIONS

Cyclization of 2-vinylbenzoic acids (LXVII) (Y = halogen, hydrogen) to lactones can be accomplished by means of halolactonization reactions, concentrated mineral acids, or peroxidation procedures. The products obtained from the cyclizationr eactions are phthalides (γ-lactones) and isocoumarins (δ-lactones). In some instances mixtures of both types of lactones

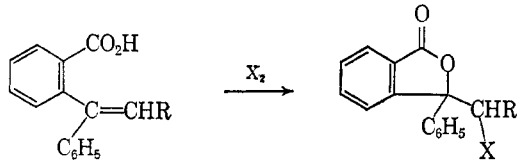


LXVII

occur and in other cases only one product is formed. Steric and electronic factors are important in determining the nature of the product or products. Several investigations in recent years have furnished information concerning the mechanism and steric requirements of the lactonization reactions.

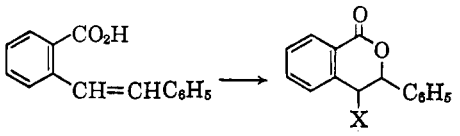
Cyclizations have been carried out using the following reagents: concentrated sulfuric acid (24, 26, 27, 31, 33, 34, 96); chlorine in chloroform, carbon tetrachloride, or water (24, 28, 30, 31, 33, 34); bromine in chloroform or acetic acid (24, 28, 30, 33, 34); peroxyphthalic acid (29); peroxybenzoic acid with or without trichloroacetic acid (29); peroxyformic acid (29); peroxyacetic acid (34).

The reaction between halogens and 2-vinylbenzoic acids is of the halolactonization type. For the case of 2-(α-phenylvinyl)benzoic acids (LXVIII) the halolactonization sequence yields phthalides (LXIX, X =



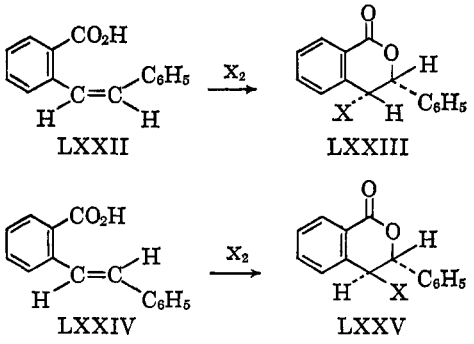
LXVIII LXIX

halogen) (25, 31). On the other hand, stilbene-2-carboxylic acids, containing no α-substituent (LXX), yield only halogenated dihydroisocoumarins (LXXI) (30).

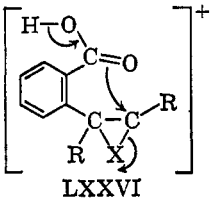


LXX LXXI

The lactones are formed by the halolactonization in a a stereospecific manner, depending on the configuration (*cis* or *trans*) of the 2-vinylbenzoic acids. Thus, *cis*-(LXXII) and *trans*-stilbene-2-carboxylic acid (LXXIV), yield *cis*- (LXXIII) and *trans*-3-phenyl-4-halo-3,4-dihydroisocoumarin (LXXV), respectively, when treated with chlorine in chloroform or bromine in acetic acid or chloroform. This reaction probably proceeds through the intermediate LXXVI (30). The cationic

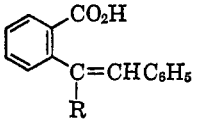


structure LXXVI seems reasonable since the products are formed in a completely stereospecific manner. Additional discussion may be found in ref. 30. The nature of the lactone formed in this reaction is independent of the relative stability of the γ- *vs.* the δ-lactone products. The direction of lactonization is determined mainly by steric effects, electronic factors, and solvent effects in the 2-vinylbenzoic acid series.



The steric influence of the halolactonization reaction in determining whether a γ- or δ-lactone will form is demonstrated by the data in Table II. The per cent yields of 3,4-dihydroisocoumarins (δ-lactones) are shown for several 2-vinylbenzoic acids using a variety

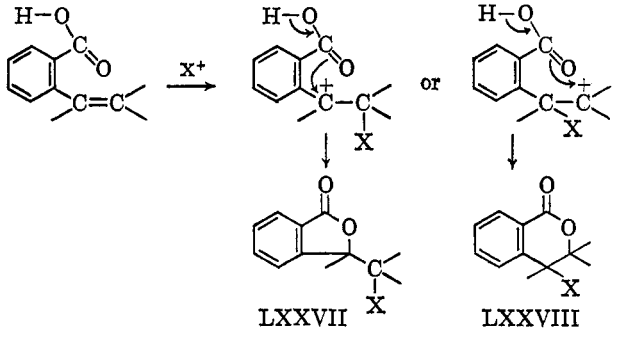
TABLE II



R	Sulfuric acid	Chlorine in chloroform	Chlorine in carbon tetrachloride	Chlorine in acetic acid	Chlorine in water	Perchloric acid in acetic acid	Bromine in chloroform
H	100[a]	100	..	..	..	100	100
CH_3	92	48	39	..	35	0	0
C_2H_5	90	41	25	36	30	0	0
i-C_3H_7	89	37	..	..	26	0	0
C_6H_{11}	84	24	..	..	23	0	0

[a] The table values are based on the total yield of lactone from the reaction.

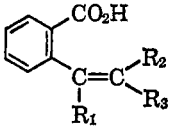
of reagents (34). The effect of steric factors is readily apparent on going from an α-hydrogen to the alkyl groups. The direction of lactonization is influenced by the center of lowest electron density (electron factors) as indicated below. Clearly, an attack at the center of lowest electron density would give γ-lactone

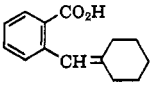
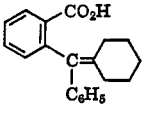


LXXVII in the first instance and δ-lactone LXXVIII for the second case (33, 34). Data indicating the electronic influence on the nature of the lactone obtained from halolactonization reactions are given in Table III (33). These data also include steric factors.

The nature of the solvent has an influence in the halolactonization reaction, evidenced by the data in Table II. This effect probably represents variations in electronic factors due to changes in the environment surrounding the intermediate LXXVI.

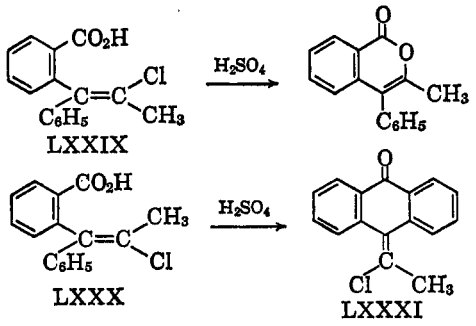
TABLE III



R_1	R_2	R_3	Sulfuric acid	Chlorine	Bromine
H	CH_3	H	...	γ	...
CH_3	H	H	γ	γ	γ
C_2H_5	CH_3	H	γ	γ	γ
H	CH_3	CH_3	δ	δ	...
i-C_3H_7	CH_3	CH_3	δ	δ	δ
C_6H_5	CH_3	H	...	γ	...
C_6H_5	CH_3	Cl	...	γ	...
C_6H_5	Cl	C_6H_5	...	γ	...
H	C_6H_5	H	δ	δ	δ
CH_3	C_6H_5	H	γ and δ	γ and δ	...
			δ[a]	δ[a]	...
			δ[a]	δ and γ	δ[a]

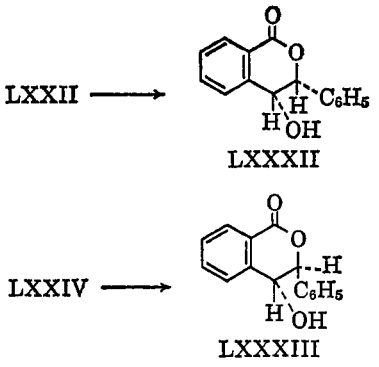
[a] A small amount of γ-lactone also was found.

Concentrated sulfuric acid effects cyclization of 2-vinylbenzoic acids to isocoumarins. Tables II and III show the influence that changes in the nature of the substituent have on determining which type of lactone will be obtained. Treatment of *cis*-2-(1-phenyl-2-chloropropenyl)benzoic acid (LXXIX) with sulfuric acid results in rapid cyclization to 3-methyl-4-phenylisocoumarin, whereas the *trans* isomer (LXXX) yields



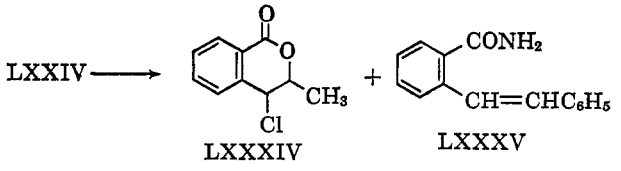
mainly 9-(α-chloroethylidene)anthrone (LXXXI) and reacts more slowly (26).

Lactonization of *cis*- (LXXII) and *trans*-stilbene-2-carboxylic acid (LXXIV) using peroxyphthalic acid



yields the δ-lactones, *cis*- (LXXXII) and *trans*-3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (LXXXIII) (29). This reaction involves a *trans* addition to the double bond which explains the stereochemistry of the products. Several possible mechanisms are discussed in ref. 29. Under the same conditions peroxyformic and peroxybenzoic acids give the same products as for peroxyphthalic acid. However, at or below room temperature peroxybenzoic acid in chloroform produces mainly the γ-lactones (phthalides), but at reflux temperature only the δ-lactones (3,4-dihydroisocoumarins) are obtained. Peroxybenzoic acid in the presence of trichloroacetic acid gives high yields of 3,4-dihydroisocoumarins and is the best method for their preparation (29).

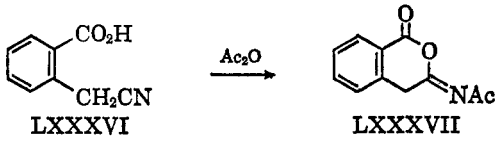
Treatment of *trans*-stilbene-2-carboxylic acid (LXXIV) with phosphorus pentachloride at 100° for 30 min. followed by ammonia gives a mixture of 3-phenyl-4-chloro-3,4-dihydroisocoumarin (LXXXIV)



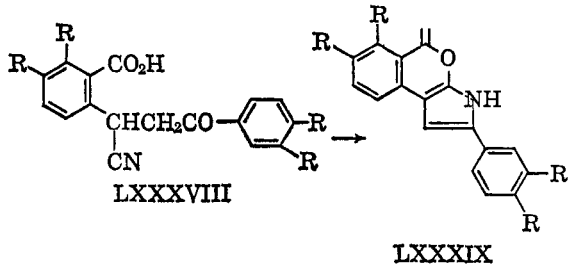
and *trans*-stilbene-2-carboxamide (LXXXV). The same reaction at 135° yields only traces of LXXXV and large amounts of isocoumarin (LXXXIV) (28).

G. CYCLIZATION OF α-CYANOHOMOPHTHALIC ACIDS AND ANHYDRIDES

Homophthalonitrile (LXXXVI) can be cyclized to 3-(N-acetylimino)-3,4-dihydroisocoumarin (LXXXVII)



with acetic anhydride (67). Hydrochloric acid or heat is sufficient to cyclize homophthalonitriles such as LXXXVIII (where R = methoxy and methyl groups) to isocoumarins of type LXXXIX. Table IV is a



compilation of the various nitriles of type LXXXVIII which have been cyclized to isocoumarins (12). This

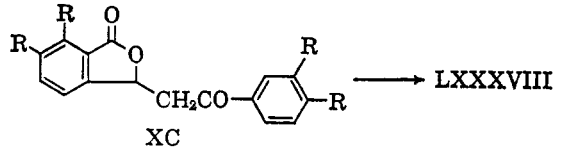
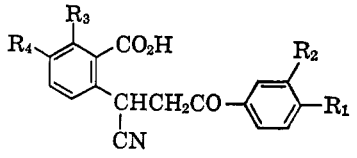


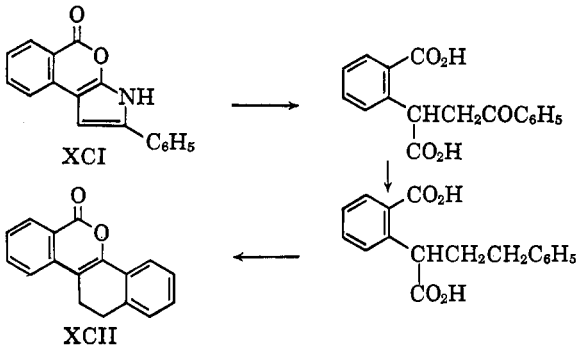
TABLE IV



Case	R_1	R_2	R_3	R_4
1	H	OCH_3	OCH_3	OCH_3
2	H	CH_3	OCH_3	OCH_3
3	H	H	H	H
4	H	H	OCH_3	OCH_3

sequence has been used as a route to the chelidonine–sanguinarine alkaloids (11–13). The nitriles are readily available from phthalides XC through the addition of hydrogen cyanide. For case 3 in Table IV, the nitrile was very sensitive to acids, and during the work-up of the hydrogen cyanide reaction mixture some of the nitrile cyclized to the corresponding isocoumarin. Presumably the nitrile is deactivated by the methyl and methoxy groups in the other cases so cyclization does not occur as easily.

Alkaline hydrolysis of isocoumarins of type XCI furnishes substituted homophthalic acids which have

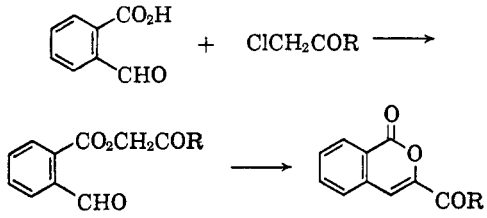


XCI XCII

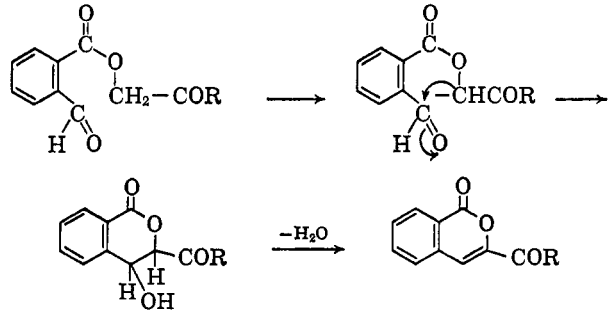
been reduced and cyclized to isocoumarins of type XCII.

H. CYCLIZATION OF 2-FORMYLBENZOATES

Alkali metal salts of phthaldehydic acids condense with halogenated methyl ketones to give esters in high

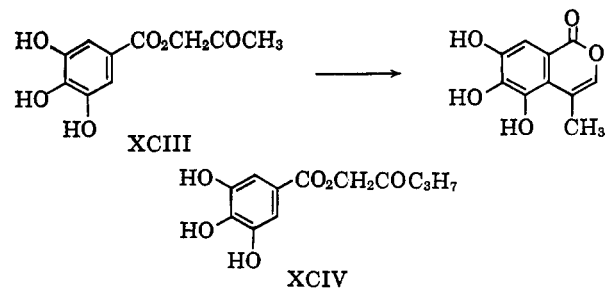


yield. These esters cyclize when heated with an organic base such as piperidine, yielding 3-substituted isocoumarins. This reaction probably occurs through



an internal aldol condensation such as the Dieckmann type condensation (111, 113).

Certain benzoates such as XCIII cyclize in the presence of sulfuric acid to give isocoumarins. How-

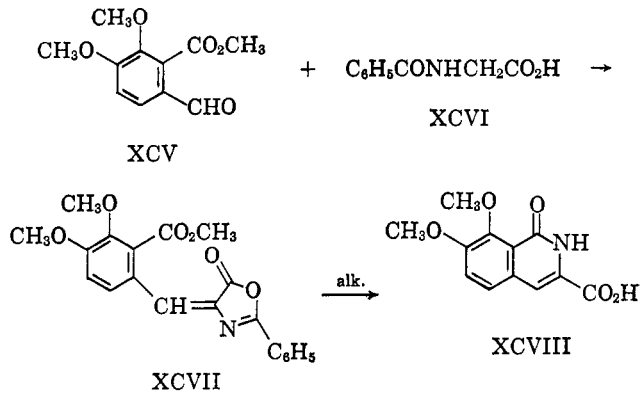


XCIII XCIV

ever, this reaction is not general since XCIV could not be cyclized (87).

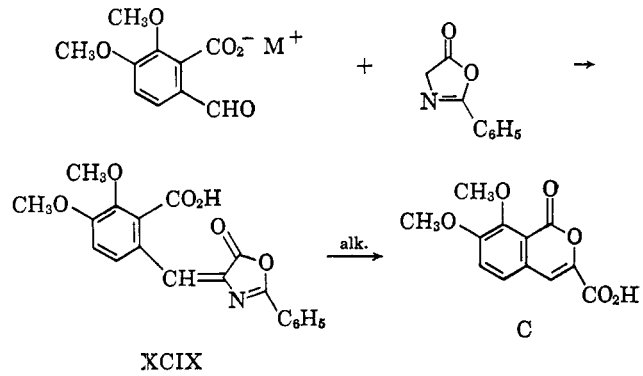
I. THE AZALACTONE SYNTHESIS

During studies directed toward the synthesis of substituted isocoumarin-3-carboxylic acids as useful drugs and as Yohimban alkaloid intermediates, the Erlenmeyer azalactone reaction was investigated (148, 149, 180). Thus, methyl opianate (XCV) yields 2-phenyl-4-(2-carbomethoxy-3,4-dimethoxybenzylidene)oxazol-5-one (XCVII) when treated with hippuric acid (XCVI) in the presence of acetic anhydride and sodium acetate. Alkaline hydrolysis of XCVII gives 7,8-dimethoxyisocarbostyril-3-carboxylic acid (XCVIII) (15). However, the condensation between the alkali metal salt of opianic acid and 2-phenyloxazol-5-one in ethanol gives the benzylideneoxazolone



XCV XCVI XCVII XCVIII

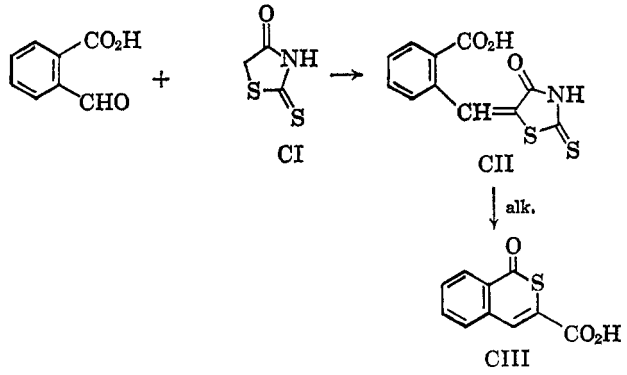
(XCIX) (43% yield), and strong alkaline hydrolysis with 20% aqueous sodium hydroxide produces 7,8-dimethoxyisocoumarin-3-carboxylic acid (C) (80%



XCIX C

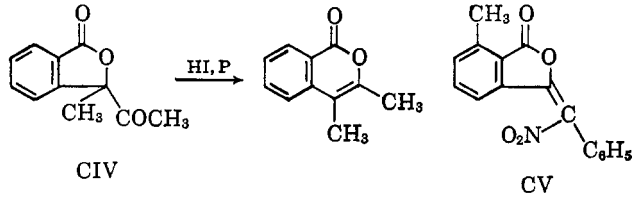
yield). The over-all yield of 7,8-dimethoxyisocoumarin-3-carboxylic acid is 34.2% based on opianic acid, and for isocoumarin-3-carboxylic acid (using phthaldehydic acid in place of opianic acid) is 33.4%. Decarboxylation of the isocoumarin-3-carboxylic acids can be effected with copper powder at 250° giving a route to isocoumarins.

Rhodanine (CI) and phthaldehydic acid esters give the corresponding benzylidene rhodanine derivative (CII) under similar conditions. Hydrolysis with alkali produces 2-thioisocoumarin-3-carboxylic acid (CIII) (110).



J. REDUCTION OF PHTHALIDES WITH HYDRIODIC ACID AND PHOSPHORUS

Treatment of 3-methyl-3-acetylphthalide (CIV) with hydriodic acid and phosphorus yields 3,4-dimethylisocoumarin (197). Similarly 3-(α-nitrobenzylidene)-7-methylphthalide (CV) furnishes 3-phenyl-8-methyliso-

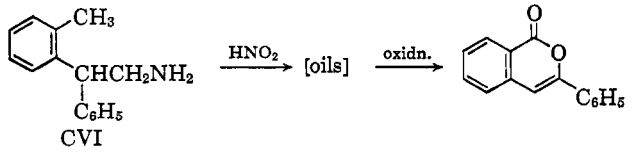


coumarin (50% yield) (135, 139). Other 3-arylidene or 3-alkylidenephthalides also can be converted to isocoumarins by this method. Addition of nitrogen sesquioxide (N_2O_3) to "isobenzylidenephthalide" is reported to yield 3-phenyl-4-nitroisocoumarin (115).

This method is not particularly good as a general synthetic route to isocoumarins since low yields are often obtained. However, in certain cases this sequence should be considered, since 3-arylidene and 3-alkylidene phthalides are easily available from the Perkin condensation between phthalic anhydrides and substituted acetic acids (including the longer chain acids).

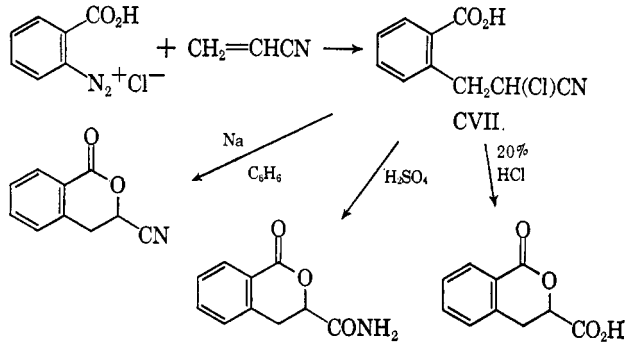
K. MISCELLANEOUS REACTIONS PRODUCING ISOCOUMARINS

During studies of the rearrangement of amines when they are treated with nitrous acid, the oils obtained from β-phenyl-β-(2-methylphenyl)ethylamine (CVI), when oxidized for a short time with alkaline



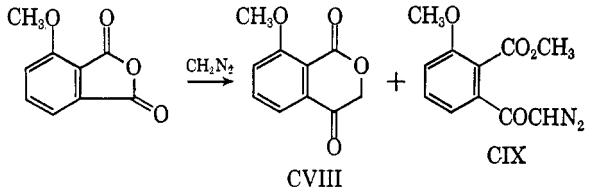
permanganate, yielded small amounts of 3-phenyl-3,4-dihydroisocoumarin (14).

Addition of cyanoethylene to 2-diazoaminobenzoic acid gives 2-(β-chloro-β-cyanoethyl)benzoic acid (CVII), which cyclizes to 3,4-dihydroisocoumarin-3-carboxylic acid with 20% hydrochloric acid, to 3-cyano-3,4-dihydroisocoumarin with sodium in benzene or toluene, and to 3,4-dihydroisocoumarin-3-carboxamide with sulfuric acid (130).

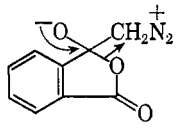


Methyl ketones condense with 3,5-dinitrobenzoic acid under alkaline conditions yielding a dark, purple powder, which is reported to give 3-alkyl or 3-aryl isocoumarins after oxidation with hydrogen peroxide in acetic acid (2).

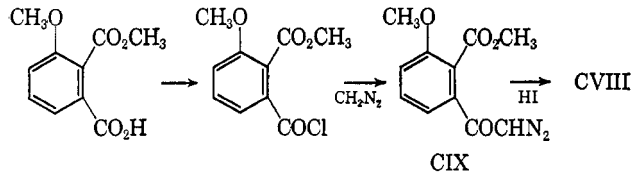
Diazomethane adds to 3-methoxyphthalic anhydride producing 8-methoxy-1,4-isochromandione (CVIII)



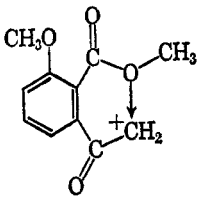
together with some diazoketo ester (CIX). This reaction probably takes place through addition of diazomethane to give the intermediate CX. Similarly 3-nitrophthalic anhydride gives 8-nitro-1,4-isochromandione. Isochromandiones also can be made by the



alternate pathway of addition of diazomethane to the half-ester of phthalic acid, followed by hydriodic acid

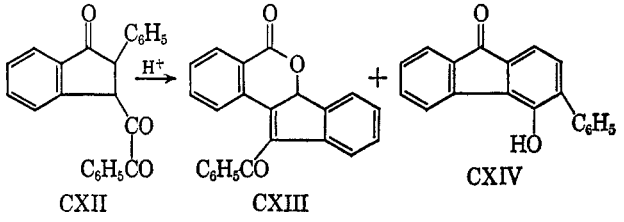


(35). The intermediate in this reaction is probably CXI.



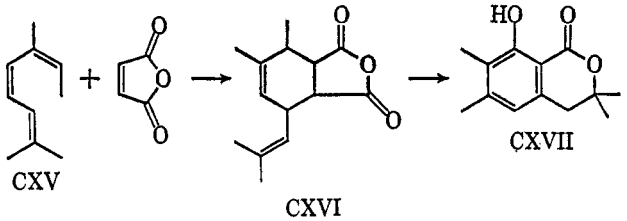
CXI

During studies of the chemistry of 3-furanones, the indenocoumarin CXIII and 3-phenyl-4-hydroxyfluorenone CXIV were obtained from 2-phenyl-3-phenylglyoxalindanone (CXII) by treatment with boiling acetic acid and hydrochloric acid (209).



CXII CXIII CXIV

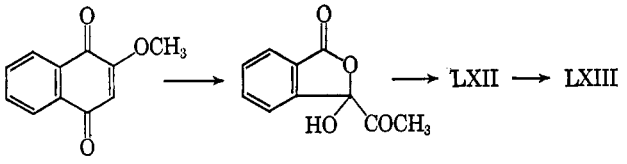
Maleic anhydride addition to allocimene (CXV) yields the tetrahydrophthalic anhydride (CXVI), which can be converted to 3,3,6,7-tetramethyl-8-hydroxy-3,4-dihydroisocoumarin (CXVII) by consecu-



CXV CXVI CXVII

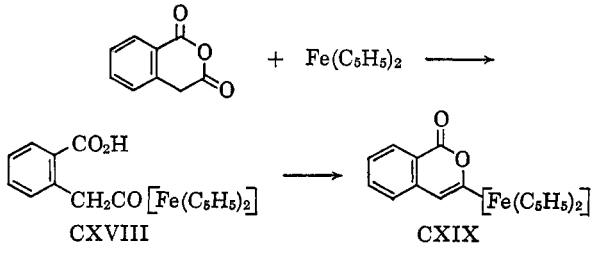
tive treatment with N-bromosuccinimide and potassium in glycol at 180° (61).

Ozonolysis of 2-methoxy-1,4-naphthoquinone yields 3-hydroxy-3-acetylphthalide which gives 2,5-bis(2-



hydroxyphenyl)-1,4-benzoquinone (LXII) when heated with alkali. In the presence of acid the quinone can be cyclized to the benzoisocoumarin (LXIII) (22, 141).

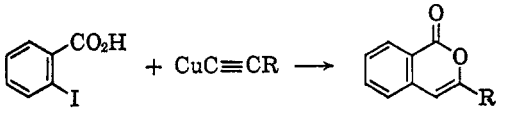
Homophthalic anhydride adds to ferrocene to produce ferrocenylhomophthalic acid (CXVIII), which



CXVIII CXIX

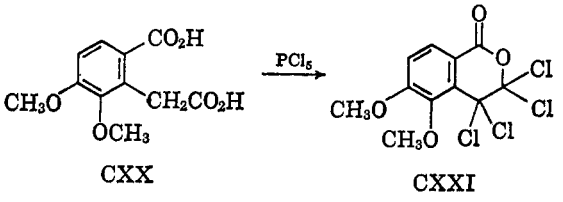
can be cyclized to 3-ferrocenylisocoumarin (CXIX) (46).

A promising route to 3-substituted isocoumarins involves the reaction between cuprous acetylides and 2-iodobenzoic acids. This sequence has been used to



prepare 3-phenylisocoumarin (53, 181).

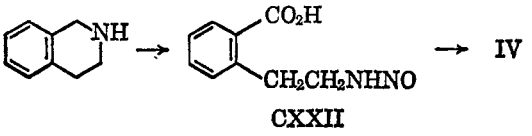
Treatment of 3,4-dimethoxyhomophthalic acid (CXX) with phosphorus pentachloride produces 3,3,-



CXX CXXI

4,4-tetrachloro-5,6-dimethoxy-3,4-dihydroisocoumarin (CXXI) (54).

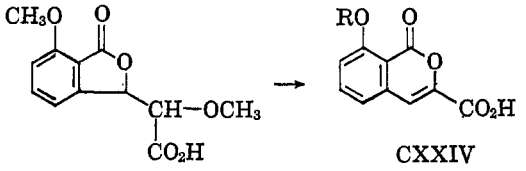
Nitrosation of 1,2,3,4-tetrahydroisoquinoline using acetic acid and sodium nitrite gives a 65% yield of 3,4-



CXXII

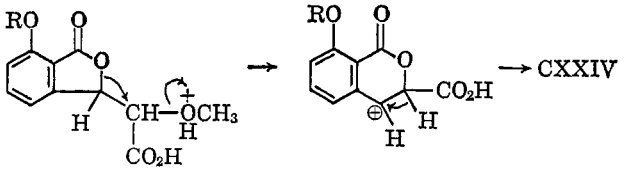
dihydroisocoumarin (IV), by way of the 2-(β-N-nitrosoaminoethyl)benzoic acid (CXXII) intermediate (192).

Hydrobromic acid transforms CXXIII into 8-hydroxyisocoumarin-3-carboxylic acid (CXXIV) (where R = H), and heat alone gives the 8-methoxyisocoumarin-3-carboxylic acid (CXXIV) (where R = CH_3).

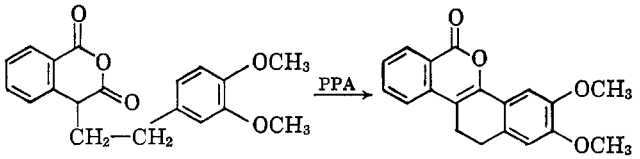


CXXIII CXXIV

This reaction probably occurs by the rearrangement as shown below (1).



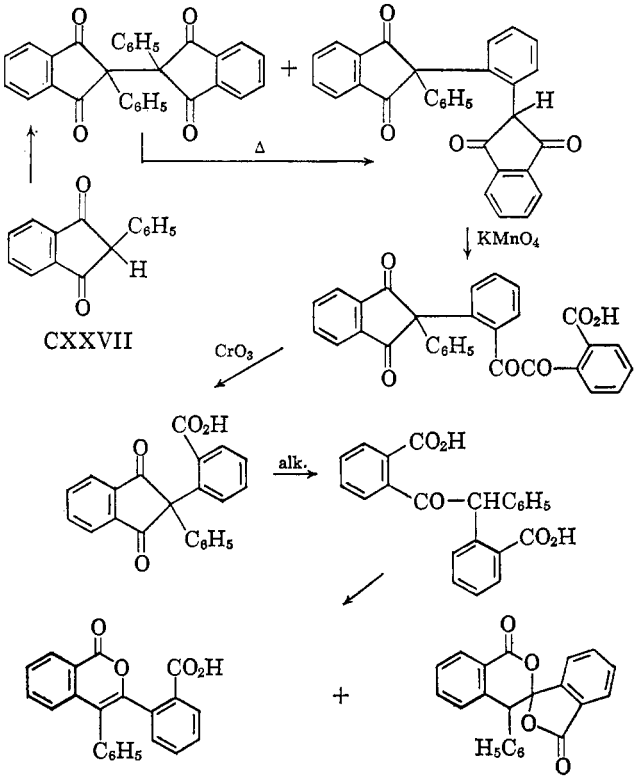
The homophthalic anhydride (CXXV) cyclizes when treated with polyphosphoric acid yielding isocoumarin (CXXVI) (13).



CXXV CXXVI

Autoxidation of 2-phenyl-1,3-indanedione (CXXVII) in pyridine with cuprous bromide catalyst, followed by the sequence shown in Scheme I, leads to two isocoumarins (CXXVIII and CXXIX) (153).

SCHEME I



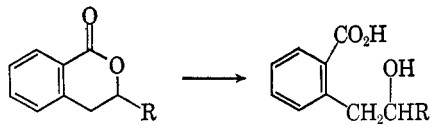
CXXVII CXXVIII CXXIX

The only heterocyclic isocoumarin with the heteroatom in the aromatic ring which has been synthesized to date is 5-vinyl-7-aza-3,4-dihydroisocoumarin (gentianine) and synthetic precursors. The 2-azaisocoumarin system was made from 2-acetyl-γ-butyrolactone, and details are discussed under gentianine in section IVD (74, 75).

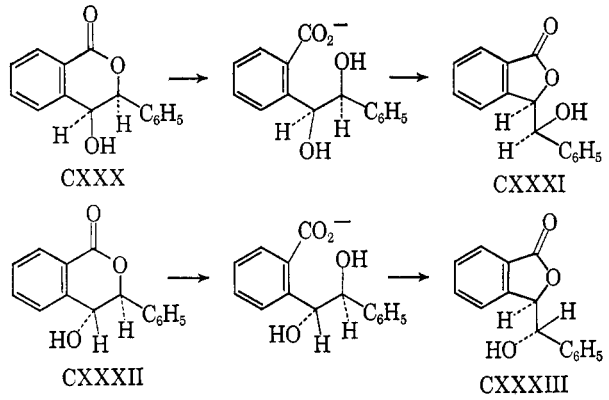
III. REACTIONS OF ISOCOUMARINS

A. HYDROLYSIS

Isocoumarins are lactones and accordingly react with base to give homophthaldehydic acids, or ketones if there is a substitution in the 3-position. For the case of 3,4-dihydroisocoumarins hydrolysis yields the corresponding β-(2-carboxyphenyl)ethyl alcohols. In some instances the acids cannot be isolated since spontaneous cyclization to the lactone occurs. In other

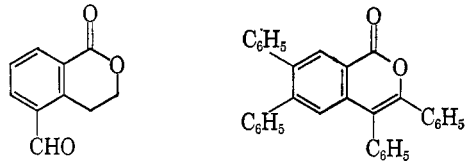


instances, such as the case of *cis*- (CXXX) and *trans*-3-phenyl-3,4-dihydroisocoumarin (CXXXII), hydrolysis gives a glycol which recyclizes under acid treatment to yield the more stable γ-lactones, *erythro*- (CXXXI), and *threo*-3-(α-hydroxybenzyl)phthalide (CXXXIII) (29, 30).



CXXX CXXXI CXXXII CXXXIII

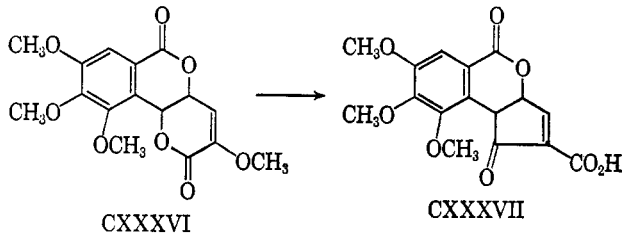
Examples of opening of the lactone ring and recovery of the isocoumarin unchanged are erythrocentaurin



CXXXIV CXXXV

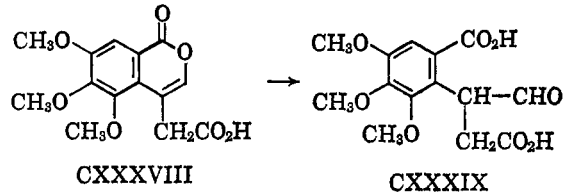
(5-formyl-3,4-dihydroisocoumarin) (CXXXIV) (121) and 3,4,5,6-tetraphenylisocoumarin (CXXXV) (97).

Some unusual consequences of hydrolysis of isocoumarins have been reported. Alkaline hydrolysis of

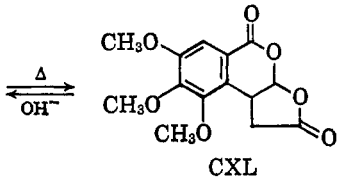


CXXXVI CXXXVII

tetra-O-methylgalloflavin (CXXXVI) gives isogalloflavin (CXXXVII) (84), and transformation of α-[4-(5,6,7-trimethoxyisocoumarinyl)]acetic acid (CXXXVIII) to homophthaldehyde (CXXXIX), followed by sublimation of the acid, produces the complex isocoumarin CXL (98). As discussed earlier (section IID3) diethyl isocoumarin-3,4-dicarboxylate, formed by

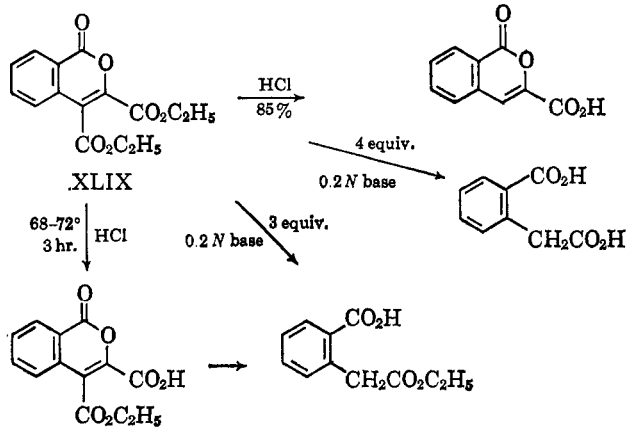


CXXXVIII CXXXIX



CXL

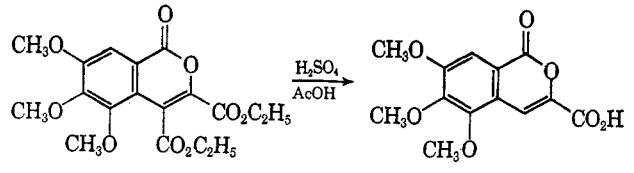
way of the diethyl oxalate condensation with diethyl homophthalate, can be hydrolyzed in several ways producing various products. Thus, boiling with hydrochloric acid or heating in a sealed tube with water at 180–190°, the ester is transformed in 84% yield to isocoumarin-3-carboxylic acid. After 3 hr. at 68–72° with hydrochloric acid, ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate is produced together with a small



XLIX

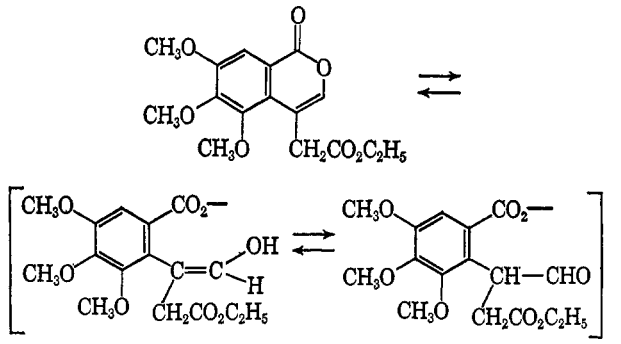
amount of isocoumarin-3-carboxylic acid (after prolonged heating). Treatment of the ester with 3 equiv. of 0.2 *N* base yields the homophthalic acid half-ester, also made from ethyl isocoumarin-3-(carboxylic acid)-4-carboxylate. On the other hand, 4 equiv. of 0.2 *N* base furnishes homophthalic acid (189).

Hydrolysis of diethyl 5,6,7-trimethoxyisocoumarin-3,4-dicarboxylate with sulfuric acid in acetic acid gave

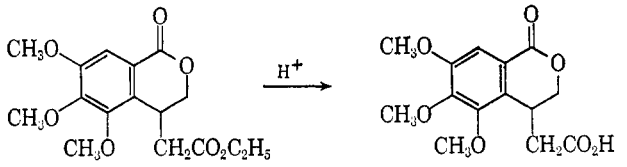


5,6,7-trimethoxyisocoumarin-3-carboxylic acid (87).

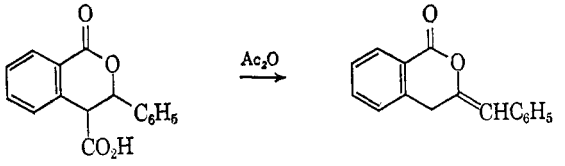
These results show that hydrolysis of the 4-carbethoxy group is difficult, and that the 4-carboxylic acid group is easily decarboxylated. Further, ethyl 4-(5,6,7-trimethoxyisocoumarinyl)acetate could not be hydrolyzed with bases, acids, or boron trifluoride in ether, presumably due to the formation of an unstable β-aldehydic acid intermediate. However, reduction of ethyl



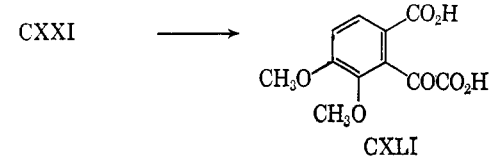
α-4-(5,6,7-trimethoxyisocoumarinyl)acetate, followed by treatment with acid, easily gave α-4-(5,6,7-trimethoxyisocoumarinyl)acetic acid (87). In this case, the lactone ring opens readily in boiling water containing a little acid.



Boiling acetic anhydride brings about the rearrangement of 3-phenyl-3,4-dihydroisocoumarin-4-carboxylic



acid yielding 3-benzylideneisocoumarin (134). Hydrolysis of 5,6-dimethoxy-3,3,4,4-tetrachloro-3,4-dihy-

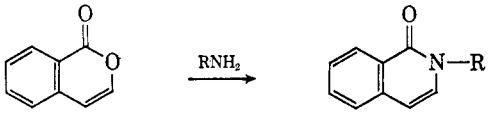


CXXI CXLI

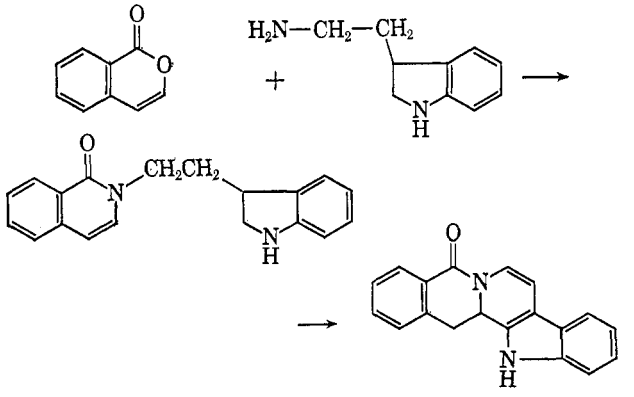
droisocoumarin (CXXI) yields phthalonic acid (CXLI) (54).

B. AMMONIA AND AMINES

Ammonia and amines add to isocoumarins yielding isocarbostyrils, a reaction typical of esters (135).



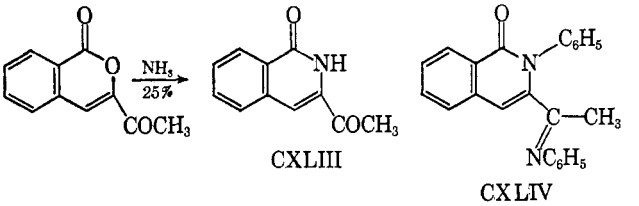
Isocoumarin and isocoumarin-3-carboxylic acid have been condensed with tryptamine, and the product sub-



CXLII

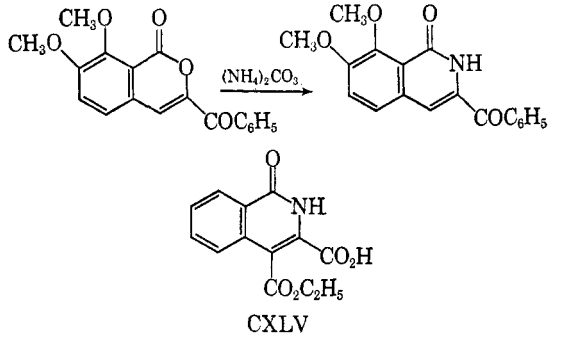
sequently converted to yobyrine (CXLII) and other derivatives (109, 148).

Refluxing 3-acetylisocoumarin with aqueous ammonia for 3 hr. gives a 25% yield of 3-acetylisocarbostyril (CXLIII). Aniline, under similar conditions gives a 50% yield of the isocarbostyril (CXLIV).



CXLIII CXLIV

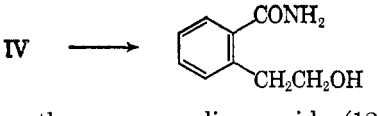
Ammonium carbonate in acetic acid produces 3-benzoyl-



CXLV

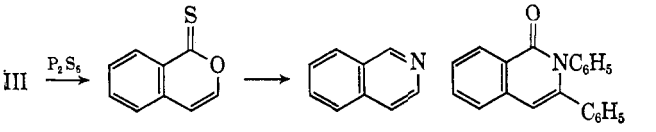
7,8-dimethoxyisocarbostyril in 100% yield from 3-benzoyl-7,8-dimethoxyisocoumarin (111). Diethyl isocoumarin-3,4-dicarboxylate yields ethyl isocarbostyril-3-(carboxylic acid)-4-carboxylate (CXLV), a reaction which involves concomitant hydrolysis of the 3-ester group (112). Hydrochloric acid in a sealed tube at 170–180° converts CXLV to isocarbostyril-3-carboxylic acid (189).

One report in the literature describes the opening of the lactone ring in 3,4-dihydroisocoumarin with am-



monia to give the corresponding amide (128). Other examples of the reaction of isocoumarins with ammonia or amines may be found in ref. 108.

Isocoumarin can be converted to 1-thioisocoumarin with phosphorus pentasulfide, and treatment of 1-thioisocoumarin with ammonium sulfide or aniline yields isoquinolines. Analogously, 3-phenylisocoumarin has

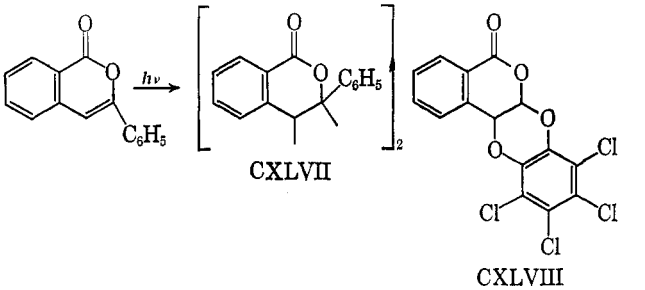


CXLVI

been converted to 1-thio-3-phenylisocoumarin, and treatment with aniline produced CXLVI (145).

C. PHOTOCHEMICAL REACTIONS

Irradiation of 3-phenylisocoumarin for 25 days in benzene yields the dimer CXLVII, but the correct



CXLVII CXLVIII

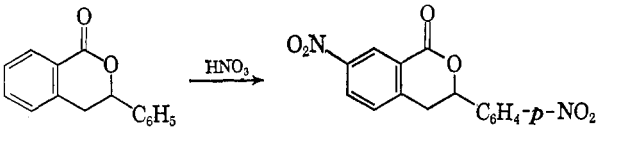
isomeric structure has not been elucidated (164). Irradiation in the presence of tetrachloro-*o*-benzoquinone yields the isocoumarin CXLVIII (165).

D. DECARBOXYLATION

Vacuum distillation effects decarboxylation of isocoumarin-3-carboxylic acid (187). Copper bronze also has been used to decarboxylate isocoumarins such as 6,7-dimethoxyisocoumarin-3-carboxylic acid (79% yield) (110), and 7,8-dimethoxyisocoumarin-3-carboxylic acid has been decarboxylated using copper powder (148).

E. NITRATION

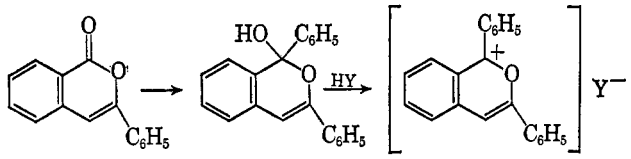
The only report of the nitration of an isocoumarin is that of 3-phenyl-3,4-dihydroisocoumarin, in which case nitric acid in sulfuric acid gives 3-(4-nitrophenyl)-7-nitro-3,4-dihydroisocoumarin (32).



F. GRIGNARD REAGENTS

Addition of Grignard reagents to isocoumarins was discussed in the previous review (191). Recent references to the addition of Grignard reagents are 3, 62, 129, 172. Addition of phenylmagnesium bromide to 3-phenylisocoumarin, followed by perchloric acid,

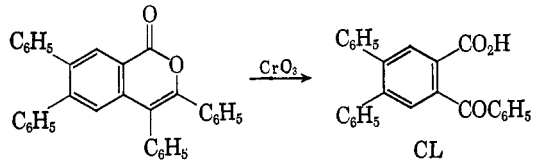
anhydrous hydrochloric acid, ferric chloride, or ferric bromide yields the isobenzopyrilium salts (CXLIX), (where Y is perchlorate, chloride, ferrichloride, and ferribromide, respectively) (171).



CXLIX

G. OXIDATION

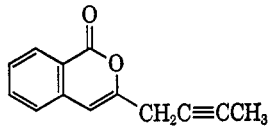
Chromium trioxide oxidation of 3,4,6,7-tetraphenylisocoumarin gives 2-benzoyl-4,5-diphenylbenzoic acid (CL) (3). Oxidation of 5-hydroxymethyl-3,4-dihydroisocoumarin with chromium trioxide in *t*-butyl alcohol



CL

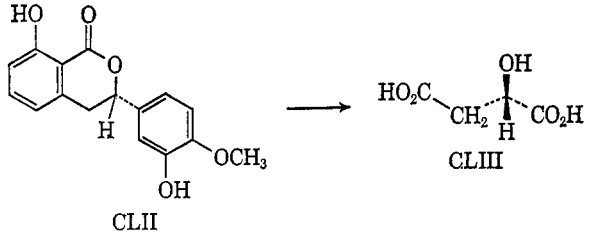
(*t*-butyl chromate), produces 3,4-dihydro-5-formylisocoumarin, isolated as the semicarbazide (122, 186). Potassium permanganate ruptures the lactone ring and gives phthalic acid derivatives (84, 89, 121, 185). Potassium dichromate has been used to prepare 3,4-dihydroisocoumarin-5-carboxylic acid from 5-formyl-3,4-dihydroisocoumarin (121, 185).

Ozonolysis of 3-(2-butynyl)isocoumarin (CLI) gives phthalic acid (43). Exhaustive oxidation of phyllodulcinol [3-(3-hydroxy-4-methoxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin] (CLII) with ozone has been



CLI

used to determine the configuration of the 3-substituent



CLII CLIII

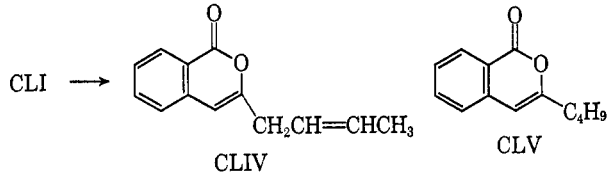
by comparison of the product, D-malic acid (CLIII), with authentic material (6).

H. REDUCTION

The 3,4-double bond of isocoumarins is readily reduced with hydrogen and palladium on charcoal or with other catalysts (1, 77, 87, 202). Catalytic reduction also has been used to remove the halogen from *cis*- and *trans*-3-phenyl-4-halo-3,4-dihydroisocoumarin (28, 30, 31).

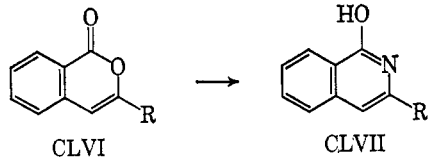
Lithium aluminum hydride reduces isocoumarins to β-(2-hydroxymethylphenyl)ethyl alcohols (76, 121, 185, 186). Meerwein–Ponndorf reduction of 3-formylisocoumarins has been used to prepare 3-hydroxymethylisocoumarins (143).

Catalytic reduction of 3-(2-butynyl)isocoumarin (CLI) using Lindlar catalyst gives 3-(2-butenyl)isocoumarin (CLIV) (40% yield) (43, 80), and platinum



CLIV CLV

oxide furnishes 3-butylisocoumarin) (CLV) (50% yield) (80). Wolff–Kishner reduction of 3-alkyl isocoumarins (CLVI) (where R is ethyl or 4-phenoxybutyl) yields

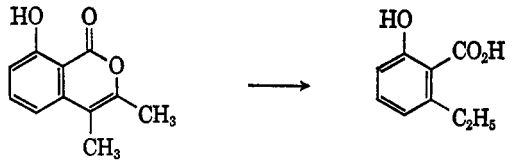


CLVI CLVII

isoquinolines of type (CLVII), and Clemmensen reduction of the phenoxy derivative is reported to give starting material and oils (100).

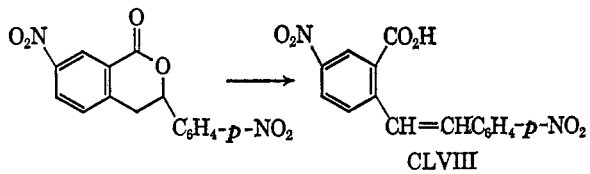
I. ALKALI FUSION

Fusion of 3,4-dihydroisocoumarins with potassium hydroxide gives vinylbenzoic acids (20, 174). Alkali fusion of 3,4-dimethyl-8-hydroxyisocoumarin yields 2-ethyl-6-hydroxybenzoic acid (6-ethylsalicylic acid) (202). This reaction may be related to the reverse



aldol type.

A useful method for preparing stilbene-2-carboxylic acids is represented by the conversion of 3-(4-nitro-

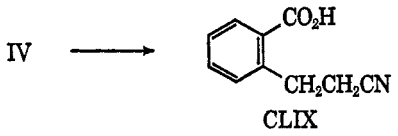


CLVIII

phenyl)-7-nitro-3,4-dihydroisocoumarin to 4,4′-dinitrostilbene-2-carboxylic acid (CLVIII) with methanolic sodium methoxide (32).

J. POTASSIUM CYANIDE

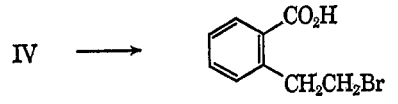
As for the case of phthalides, 3,4-dihydroisocoumarins react with potassium cyanide and in this case give β-(2-carboxyphenyl)propionitriles (CLIX) (128, 129).



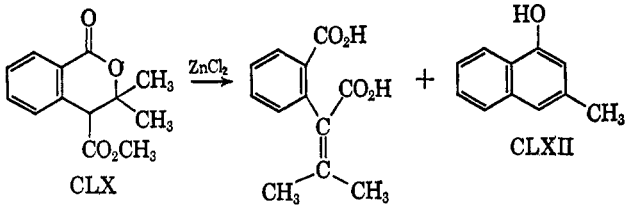
CLIX

K. MISCELLANEOUS REACTIONS

Hydrobromic acid is reported to open the lactone ring of 3,4-dihydroisocoumarin yielding β-(2-carboxyphenyl)ethyl bromide (128).



Treatment of methyl 3,3-dimethyl-3,4-dihydroisocoumarin-4-carboxylate (CLX) with zinc chloride



CLX CLXI CLXII

gives as the main product α-(2-propylidene)homophthalic acid (CLXI) and small quantities of 3-methyl-1-naphthol (CLXII) (125).

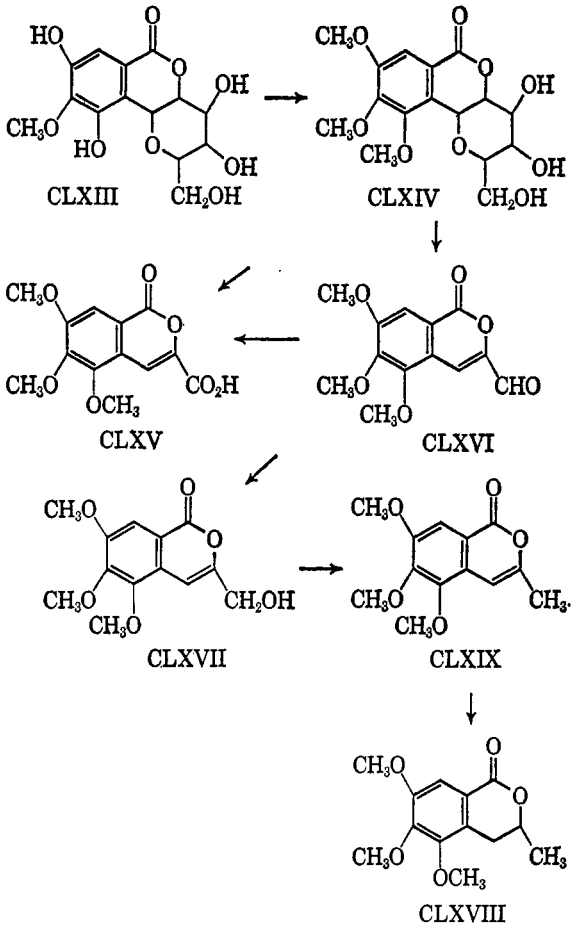
IV. NATURALLY OCCURRING ISOCOUMARINS

Isocoumarins produced by plants, molds, bacteria, and lichens will be described in this section. Also included is galloflavin, a mordant dye produced by the action of air on gallic acid under alkaline conditions.

No attempt has been made to present all of the evidence used to elucidate the structures of the isocoumarins covered in this section. Only the more important or novel reactions are given, since in many cases the reactions would be a repetition of those given in the section covering reactions of isocoumarins.

A. BERGENIN

The polyphenol, bergenin (2β-D-glucopyranosyl-4-O-methylgallic acid δ-lactone or 4-methoxy-2-(tetrahydro-3,4,5-trihydroxy-6-hydroxymethyl)pyran-2-yl-α-resorcylic acid δ-lactone) (CLXIII), has been isolated from many plants. Table V is a list of the plants from which bergenin has been isolated, together with a description of the part of the plant from which bergenin was obtained, and the yield (where reported). Vakerin, from *Shorea leprosula* (52, 89) and *Caesalpinia digyna*



(60, 89), has been shown to be identical with bergenin, as has corylopsin from *Corylopsis spicata* (71, 82, 89). The Chinese drugs "Kai-Ho-Chien" (from *Ardisia hortorium*) (101) and the antipyretic "Sheng ma" (from *Astilbe macroflora*) (98) have been shown to contain bergenin.

The structure of bergenin was established by studying its degradation products, then by synthesis. Some of the more important facets are discussed in the subsequent paragraphs.

Permanganate oxidation of di-O-methylbergenin (CLXIV) gave the known 5,6,7-trimethoxyisocoumarin-3-carboxylic acid (CLXV) (89). With 1 mole of periodate, di-O-methylbergenin yielded 3-formyl-5,6,7-trimethoxyisocoumarin (CLXVI) (87), which was reduced to 3-hydroxymethyl-5,6,7-trimethoxyisocoumarin (CLXVII) by the Meerwein–Ponndorf method (71, 89, 143). Alkali converted 3-formyl-5,6,7-trimethoxyisocoumarin to the corresponding acid (71, 143). Catalytic reduction of CLXVI in three successive steps yielded 3-hydroxymethyl-5,6,7-trimethoxyisocoumarin (CLXVII), 3-methyl-5,6,7-trimethoxyisocoumarin (CLXIX), and 3-methyl-5,6,7-trimethoxy-3,4-dihydroisocoumarin (CLXVIII) in that order (71). This series of reactions established the isocoumarin system and the position of the methoxy groups.

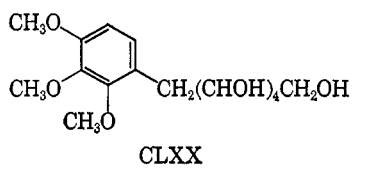
TABLE V

OCCURRENCE OF BERGENIN IN PLANTS

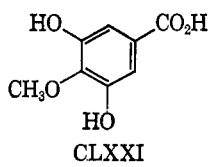
Plant	Source	Yield, %	Ref.
Family:			
Myrsinaceae			
Ardisia hortorum	...	...	101
Family:			
Humiriaceae			
Humeria balsamifera	Bark	3.0	65
Family:			
Euphorbiaceae			
Mallotus japonicus Mueller	Bark	...	95
Family:			
Dipterocarpacea			
Shorea leprosula (*Shorea meranti*)	Heartwood	0.5	52, 89
Family:			
Leguminosae			
Caesalpinia digyna	Root	...	61, 89
Family:			
Hamamelidaceae			
Corylopsis spicata	Bark	...	71, 82, 89
C. sinensis		[a]	142
C. wilmolliae		[a]	142
C. platypetala		[a]	142
C. pauciflora		[a]	142
C. glabrescens		[a]	142
Fortunearia sinensis		...	142
Family:			
Saxifragaceae			
Astilbe thumbergi Miquel	Root	0.5	170, 182, 200, 201
A. formosa Nakai	Root	1.42	182, 200, 201
A. odontophylla Miquel (var. *congesta* Hara		0.04–0.13	182, 200, 201
A. japonica	Root stocks	...	90, 200
A. macroflora	...	...	98
Bergenia crassiflora	Roots, rhizomes	...	89, 143
B. stracheyi Engler	Root	0.75	182, 200, 201
Saxifraga ligulata	Root	...	107
S. crassifolia	Root	0.05	143, 187, 189
S. sibirica	Root	...	187
Peltobaykinia tellimoides Hara	Root	1.07	182, 200, 201
Rodgersia podophylla Gray	Root	0.39	182, 200, 201

[a] Yield 0.08–1.4% depending on the species.

Catalytic reduction of di-O-methylbergenin (CLXIV) with Raney nickel at 200° and 100 atm. gave the pentol (CLXX) (71). Alkaline hydrogen peroxide oxidized bergenin, and arabinose was shown to be one of the products (71). Alkaline fusion, or barium hydroxide hydrolysis, of bergenin gave 4-O-methylgallic acid (CLXXI), a known compound (89, 187).



CLXX



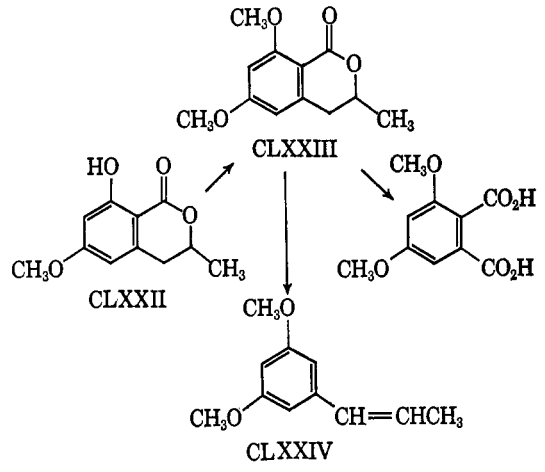
CLXXI

On the basis of these and other facts, bergenin was finally given the isocoumarin structure CLXIII. Synthesis was finally accomplished from tetra-O-acetyl-α-D-glucopyranosyl bromide and methyl 4-O-methylgallate in the presence of sodium methoxide. The product, 2-β-D-glucopyranosyl-4-O-methylgallic acid δ-lactone, was shown to be identical with bergenin (89).

Bergenin is reported to be useful for improving the brightness of electroplates at concentrations of 0.01–10 g./l. in the electroplating bath (173).

B. 3-METHYL-6-METHOXY-8-HYDROXY-3,4-DIHYDROISOCOUMARIN

One of the components of carrots is 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (CLXXII). This compound has been found in carrots which have been stored for some time, but not in those which were freshly harvested (174, 175). This compound is reported to inhibit germination and germ-tube growth of *Thielaviopsis basicola* in carrots (78). A study of the effect of ethylene and oxygen on the production of 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin



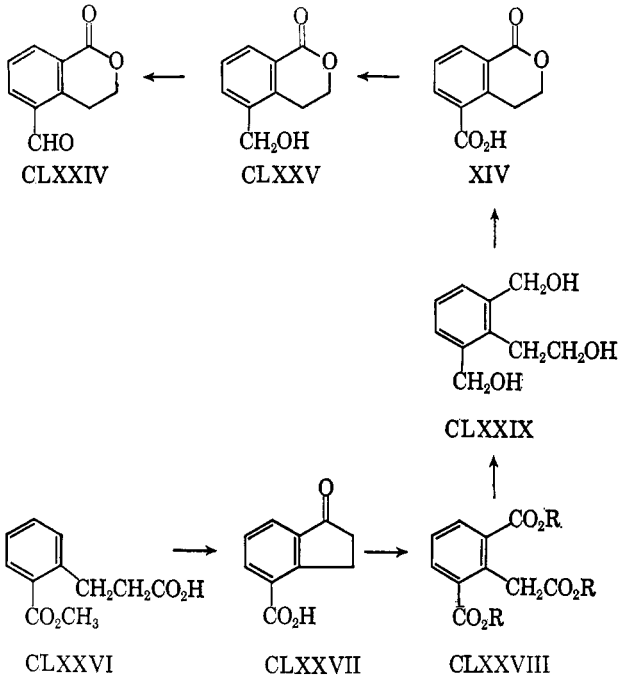
in carrots indicated that ethylene acts as a catalyst and is not incorporated into the isocoumarin. The incorporation of ethylene is prevented by short anaerobic treatments (51).

The identification of CLXXII was done in the following manner (174). Methylation with dimethyl sulfate yielded 3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin (CLXXIII). Diazomethane did not react with CLXXII due to the strong interaction between the phenolic 8-hydroxy group and the nearby carbonyl. This behavior has been observed for other 8-hydroxyisocoumarins (one such report in the literature describes the lack of reaction of the 8-hydroxy group of 3-propyl-6-methoxy-8-hydroxyisocoumarin (132)).

Permanganate oxidation of CLXXIII gave 3,5-dimethoxyphthalic acid. The presence of the 3-methyl group was established by the iodoform test, and alkali fusion of CLXXIII produced CLXXIV, identified by ozonolysis.

C. ERYTHROCENTAURIN

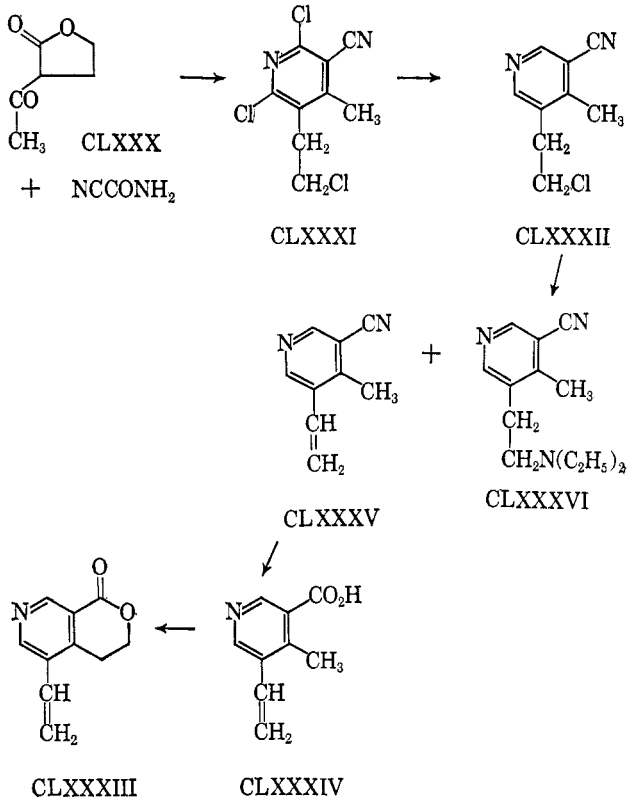
Swertiamarin, a bitter substance isolated from *Swertia japonica* Makino (114, 121, 122, 184–186), yields erythrocentaurin (5-formyl-3,4-dihydroisocoumarin) (CLXXIV) when hydrolyzed with emulsin. Identity of erythrocentaurin as 5-formyl-3,4-dihydroisocoumarin is based on synthesis. Thus, β-(2-carbomethoxyphenyl)propionic acid (CLXXVI) was cyclized to indanone-4-carboxylic acid (CLXXVII) with polyphosphoric acid, followed by oxidation to 2,6-dicarboxyphenylacetic acid (CLXXVIII) (where R = H) with sodium hypobromite. Reduction of the ester CLXXVIII (where R is methyl) with lithium aluminum hydride gave β-[2,6-bis(hydroxymethyl)-phenyl]ethyl alcohol (CLXXIX), which was converted to 3,4-dihydroisocoumarin-5-carboxylic acid (XVI) with chromium trioxide. The acid chloride of XVI was reduced with sodium borohydride to 5-hydroxymethyl-3,4-dihydroisocoumarin (CLXXV), and chromium trioxide in *t*-butyl alcohol oxidized CLXXV to 5-formyl-3,4-dihydroisocoumarin (CXXXIV), isolated as the semicarbazide. The semicarbazide of erythrocentaurin was identical (122, 186).



D. GENTIANINE

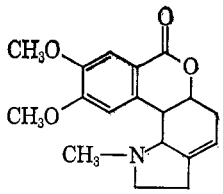
The alkaloid gentianine (5-vinyl-7-aza-3,4-dihydroisocoumarin) (CLXXIII) has been isolated from *Enicostemma littorale* Bl. (72, 74, 106, 146, 147), *Gentiana axillariflora*, *Gentiana scabra*, and *Swertia japonica* (168).

Gentianine has been synthesized in the following way. α-Acetyl-γ-butyrolactone (CLXXX) was condensed with cyanoacetamide to give 2,6-dichloro-3-cyano-4-methyl-5-(β-chloroethyl)pyridine (CLXXXI). Catalytic reduction of (CLXXXI) with palladium gave 3-cyano-4-methyl-5-(β-chloroethyl)pyridine (CLXXXII), which was converted to a mixture of 3-cyano-4-methyl-5-(β-diethylaminoethyl)pyridine (CLXXXVI) and 3-cyano-4-methyl-5-vinylpyridine (CLXXXV) with diethylamine. Hydrolysis of CLXXXV to 4-methyl-5-vinylpyridine-3-carboxylic acid (CLXXXIV), followed by condensation of the sodium salt of CLXXXIV with excess formaldehyde, gave 5-vinyl-7-aza-3,4-dihydroisocoumarin (CLXXXII), identical with gentianine (74, 75).



E. HOMOLYCORINE

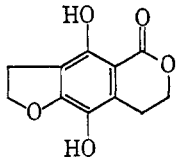
Homolycorine has been assigned the isocoumarin structure CLXXXVII. This compound occurs among



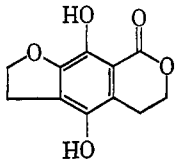
the alkaloids of *Lycoris radicata*, *Narcissus poeticus*, and *Leucojum vernum* L. (47, 118, 119).

F. BLEPHERIGENIN

Blepherin is a colorless crystalline principle of *Blespheria edulis* Pers. obtained in yields as high as 0.7%



CLXXXVIII

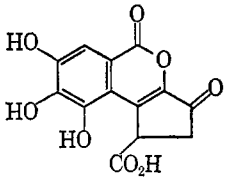


CLXXXIX

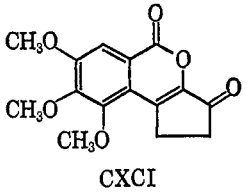
(123, 124). Hydrolysis of blepherin yields D-glucose and the aglycone blepherigenin. Based on its physical and chemical properties, blepherigenin has been assigned structure CLXXXVIII or CLXXXIX (59).

G. BREVIFOLIN AND BREVIFOLINCARBOXYLIC ACID

A major component of the pods of *Caesalpinia brevifolia* is brevifolincarboxylic acid (CXC) (23, 76, 77, 83, 157). Methylation of brevifolincarboxylic acid using diazomethane, followed by decarboxylation,



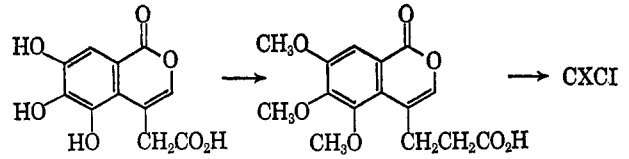
CXC



CXCI

gives tri-O-methylbrevifolin (CXCI). Extensive degradation studies were carried out in order to elucidate the structures of brevifolincarboxylic acid and brevifolin.

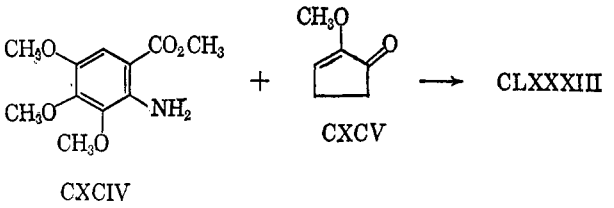
Synthesis of tri-O-methylbrevifolin was accomplished in two independent ways. Methylation of α-[4-(5,6,7-trihydroxyisocoumarinyl)]acetic acid (CXCII), followed by the Arndt–Eistert method for extending



CXCII CXCIII CXCI

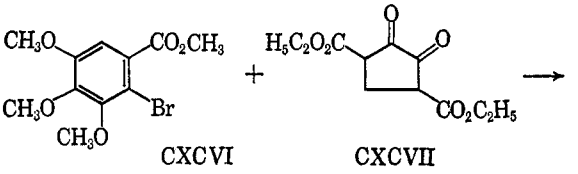
the acid chain gave β-[4-(5,6,7-trimethoxyisocoumarinyl)]propionic acid (CXCIII). This acid was cyclized with phosphorus pentoxide in boiling benzene, giving good yields of tri-O-methylbrevifolin (76, 83).

The alternate method of synthesis of tri-O-methylbrevifolin involved coupling of methyl 2-amino-3,4,5-trimethoxybenzoate (CXCIV) with 2-methoxycyclopent-2-en-1-one (CXCV) (23).

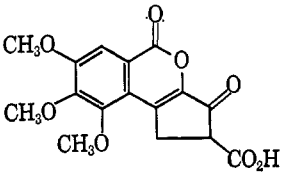


CXCIV CXCV CLXXXIII

In order to establish the position of the carboxylic acid group, the two possible isomers were synthesized. Thus, methyl 2-bromo-3,4,5-trimethoxybenzoate (CXCVI) was condensed with diethyl 1,2-cyclopenta-

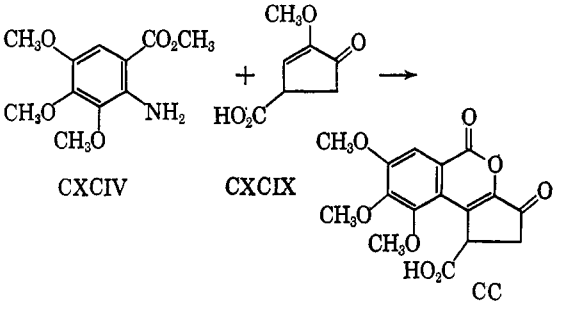


CXCVI CXCVII



CXCVIII

dione-3,5-dicarboxylate (CXCVII) yielding brevifolin-11-carboxylic acid (CXCVIII) which was not identical with tri-O-brevifolincarboxylic acid. The ester CXCIV coupled with 1-methoxycyclopent-1-en-5-one-3-carboxylic acid (CXCIX) to give tri-O-methylbrevifolin-12-carboxylic acid (CC), identical with the trimethyl ether of the natural product (158).

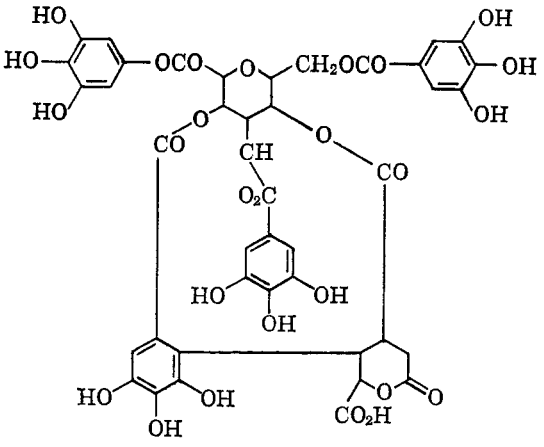


CXCIV CXCIX CC

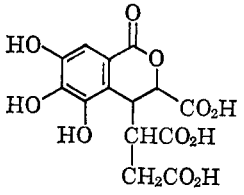
H. CHEBULIC ACID

The fruit of *Terminalia chebula*, commonly referred to as myrobalan, contains a substance called chebulagic acid (68–70, 85, 156, 159–163) with the proposed structure CCI (160). Partial hydrolysis of chebulinic acid gives equal amounts of gallic acid, 3,6-digalloylglucose, and chebulic acid ("split acid") (CCII) (162).

The structure of chebulic acid has been derived from a study of various chemical transformations, but no synthesis has been accomplished (162). A noteworthy point in the chebulic acid series is the formation of suc-

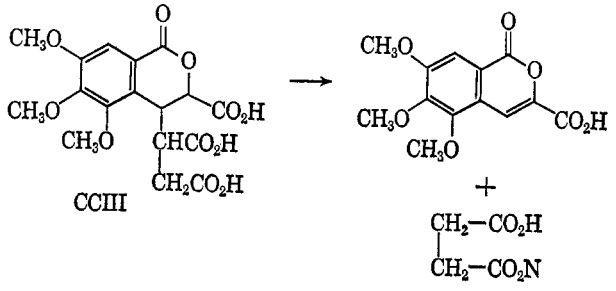


CCI



CCII

cinic acid and 5,6,7-trimethoxyisocoumarin-3-carboxylic acid when tri-O-methylchebulic acid (CCIII) is heated with copper or copper powder. This is a case of a reverse Michael reaction (86).

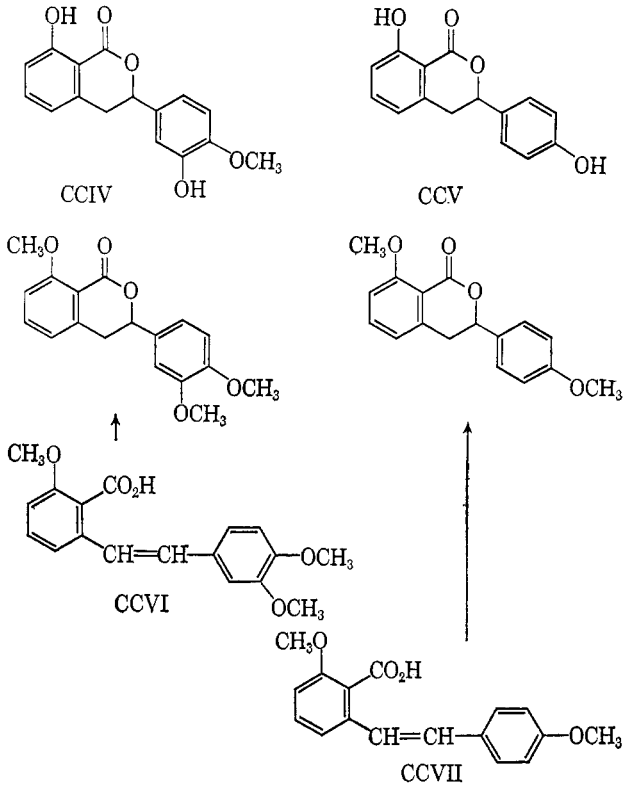


CCIII

I. HYDRANGENOL AND PHYLLODULCINOL

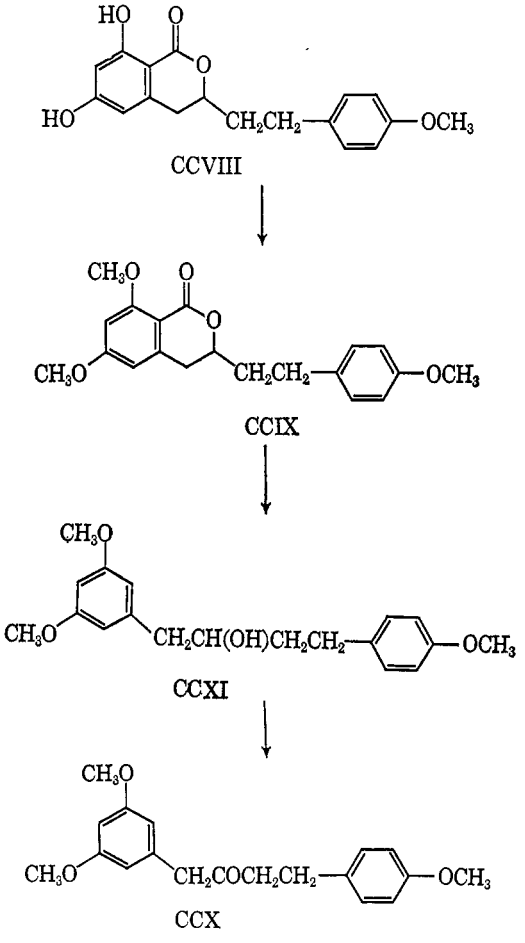
Phyllodulcinol, 3-(3-hydroxy-4-methoxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin (CCIV), and hydrangenol, 3-(4-hydroxylphenyl)-8-hydroxy-3,4-dihydroisocoumarin (CCV), are sweet principles of *Hydrangea macrophylla* Seringe var. *Thunbergii* Makino (7–9). Called "Amacha," the dried leaves are served at "Hanamatsuri" (Flower Festival Time) celebrating the birth of Buddha (6).

Synthesis of di-O-methylphyllodulcinol and di-O-methylhydrangenol was accomplished by cyclization of 3,3′,4′-trimethoxystilbene-2-carboxylic acid (CCVI) and 3,4′-dimethoxystilbene-2-carboxylic acid (CCVII), respectively (7–9). The absolute configuration of phyllodulcinol was established by ozonization and subsequent degradation of the intermediate ozonide to D-malamide (5, 6).



CCIV CCV CCVI CCVII

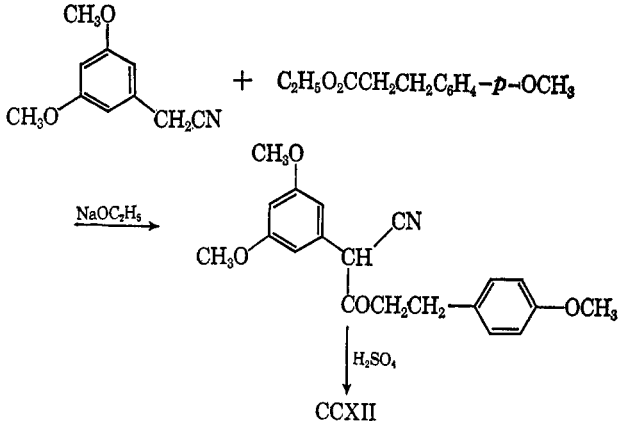
J. AGRIMONOLIDE



CCVIII CCIX CCXI CCX

Agrimonolide, which occurs in the roots of *Agrimona pilosa*, has been identified as 3-[β-(4-methoxyphenyl)-ethyl]-6,8-dihydroxy-3,4-dihydroisocoumarin (CCVIII) (205–207).

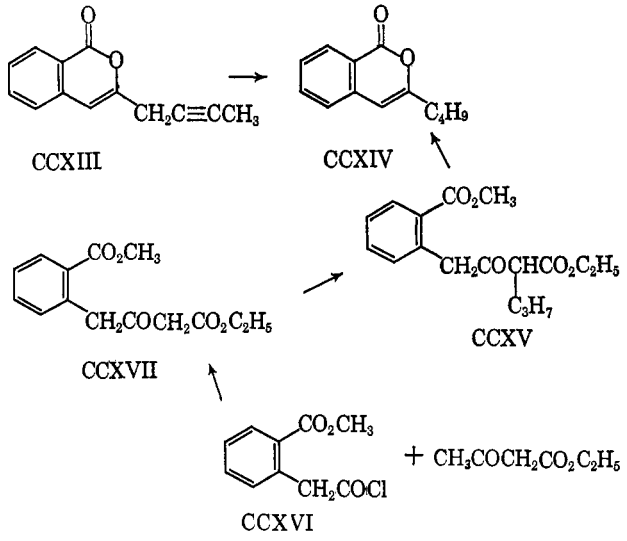
Methylation of agrimonolide with diazomethane, followed by methyl iodide and potassium carbonate, gave di-O-methylagrimonolide (205). As mentioned previously, diazomethane does not methylate the 8-hydroxy group; thus the methyl iodide treatment was necessary. Treatment of CCIX with barium hydroxide and hydrogen gave di-O-methylagrimonol (CCXI), which was oxidized with chromium trioxide–pyridine to di-O-methylagrimonone (CCX). The assignment of the isocoumarin structure to agrimonolide is based on the identity of CCX which made by the route shown below (206, 207). Based on these and several



reactions which confirmed the presence of the lactone ring and the phenolic hydroxyl groups, agrimonolide was assigned structure CCVIII.

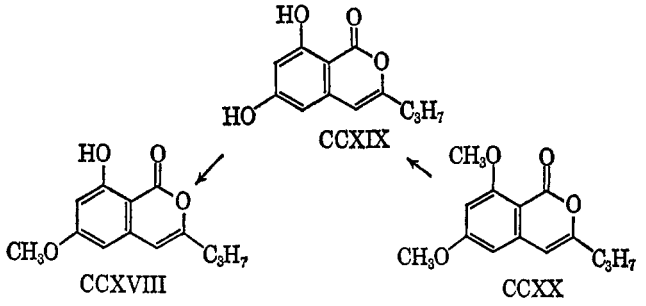
K. CAPILLARIN

One of the acetylenic components of *Artemisia dracunulua*, *Artemisia capillaris*, and *Chrysanthemum frutescens* is capillarin [3-(2-butynyl)isocoumarin] (CCXIII) (43, 44, 79, 80). Catalytic reduction of capillarin with Lindlar catalyst gives tetrahydrocapillarin (CCXIV) in 40% yield. This reduction product (CCXIV) was synthesized from the acid chloride CCXVI by treatment with ethyl acetoacetate which gave CCXVII and was converted to CCXV with propyl iodide in the presence of potassium *t*-butoxide. Alkaline hydrolysis of CCXV at 50° gave decarboxylation, and cyclization of the resulting acid with formic acid gave CCXIV (79).



L. GLOMELLIN

Glomellin (3-propyl-6-methoxy-8-hydroxyisocoumarin) (CCXVIII), is the alkaline decomposition product of glomellifera, obtained from *Parmellia glomellifera*, *Thamnolia vermicularis* var. *taurica*, and other lichens (10, 120, 132, 210). The structure of glomellin was established by synthesis. Quinoline and hydrobromic acid cleaved the two methoxy

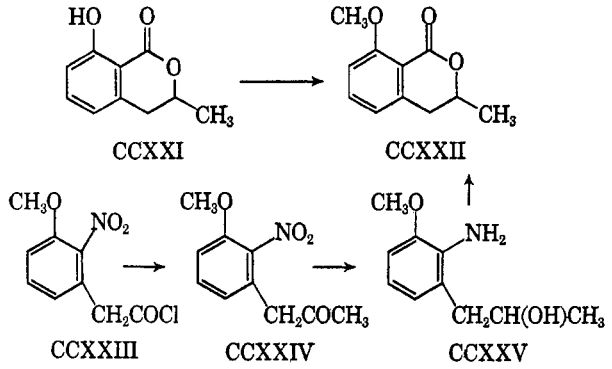


groups of 3-propyl-6,8-dimethoxyisocoumarin (CCXX) (made by known methods), and the product, CCXIX, was methylated with diazomethane only in the 6-position (in accordance with the nonreactivity of the 8-hydroxy group of isocoumarins toward diazomethane) (132).

M. MELLEIN

The mold of *Aspergillus melleus*, when grown in a sucrose- or maltose-containing media, produces mellein [(−)-3-methyl-8-hydroxy-3,4-dihydroisocoumarin] (CCXXI) (41, 42, 137, 138, 199). Ochracin, from *Aspergillus ochraceus* (198), has been shown to be identical with mellein (41, 42, 199).

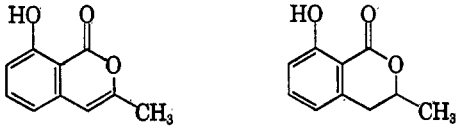
Proof of the structure of mellein has been accomplished by synthesis. The ethoxymagnesiomalonate method was used to convert 2-nitro-3-methoxyphenylacetyl chloride (CCXXIII) to 2-nitro-3-methoxybenzyl methyl ketone (CCXXIV). Reduction, first with sodium borohydride then hydrogen in the presence of nickel, produced α-(2-amino-3-methoxybenzyl)ethyl alcohol (CCXXV). By the Sandmeyer procedure, the amine was converted to the corresponding nitrile which was hydrolyzed and cyclized to 3-methyl-8-methoxy-3,4-dihydroisocoumarin (CCXXII), identical with the methylation product of mellein, except that



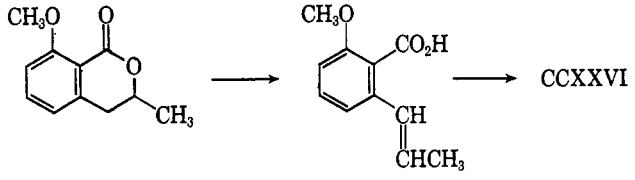
it was the racemic lactone (41, 42).

N. 3-METHYL-8-HYDROXYISOCOUMARIN

Two different strains of *Marasmius ramealis* produce 3-methyl-8-hydroxyisocoumarin (CCXXVI) (20, 21). Identity of this compound arises from reduction to racemic mellein (CCXXVII) using sodium boro-



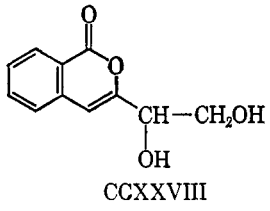
hydride. Secondly, alkali fusion of 3-methyl-8-methoxy-3,4-dihydroisocoumarin (mellein methyl ether) produced 2-(1-propenyl)-6-methoxybenzoic acid, which



was converted to CCXXVI by the halolactonization reaction (20, 21).

O. 3-(α,β-DIHYDROXYETHYL)ISOCOUMARIN

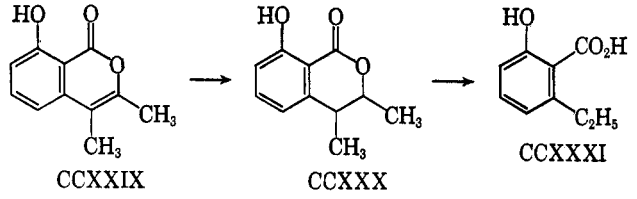
The Saprophytic culture of *Oospora astringenes* is re-



ported to produce 3-(α,β-dihydroxyethyl)isocoumarin (CCXXVIII) (208).

P. 3,4-DIMETHYL-8-HYDROXYISOCOUMARIN

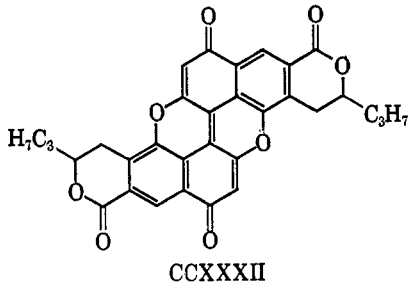
The mycelium and cell filtrate of *Oospora*, a microorganism obtained from air, is reported to produce 3,4-dimethyl-8-hydroxyisocoumarin (oospolactone) (CCXXIX) (202–204). Assignment of the isocoumarin structure is based on catalytic reduction to 3,4-dimethyl-8-hydroxy-3,4-dihydroisocoumarin (CCXXX) and alkali fusion of CCXXX with potassium hydroxide to give 6-ethylsalicylic acid



(CCXXXI). Alkali fusion of 3,4-dimethyl-8-hydroxyisocoumarin also gave CCXXXI. Treatment of the hydrolyzed form of CCXXIX with acetic anhydride and sodium acetate gave 3,4-dimethyl-8-acetoxyisocoumarin, identical with the acetate obtained from treatment of CCXXIX with acetic anhydride. Ozonolysis of 3,4-dimethyl-8-hydroxyisocoumarin gave 3-hydroxyacetophenone-2-carboxylic acid (203).

Q. XYLIDEIN

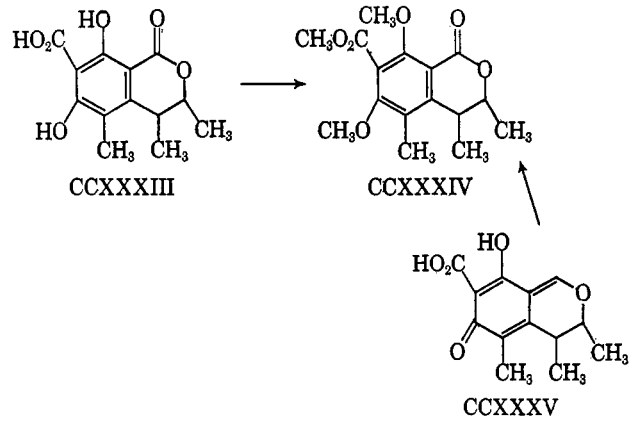
The green pigment obtained from cultures of *Chlorocibaria aeruginosa* grown on a cellulose base in aqueous malt extract is called xylidein. Structure CCXXXII



has been assigned to xylidein based on its physical and chemical properties (40).

R. 3,4,5-TRIMETHYL-6,8-DIHYDROXY-3,4-DIHYDROISOCOUMARIN-7-CARBOXYLIC ACID

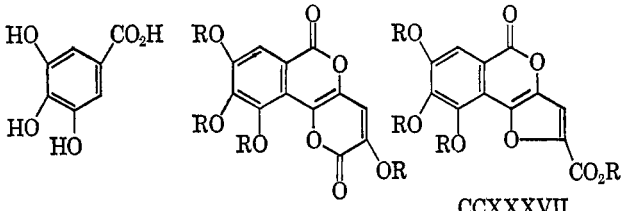
A mutant strain of *Aspergillus terreus* Thom. makes 3,4,5-trimethyl-6,8-dihydroxy-3,4-dihydroisocoumarin-7-carboxylic acid (CCXXXIII). The identity of this



compound arises from its conversion to methyl O-dimethyldihydrocitrinone (CCXXXIV), previously described during investigations directed toward the identity of citrinin (CCXXXV) (49, 81).

S. GALLOFLAVIN AND ISOGALLOFLAVIN

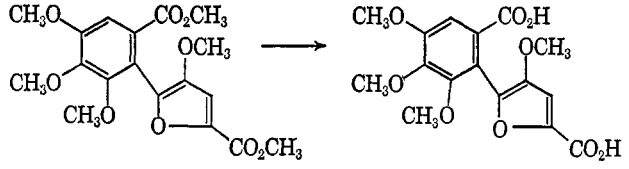
Aeration of alkaline solutions of gallic acid produces the yellow mordant dye, galloflavin (CCXXXVI) (where R = H) (45, 76, 77, 84). Treatment of gallo-



CCXXXVI CCXXXVII

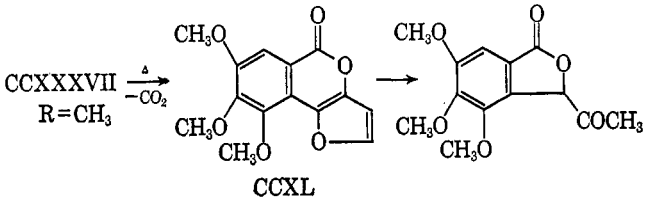
flavin with potassium hydroxide under nitrogen gives a quantitative yield of isogalloflavin (CCXXXVII) (77). Extensive investigations have been carried out in order to determine the structures of galloflavin and isogalloflavin (76, 77, 84, 91–94).

Methylation of galloflavin with diazomethane gives tetramethylgalloflavin (CCXXXVI) (R = CH_3), which can be hydrolyzed under alkali conditions to trimethylisogalloflavin (CCXXXVII) (R = CH_3). Methylation of trimethylisogalloflavin with dimethyl sulfate, followed by diazomethane, gave the hexamethyl derivative CCXXXVIII which was hydrolyzed



CCXXXVIII CCXXXIX

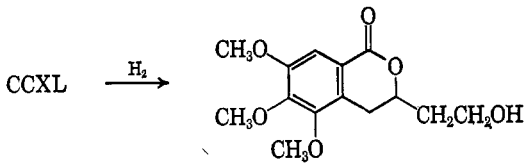
to CCXXXIX. Decarboxylation of trimethylisogalloflavin by heat gave CCXL, and alkaline degradation of CCXL yielded 3-acetyl-4,5,6-trimethoxyphthalide.



CCXL

Additional evidence for the methoxy grouping on the aromatic nucleus was obtained by potassium permanganate oxidation of tetramethylgalloflavin to 3,4,5-trimethoxyphthalic acid (84).

Catalytic reduction of CCXL gave a hexahydro derivative formulated as 3-(β-hydroxyethyl)-5,6,7-trimethoxy-3,4-dihydroisocoumarin (CCXLI), which was conclusively identified by synthesis from 5,6,7-trimethoxyisocoumarin-3-carboxylic acid (this involved

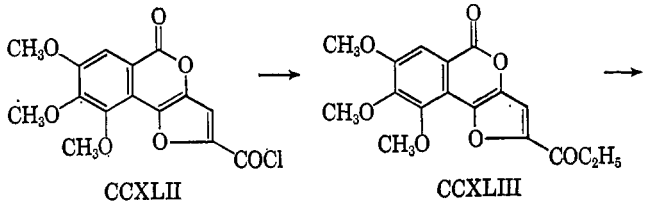


CCXLI

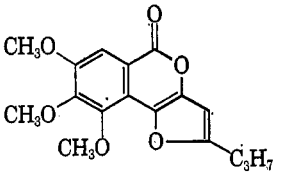
extending the 3-carboxylic acid to the next higher homolog and subsequent reduction).

This work is considered proof of the isocoumarin structure for isogalloflavin, although the location of the carboxylic acid group could not be assigned.

The position of the carboxylic acid group in trimethylisogalloflavin was established by conversion into 5,6,7-trimethoxy-5′-propylfurano(3′,2′:3,4)isocoumarin (CCXLIV). Thus, the acid chloride of isogalloflavin (CCXLII) was treated with diethylcadmium and converted to the ketone CCXLIII, which was reduced in low yield to CCXLIV. Alkaline hydrolysis of CCXLIV gave 3-acetyl-4,5,6-trimethoxyphthalide, 4,5,6-tri-



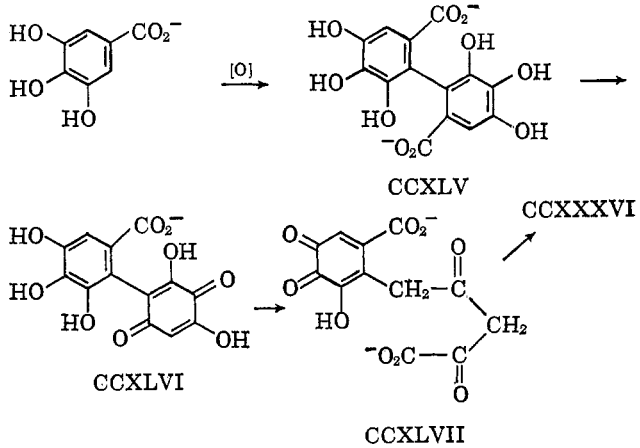
CCXLII CCXLIII



CCXLIV

methoxyphthalide-3-carboxylic acid, 2-pentanone, and butyric acid. Based on the products obtained from hydrolysis of CCXLIV, structure CCXXXVII was assigned to isogalloflavin.

Galloflavin was given structure CCXXXVI on the basis of its likely mode of formation from gallic acid. Aeration of an alkaline gallic acid solution probably



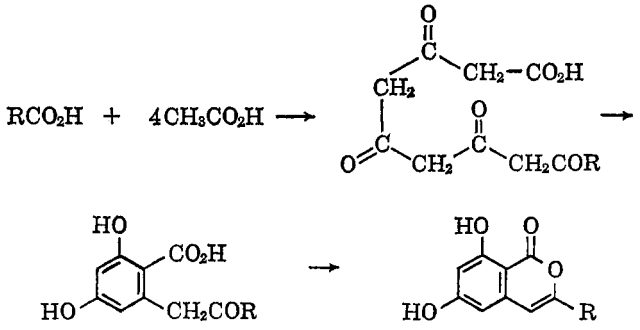
CCXLV CCXLVI CCXLVII CCXXXVI

gives the anion CCXLV which could be further oxidized to CCXLVI, by several routes converted to CCXLVII, and formation of galloflavin could easily occur (76, 77).

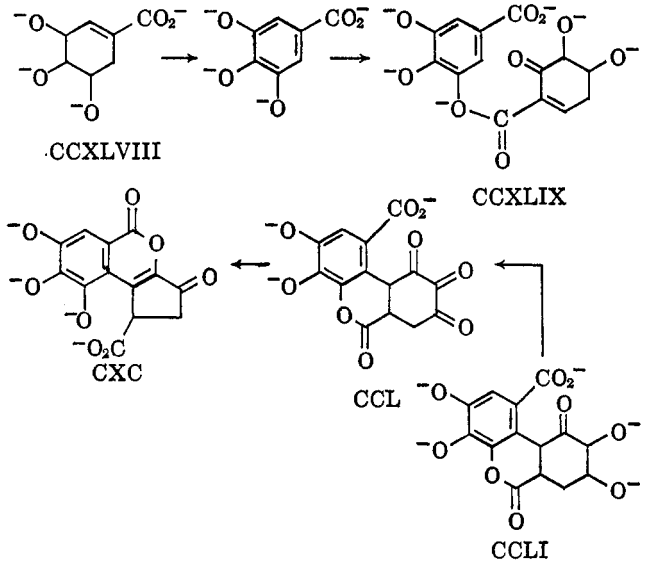
V. BIOGENESIS OF ISOCOUMARINS

Biogenesis of aromatic compounds is currently considered to follow two main routes (183), that of head-to-tail linkage of acetate units (38, 39), and the build-up of carbohydrate units (64, 194–196). No one route is believed to lead to all aromatic compounds so both must be considered.

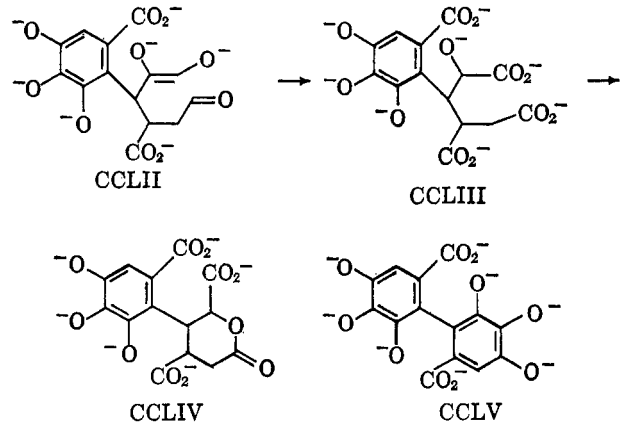
Isocoumarins can derive from the acetate route as outlined below. This sequence has been used to predict the correct structure of mellein (section IVM) before the exact structure was known (39).

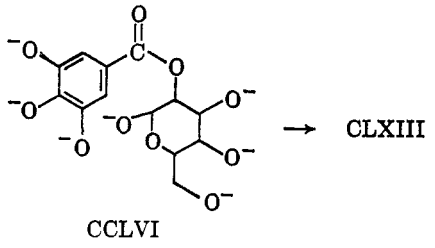


The carbohydrate route for the biosynthesis of some isocoumarins is considered to take place by way of the oxidation of dehydroshikimate (CCXLVIII) to gallate, followed by combination of CCXLVIII and gallate to give the complex CCXLIX. Ultimately, *via* CCLI, benzillic acid rearrangement of CCL gives one of two possible α-oxy-β-keto acids, which can be oxidized and decarboxylated to CXC. Structure CXC is brevifolincarboxylic acid (see section IVG); thus the structure can be predicted using this approach.

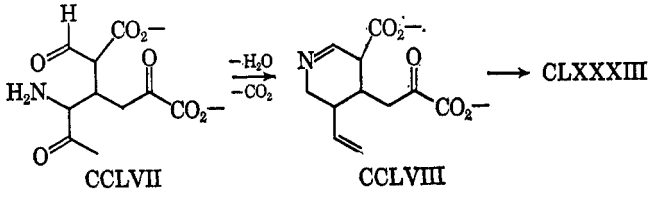


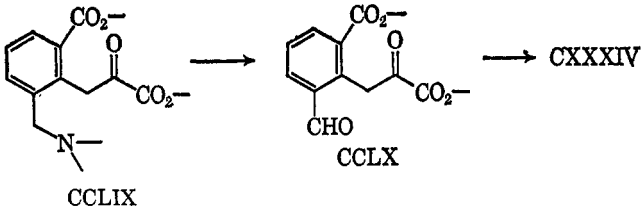
Alternately, CCLI could go to CCLII, followed by oxidation to CCLIII and CCLIV. The chebulinate unit CCLIV and the hexaoxydiphenate unit CCLV (which could also arise from CCLI) could combine to give chebulagic acid (CCI). The origin of bergenin (CLXIII) (see section IVA) has been considered using the same ideas, in which case, two 2-gallylglucopyranose units (CCLVI) combine (194).



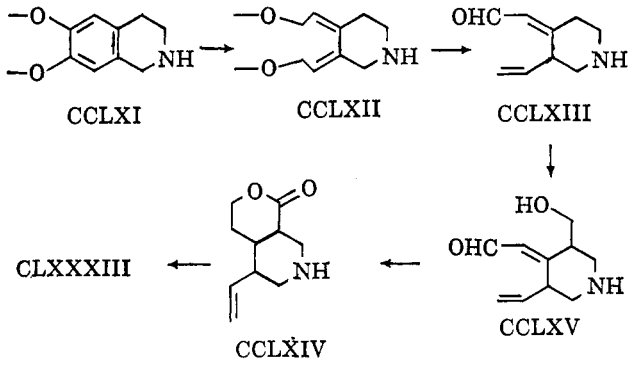


The biosynthesis of gentianine (section IVD) and erythrocentaurin (section IVC) also has been considered using the carbohydrate approach. Thus, loss of water and carbon dioxide from CCLVII to give the intermediate CCLVIII, followed by an oxidation–reduction sequence with loss of carbon dioxide could yield gentianine (CLXXXIII). Further, cyclization of CCLIX to CCLX, followed by oxidation, yields erythrocentaurin (CXXXIV). Indeed, the structure for erythrocentaurin was predicted before confirmation was obtained by chemical means (196).



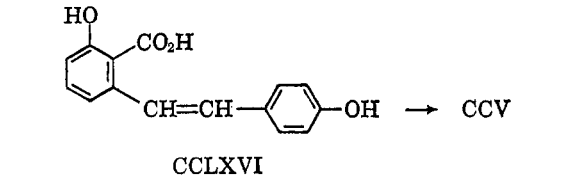


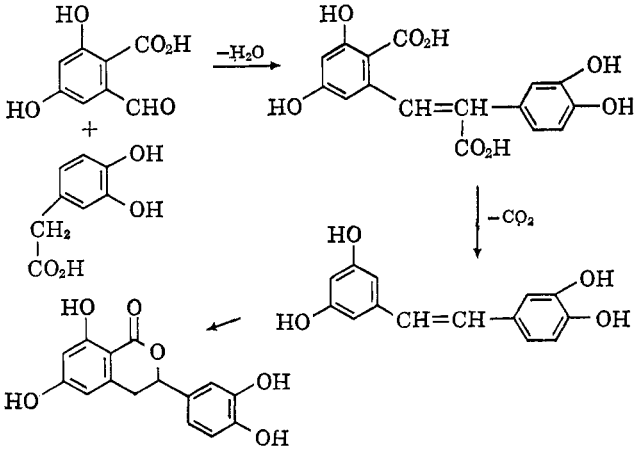
An alternate biogenetic route to gentianine (73) involves the intermediate, 1,2,3,4-tetrahydro-6,7-dihydroxyisoquinoline (CCLXI), and conversion to CCLXII, which could undergo an oxidation–reduction sequence with loss of water to give CCLXIII. Addition of formaldehyde or a similar unit could give CCLXV, and conversion of CCLXV to CCLXIV followed by



oxidation–reduction steps gives gentianine.

Naturally occurring stilbenes such as 3,4′-dihydroxystilbene-2-carboxylic acid (CCLXVI) and 3,3′-dihydroxy-4′-methoxystilbene-2-carboxylic acid (CCLXVII) may be the precursors of 3-aryl isocoumarins such as hydrangenol (CCV) and phyllodulcinol (CCIV) (see section IV-I). Stilbenes could arise from the condensation of a phenylacetic acid molecule such as 3,4-dihydroxyphenylacetic acid and an aromatic aldehyde such as 4,6-dihydroxyphthaldehydic

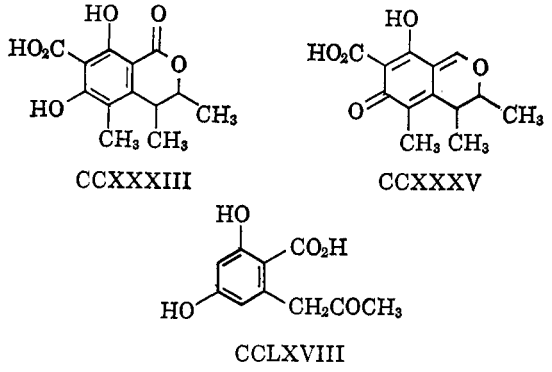




acid, followed by decarboxylation and cyclization to isocoumarin (167). However, in view of the more recent developments in biogenetic sequences, this probably is not the case. Indeed, the carbohydrate or acetate routes could be used to explain the occurrence of isocoumarins such as hydrangenol and phyllodulcinol.

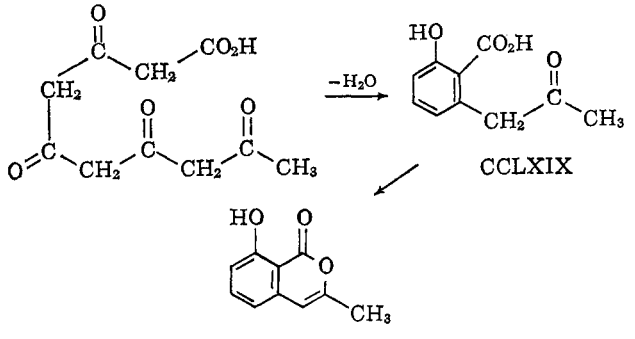
Studies of the biosynthesis of hydrangenol by *Hydrangea macrophylla* were carried out using glucose-C^{14} and acetate-C^{14}. Labeled hydrangenol was found and, based on the level of radioactivity in hydrangenol using glucose-C^{14} and acetate-C^{14}, hydrangenol was made more rapidly by way of glucose than acetate (36, 37). This result adds credence to the carbohydrate sequence for isocoumarin biogenesis. Administration of L-phenylalanine-U-1-C^{14} and -3-C^{14}, cinnamate-2-C^{14}, and acetate-2-C^{14} to root tissues of *Hydrangea macrophylla* indicated hydrangenol is synthesized by condensation of an intact phenylpropionate molecule with three acetate units (102).

A mutant strain of *Aspergillus terreus* produces 3,4,5-trimethyl-6,8-dihydroxy-3,4-dihydroisocoumarin-7-carboxylic acid (CCXXXIII). *Aspergillus terreus* regularly produces citrinin which could derive from



CCLXVIII, a known metabolite of *Penicillium brevicompactum*. Since the mutant strain did not produce citrinin, its formation may require reduction of the acid CCLXVIII, which occurs at a later stage in the biosynthesis of citrinin (CCXXXV) (81).

Formation of oospolactone (202) can be considered as a head-to-tail condensation of acetate units. Thus, acetylorsellinic acid (CCLXIX) could cyclize to 3-methyl-8-hydroxyisocoumarin which, upon methyla-



tion, could give 3-methyl-8-methoxyisocoumarin and by reduction mellein (3-methyl-8-hydroxy-3,4-dihydroisocoumarin) (section IVM) (20, 21).

A preliminary communication describing the green pigment CCXXXII from *Chlorociboria aeruginosa* suggests the compound arises from a condensation of two naphthalene units (40).

VI. Biological Activity of Isocoumarins

Very few reports have been published describing the biological activity of isocoumarins. The only important activity reported to date is the purgative property of 3-(4-hydroxyphenyl)isocoumarin.

Isocoumarincarboxylic acid derivatives have been tested for hypothermal activity and reportedly show a weak effect (117). A series of isocoumarin-3-carboxylic acid and isocoumarin-4-carboxylic acid derivatives (amides and esters) showed no hypnotic action. However, β-diethylaminoethyl 3,4-dihydroisocoumarin-4-carboxylate, β-dimethylaminoethyl 3,4-dihydroisocoumarin-4-carboxylate, and β-dimethylaminoethyl isocoumarin-3-carboxylate showed a paralytic effect (104, 105).

A comparison of the purgative properties of 3-(4-hydroxyphenyl)isocoumarin, the corresponding acid (2-carboxybenzyl 4-hydroxyphenyl ketone), and 3-phenylisocoumarin showed that 3-(4-hydroxyphenyl)isocoumarin was a strong purgative, whereas the other compounds were inactive (50, 155).

Isocoumarin-3-N,N-diethylcarboxyamide caused an increase in oxygen uptake of rat brain tissue in low concentrations, but above 2×10^{-4} *M* concentration suppression occurred and became stronger with increasing time (116).

Oospolactone (3,4-dimethyl-8-hydroxyisocoumarin, section IVP) is not as effective as 3-(α,β-dihydroxyethyl)isocoumarin against tracheal or respiratory contractions (208).

Two aminoalkyl esters of isocoumarin-3-carboxylic acid, namely the β-diethylaminoethyl and γ-diethylaminopropyl esters, showed no local anesthetic effect on rabbit eyes (169).

The coronary-dilating action and antispasmotic activity of 3-(4-hydroxyphenyl)-, 3-(2,5-dihydroxyphenyl)-, and 3-(2-methyl-5-hydroxyphenyl)isocoumarin, tested in the isolated fibrillating rabbit heart was negligible (66).

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