THE SYNTHESIS OF COMPOUNDS RELATED TO KHELLIN

By

Raymond Merritt Burgison

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1950

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
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INTRODUCTION

Among the peoples of the Near East a decoction of the dried fruit of the umbelliferous plant Ammi visnaga (Arabic, khella) has long been used as a diuretic, for dislodging impacted ureteral stones and for a number of common ailments. The drug has been prescribed for centuries and even today is official in the Egyptian Pharmacopoeia. Ammi visnaga is a weed that grows widely throughout the Near East, being especially abundant in the fertile regions of the Valley of the Nile.

The first attempt to isolate active principles from the fruit of Ammi visnaga was made by Mustapha (1) in 1879. He obtained white silky needles, bitter in taste and sparingly soluble in water, by extraction of the dried fruit with alcohol and ether. To this principle, Mustapha gave the name khellin. In 1881, Malosse (2) described three crystalline principles which he named α-visnagine, β-visnagine and γ-visnagine. Malosse stated that Mustapha's khellin was not identical with α-visnagine, but appeared to be formed during the process of extraction. No further reports on isolation and identification of principles of Ammi visnaga appear in the literature until 1930[1] when Fantl and Salem (3) reported the isolation from the fruits of Ammi visnaga of a compound

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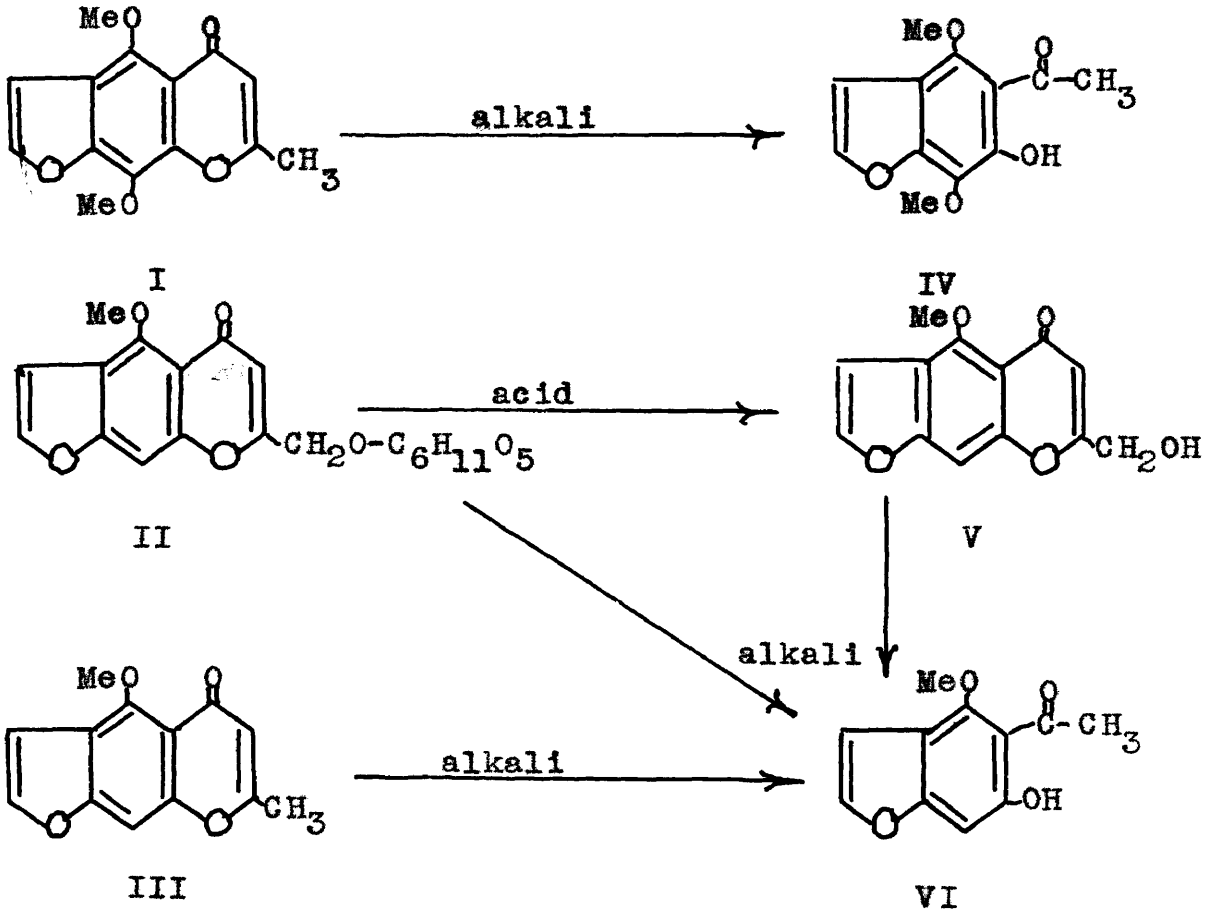
[1] An Egyptian dissertation by Best, Malek and Hassan dealing with the isolation of a bitter principle, m.p. 153°, from khella seeds appeared some years ago. Späth and Gruber (4) were unable to locate this dissertation, however, and inquiries addressed to the authors remained unanswered.

khellin, $C_{14}H_{12}O_5$, m.p. 153°, from which was obtained $C_{12}H_{12}O_5$, m.p. 100°, by cleavage with barium hydroxide. They found two methoxyl groups in both compounds and assigned a coumarin structure to the parent compound. Samaan (5) later reported the isolation of another substance which he called visammin, $C_{11}H_{10}O_4$, m.p. 153°, from the same drug. Since he did not publish his analytical data and the values calculated for $C_{11}H_{10}O_4$ agree quite closely with those for khellin, it is probable that the two substances are identical. Fahmy and El Keiy (6) and Samaan (7) have carried out further chemical studies on the same drug. Since the crystalline substances obtained by these workers were, in some instances, not subjected to a satisfactory chemical analysis, the proof of their purity rested mainly on a rough examination of their physical properties. The failure of most of these authors to give sufficient consideration to the results obtained by earlier workers led to a considerable confusion of nomenclature, and quite often different names were assigned to what appeared to be the same substance. A similar confusion exists also in the pharmacological literature concerning Ammi visnaga, different properties being sometimes attributed to the same crystalline substance (4).

The work of Späth and Gruber (4) finally placed the problem on a sound chemical basis. These authors obtained from the fruit of the plant, three well-defined crystalline substances which they designated Khellin (I), Khellol glycoside(II),

and Visnagin(III). In addition, Professor Gruber, in a personal communication to G. V. Anrep (8), said that he had detected the presence of a small quantity of another substance, a coumarin, the analysis of which had not at that time been completed. According to Späth and Gruber, the following structures represent the three principles mentioned above as well as their chemical inter-relationships:



It can be seen from these structures that the simplest compound is visnagin, that khellin is a methoxy-visnagin, and that khellol, which occurs as a glycoside, is the carbinol corresponding to visnagin.

According to conventional nomenclature, these compounds are designated as follows:

Khellin: 5,8-dimethoxy-6,7,4',5'-furanochromone[1]

Visnagin: 5-methoxy-2-methyl-6,7,4',5'-furanochromone

Khellol glycoside: 5-methoxy-2-(1'-glucosidomethyl)-6,7,4',5'-furanochromone

Khellol: 5-methoxy-2-(hydroxymethyl)-6,7,4',5'-furanochromone

Khellinone: 6-hydroxy-4,7-dimethoxy-5-acetylcoumarone

Visnaginone: 6-hydroxy-4-methoxy-5-acetylcoumarone

Khellin (I) and visnagin (III) readily undergo hydrolysis in the presence of dilute alkali (1%) to give the corresponding coumarone derivatives (IV and VI), whereas the glycoside (II) undergoes alkaline hydrolysis to yield visnaginone (VI) and Fischer's d-glucosidoglycollic acid ($C_6H_{11}O_5$-O-CH_2COOH). Acid hydrolysis of the glycoside gives glucose and khellol (V). Khellol (V) also yields visnaginone(VI) on alkaline hydrolysis.

PHARMACOLOGY AND CLINICAL STUDIES

Interest in the crystalline components isolated from Ammi visnaga was stimulated when it was demonstrated by Anrep and coworkers (9,10) that khellin and visnagin possess coronary vasodilating properties, increasing the blood flow through the heart without raising the blood pressure or increasing the pulse rate. On the basis of these physiological properties of khellin, Anrep and collaborators (11,12) conducted

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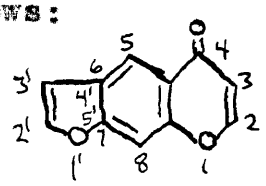
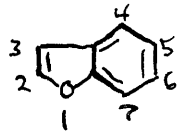
[1] Furanochromones (A) and coumarones (B) are numbered as follows:



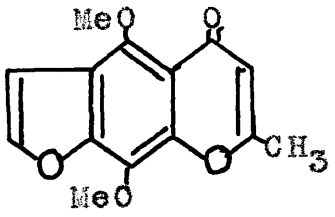


an extensive clinical study of khellin in the treatment of angina pectoris, and the drug was found to be extremely helpful to the majority of patients suffering from this ailment. Of the three crystalline principles isolated from khella, khellin was found to be the most active physiologically, visnagin possessed slight activity, and khellol glycoside was found to be inactive (8). Greiner, Gold, and collaborators, in a recent clinical study based on a method developed for testing "cardiac pain of angina of effort", could not substantiate Anrep's findings and were unable to detect any difference in the effect of khellin and a lactose placebo on the severity of the anginal syndrome (13). At a recent meeting of the American College of Physicians, on the other hand, Osher and Katz (14) reported using khellin in the treatment of 28 "bad cases" of angina pectoris, and all but three were much relieved, with the frequency of attacks reduced and a noted improvement in muscular activity. The amount of glyceryl trinitrate needed by some patients was also reduced by khellin. Khellin has also been reported to have value in the treatment of bronchial asthma (15,8) and whooping cough (16) and its powerful bronchodilating activity was found to be of longer duration than that of epinepherine or ephedrine (8).

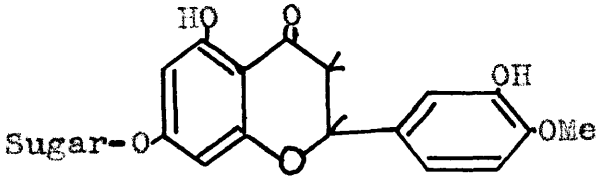
The extensive pharmacological study of khellin and related compounds which has been conducted by Samaan and coworkers and by Anrep and coworkers has recently been reviewed (8,17). The controversial pharmacological findings previously reported

prompted Pellows and coworkers (18,19) to reinvestigate the effect of khellin and related compounds on coronary flow, as well as their smooth muscle spasmolytic activity and histaminolytic activity.

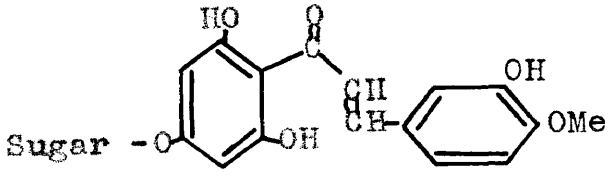
An interesting relationship is found in the structures of khellin (I) and other compounds known to have an effect on the circulatory system; e.g., hesperidin (VII), hesperidin chalcone (VIII), and rutin (IX).



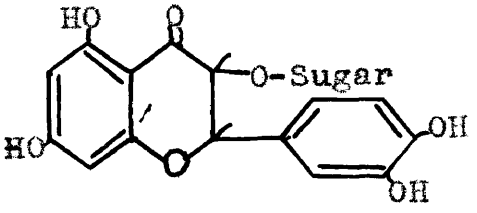
I



VII



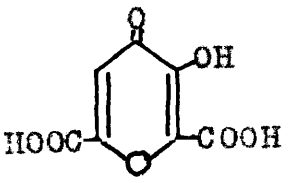
VIII



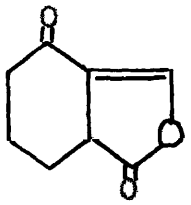
IX

Each of these molecules is a γ-pyrone (I,VII,IX) or a corresponding chalcone (VIII), which results from mild alkaline hydrolysis (ring opening) of the γ-pyrone. In a series of compounds studied by Giarman (20), those possessing the γ-pyrone structure, e.g., meconic acid (X) and clavicin (XI), displayed a surprisingly high order of cardiotonic activity

in comparison with that of other members of the series, when tested on the isolated frog heart rendered hypodynamic with Ringer's solution low in calcium ion.



X



XI

Hughes and Parkes (21), prepared a number of hydroxy and methoxy substituted chalcones and found several of these compounds to be quite active in reducing capillary fragility. The sodium salts of phosphorylated chalcones having phenolic or alkoxyl groups have also been found to increase capillary resistance (22). The physiological activity of compounds of the types mentioned above, has recently been reviewed by Steinegger (23).

DETERMINATION OF STRUCTURE OF KHELLIN

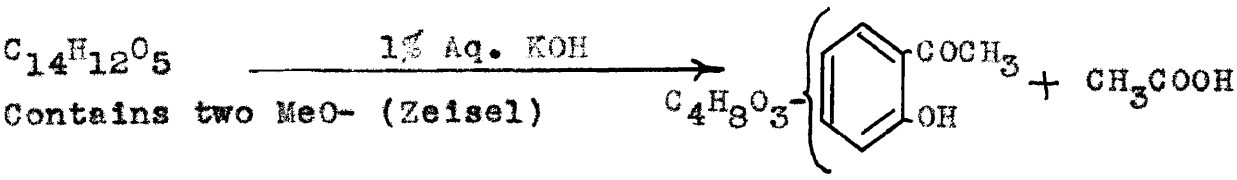
The structure of khellin was established largely through the work of Späth and Gruber (4) by reactions that are summarized in Charts I and II.

SYNTHESIS OF KHELLIN

Although Späth and Gruber (4) have resynthesized khellin from its hydrolysis product, khellinon, their synthesis was not entirely unambiguous, since they employed the classical

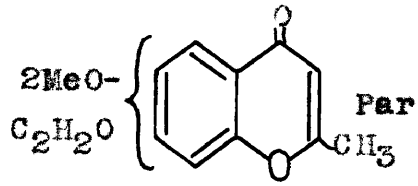
CHART I

DETERMINATION OF THE STRUCTURE OF KHELLIN (4)



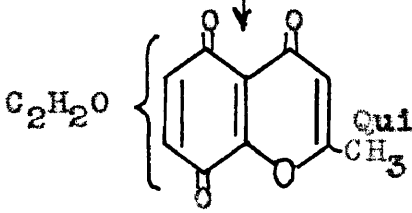
Khellinone

-OH to -C- :Green color with $FeCl_3$ in EtOH
phenolic -OH :Soluble in NaOH, ppt'd. by CO_2
carbonyl :Forms semicarbazone
CH_3CO- :Positive iodoform
Ease of ring opening probably indicates chromone

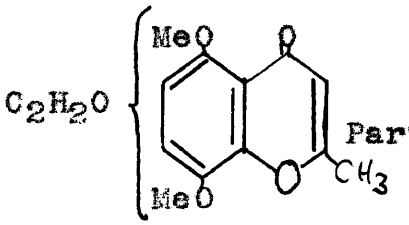


Partial formula based upon above evidence.

HNO_3 in ether

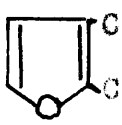


Quinone : Two MeO- para to each other.



Partial formula based upon above evidence.

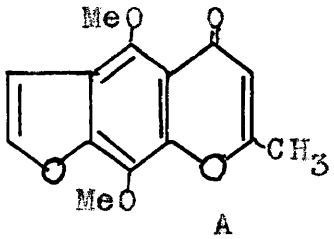
H_2O_2 in alkaline solution



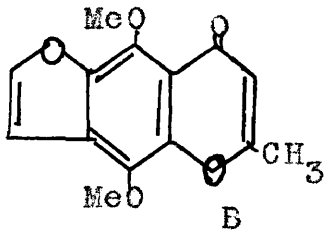
Furane-2,3-dicarboxylic acid : Furane der.

On the basis of the above analytical data, two possible structures were postulated:

CHART II

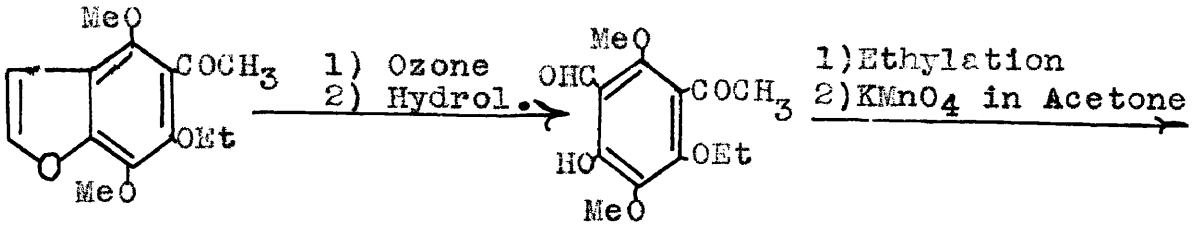


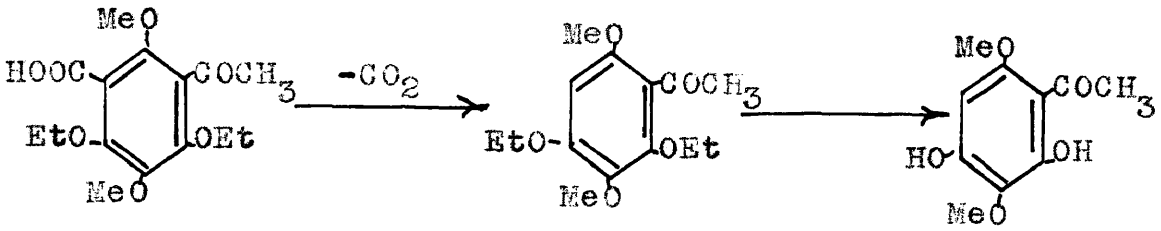
A



B

In order to decide which of the above two structures represents khellin, the following reactions were carried out.





XIII XII

The 3,6-dimethoxy-2,4-diethoxyacetophenone (XIII) produced by the above reactions, was identical with a sample prepared by ethylation of Wesseley and Moser's 2,4-dihydroxy-3,6-dimethoxyacetophenone (XII) (23). Khellin, therefore, is represented by structure A.

The chromone-nature of khellin was further confirmed by partial synthesis from khellinone (4, 24).

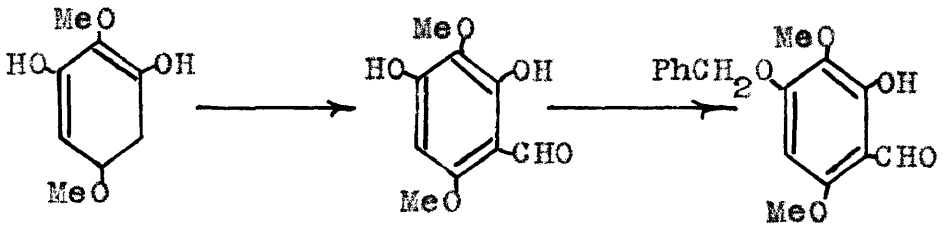
Kostanecki reaction to complete the chromone ring. It is known, however, that the Kostanecki reaction (to be discussed later) does not invariably lead to chromone formation, for many workers have observed that quite often coumarins or mixtures of coumarins and chromones, which are difficult to distinguish, are obtained. The demonstration that Späth and Gruber's product was actually the chromone was accomplished by Geissman (24) who repeated the work of these investigators and was able to synthesize khellin from khellinon by methods which are known to lead unambiguously to the formation of chromones.

The first total synthesis of khellin was described by Clarke and Robertson (25). Other syntheses have since been reported by Baxter, Ramage, and Timson (26), and by Murti and Seshadri (27).

As starting material Clarke and Robertson (25) employed 2,5-dimethoxyresorcinol (XIV) which was obtained from pyrogallol tribenzyl ether by oxidation with nitric acid, reduction of the quinone, methylation of the hydroquinone, and catalytic debenzylation (28). This was then converted into 2,4-dihydroxy-3,6-dimethoxybenzaldehyde (XV) in an almost quantitative yield by application of the Gatterman reaction[1]. The orientation of this aldehyde was proved by

[1] In the Gatterman reaction, the formyl group usually goes ortho to the phenolic hydroxyl (or alkoxyl); or, if the ortho position is blocked, para substitution occurs. In alkylation or benzylation the hydroxyl group adjacent to a carbonyl resists alkylation or benzylation, even with diazo alkanes; or, if reaction does take place, it proceeds only with difficulty and in the presence of a large excess of alkylating or benzylating reagent.

formation of a color with alcoholic ferric chloride and ultimate conversion to a coumarone (29) . The aldehyde was mono-benzylated and the resulting compound (XVI) treated with ethyl bromoacetate in the presence of anhydrous potassium carbonate in dry acetone to form the substituted phenoxyacetic ester (XVII). Cyclization of the product with alcoholic sodium ethoxide produced the coumarone-2-carboxylate (XVIII) which was debenzylated by means of hydrogen and a palladium-charcoal catalyst, yielding ethyl 6-hydroxy-4,7-dimethoxycoumarone-2-carboxylate (XIX).



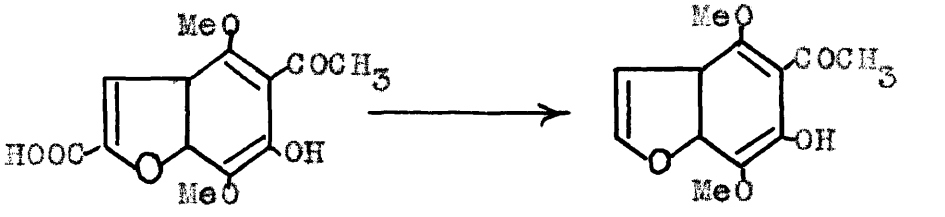
XIV XV XVI

XVII XVIII

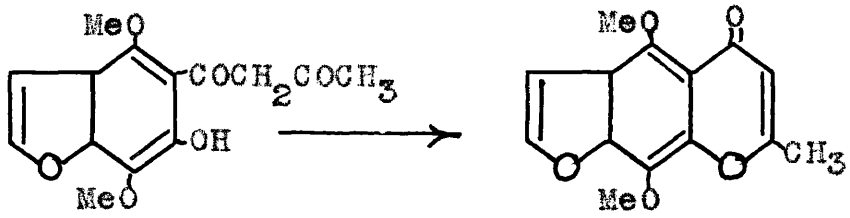
XIX XX

The presence of the carbethoxy group in the 2 position of (XIX) served to inhibit the saturation of the reactive double bond of the furane ring during hydrogenolysis, while in (XX) this group served to protect the same position during the subsequent Friedel-Crafts reaction.

The condensation of (XIX) with acetyl chloride in the presence of aluminum chloride in nitrobenzene and subsequent isolation of the product with the aid of aqueous sodium hydroxide furnished mainly the ketonic acid (XX), although this was invariably accompanied by a small amount of the expected acetate. Decarboxylation of the ketonic acid by heating with copper-bronze powder in quinoline gave rise to khellinon (IV), identical with a specimen obtained from khellin. The Claisen condensation of khellinon with ethyl acetate and sodium resulted in the formation of the diketone (XXI) which, on cyclization in alcohol with hydrochloric acid, yielded khellin (I), identical with the natural material.



XX IV

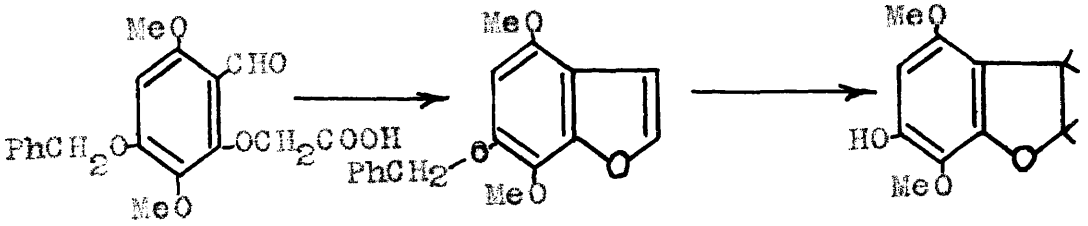


XXI I

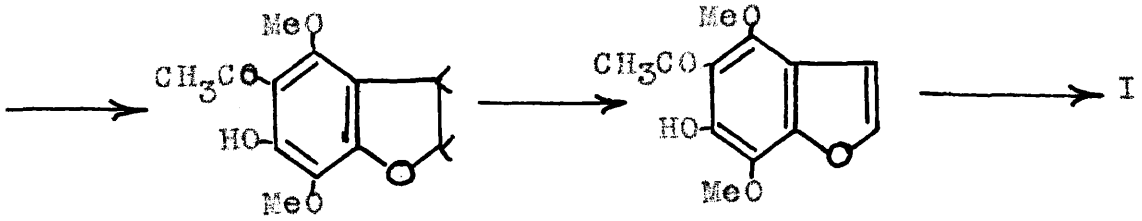
The synthesis developed by Baxter, Ramage and Timson (26) follows essentially the route used by Clarke and Robertson up to the formation of the coumarone carboxylate (XVII). They found that better yields were obtained if methyl bromoacetate were substituted for the ethyl ester in preparation of (XVII), and that the use of magnesium methoxide for the cyclization to the coumarone-2-carboxylate (XVIII) doubled the yield. They were unable to prepare the acetyl derivative (XX), obtained by Clarke and Robertson, however, since all attempts to carry out the acylation under Hoesch or Friedel-Crafts conditions failed and attempts to bring about the rearrangement of the O-acetate to (XX) under conditions of the Fries reaction were also unsuccessful.

Attention was then directed to the coumaran series for the introduction of the acetyl group. Cyclization and simultaneous decarboxylation of 5-benzyloxy-3,6-dimethoxy-2-formyl-phenoxyacetic acid obtained from (XVII) by hydrolysis with acetic anhydride and sodium acetate gave 6-benzyloxy-4,7-dimethoxycoumarone(XXIII), which on catalytic reduction at 3 atmospheres pressure absorbed 2 moles of hydrogen to give 6-hydroxy-4,7-dimethoxycoumaran (XXIV). This coumaran reacted smoothly with acetonitrile and zinc cyanide under Hoesch conditions, but the intermediate imine hydrochloride required refluxing with 2 N sulfuric acid to form 6-hydroxy-4,7-dimethoxy-5-acetylcoumaran (XXV). Dehydrogenation of this coumaran to khellinon (IV)was affected by subliming

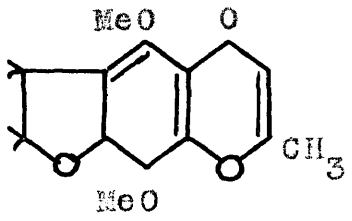
it under reduced pressure through a heated tube containing 30% palladium-norite, prepared as described by Linstead and Thomas (30). The γ-pyrone ring was then completed in the same way as in Clarke and Robertson's synthesis (25).



XXII XXIII XXIV



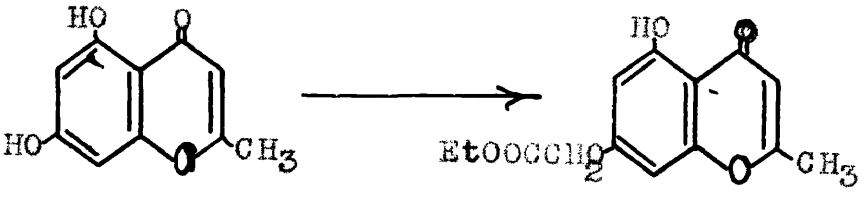
Dihydrokhellin, or 5,8-dimethoxy-2-methyl-2',3'-dihydro-(6,7,4',5')-furanochromone (XXVI), was obtained when 6-hydroxy-4,7-dimethyl-5-acetylcoumaran (XXV) was condensed with ethyl acetate and the resulting diketone cyclized.



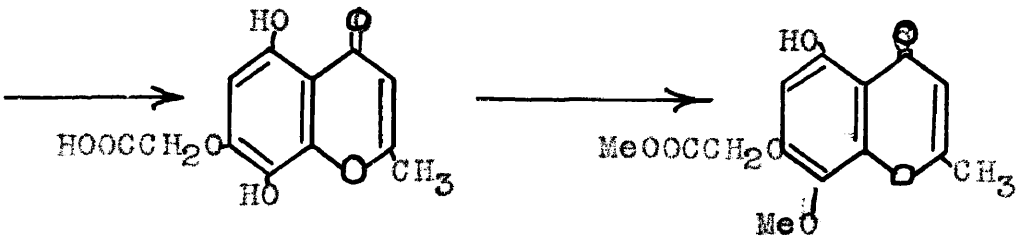
XXVI

In a third method for synthesis of khellin devised by

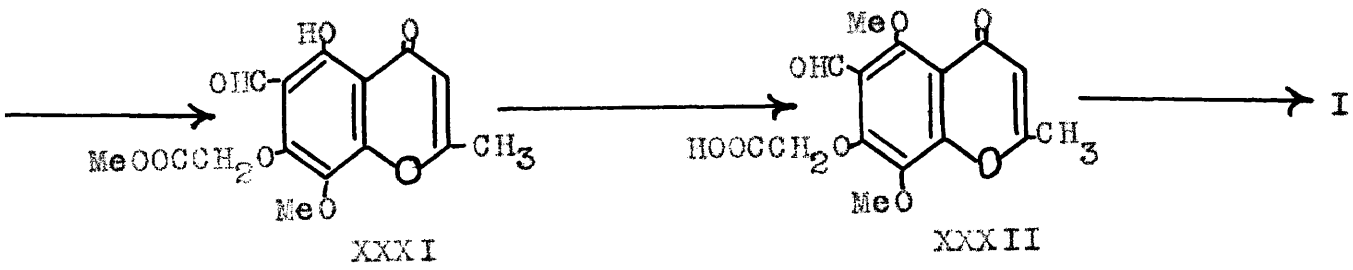
Murti and Seshadri (27), a novel and apparently very practical procedure was employed. It was based on their previous studies on the oxidation of flavones and related compounds (31), and proceeded as follows: 5,7-dihydroxy-2-methylchromone (XXVII), readily prepared from phloroglucinol, was condensed with one mole equivalent of ethyl bromoacetate in the presence of potassium carbonate in acetone, to form compound (XXVIII). As has been found in reactions of flavones (31), hydroxylation in the 8-position of (XXVIII) took place on treatment with alkaline potassium persulfate, producing (XXIX). Partial methylation converted (XXIX) to (XXX), which was then converted to the aldehyde (XXXI) by use of hexamethylene tetramine in glacial acetic acid. The aldehydo acid (XXXII) was subsequently formed by methylation and hydrolysis. Treatment of the aldehydo acid with sodium acetate in acetic anhydride resulted in ring closure and decarboxylation with formation of khellin (I).



XXVII XXVIII



XXIX XXX



OBJECT OF INVESTIGATION

The controversial clinical and pharmacological findings reported in the investigation of khellin and related compounds, and the known effects of γ-pyrones and chalcones on the circulatory system, justified further study of γ-pyrones and chalcones which can be prepared from khellin or closely related compounds and which might serve as intermediates in the preparation of other compounds related to khellin. The synthesis of a compound or compounds of greater potency than khellin, but devoid of the element of uncertainty of physiological response, was greatly desired.

Starting with khellin[1] (I) or khellinone (IV), three series of compounds were prepared:

1- A series of chalcones (XXXIII) derived from khellinone by condensation with various aromatic and heterocyclic aldehydes. Hesperidin chalcone is the prototype of this series.

The chalcones prepared from khellinone readily undergo ring closure as demonstrated by Clarke and Robertson (25), to form 2-substituted 5,8-dimethoxy-6,7,4',5'-furanochromones closely related to khellin. As was previously

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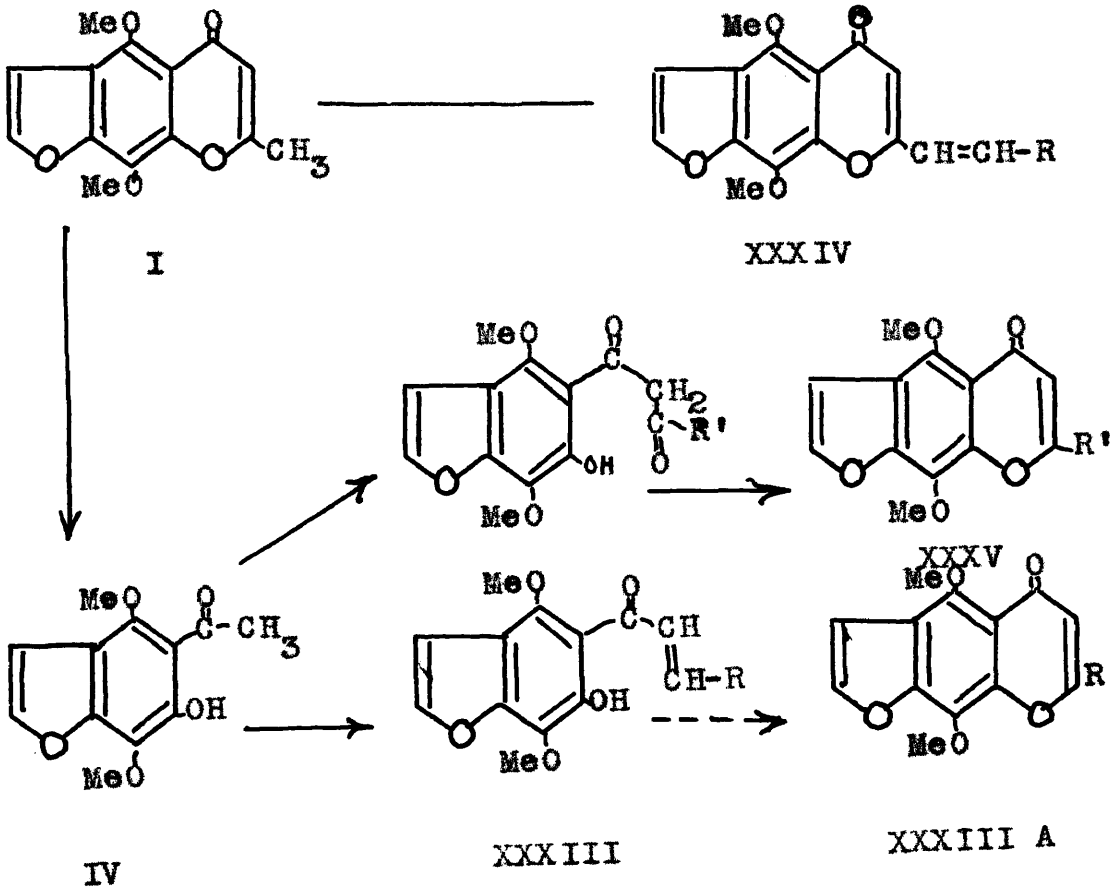
[1] Khellin is readily available commercially. See EXPERIMENTAL.

pointed out, khellin is 2-methyl-5,8-dimethoxy-6,7,4',5'-furanochromone.

2- A series of styryl derivatives (XXXIV) formed by condensation of various aromatic and heterocyclic aldehydes with the reactive 2-methyl group of khellin. In this series, the γ-pyrone ring remains intact and the compounds may be regarded as vinylogs of khellin.

3- The synthesis of a homologous series (XXXV) in which the group in the 2-position of khellin varies from hydrogen to propyl. Attempts to prepare homologs higher than propyl were unsuccessful.

The relationship between the various types of compounds prepared and khellin and the route of their formation is outlined in the following series of equations:



In the above equations:

R = aryl, aralkyl or substituted derivatives thereof.

R' = hydrogen or alkyl.

The cyclization of the chalcones, indicated by the dashed arrow in the above equation, has not been accomplished in the present investigation, but should proceed smoothly under conditions usually employed to form flavones (25).

In addition to the above series, a number of compounds having some structural feature in common with the khellin molecule were prepared for pharmacological testing. These compounds will be discussed individually.

SYNTHESIS OF HOMOLOGS OF KHELLIN

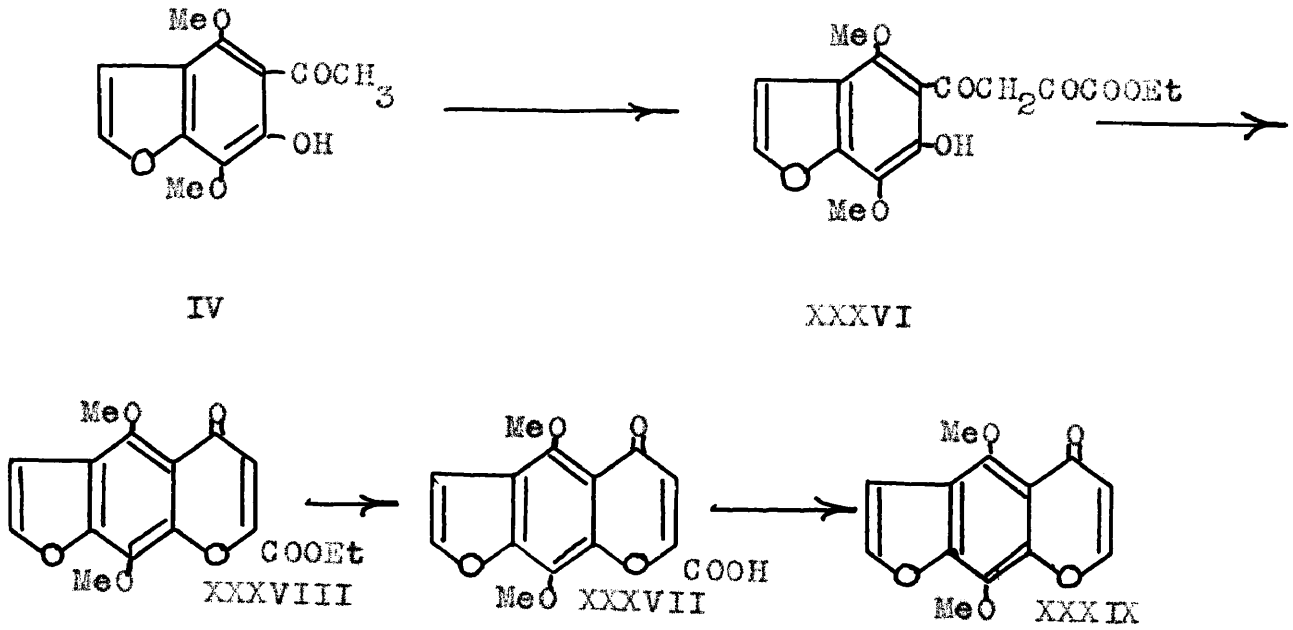
A review of the literature reveals that chromones having 2-alkyl substituents higher than propyl have apparently never been reported. Phenyl (flavone) (32), benzyl (33), furyl (34), and styryl (35) derivatives have all been synthesized, but a careful search of Chemical Abstracts and Beilstein failed to reveal the reason for the limitation of the length of the 2-alkyl side chain. In chromones substituted in the 3-position, a great variety of alkyl side chains have been present, since these compounds are readily prepared from substituted acetoacetic esters and phenols (36). For example, homologs as high as palmityl and stearyl have been prepared by Dasai and Waravdekar (37).

In the work herein reported, it was originally planned to build up the homologous series of alkyl groups in the 2-

position of khellin, beginning with norkhellin and proceeding higher homologs of khellin. In this series, the compounds up to propyl have been prepared, but attempts to prepare longer chain members resulted only in the formation of tars from which nothing could be isolated.

Synthesis of Norkhellin.- Several methods are available for the synthesis of chromones unsubstituted in the 2-position (38), but with khellinone only two procedures seem practical; the ethyl oxalate method of Auwers (39), and the ethyl formate condensation employed by Mentzer and Meunier (40). Auwers condensed diethyl oxalate with ortho-hydroxyacetophenone derivatives in the presence of sodium to obtain the α-keto ester (XXXV), which readily underwent ring closure and hydrolysis on boiling with concentrated hydrochloric acid. The resulting chromone-2-carboxylate (XXXVII) underwent decarboxylation when heated to yield the parent chromone (XXXIX). Schönberg and Sina (41) have applied these reactions to khellinone in the synthesis of ethyl norkhellin-2-carboxylate (XXXVIII), but they modified the Auwers procedure by carrying out the initial condensation in dry ether. No yields were reported, but sufficient quantities were obtained to characterize the intermediate α-keto ester.

When dilute alcoholic hydrochloric acid (1.5 cc. HCl, 10 cc. EtOH) was used to effect cyclization of the α-keto ester (XXXVI), hydrolysis of the ester linkage did not take place and the ethyl ester was obtained.

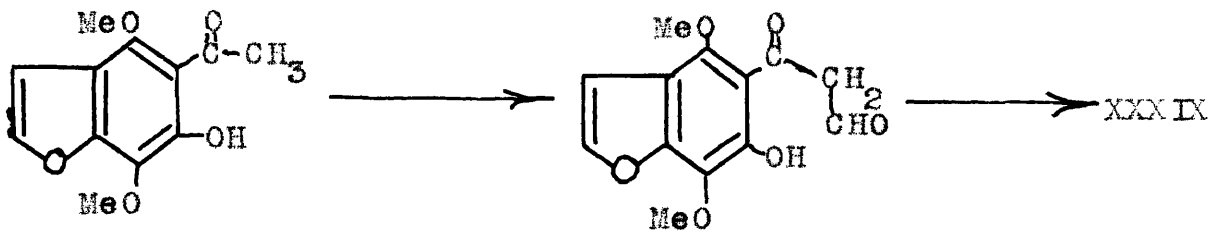


IV XXXVI XXXVIII XXXVII XXXIX

As one phase of the present investigation of khellin and its derivatives, the attempt was made to synthesize norkhellin by application of Auwers' procedure. The original directions were followed, using an excess of diethyl oxalate as solvent. Condensation with khellinone apparently took place, but no effort was made to isolate the intermediate α-keto ester. As an alternative to the isolation of the ester, the excess diethyl oxalate was removed and the residue refluxed with 20 percent hydrochloric acid in alcohol. A large amount of tarry material was formed, but a small amount of colorless tiny-crystalline material was obtained after repeated treatment of the alcoholic solution with decolorizing carbon. Carbon dioxide was evolved when the crystalline material was heated (identified by passage through lime water), and the residue remaining, after recrystallization

from a small amount of alcohol, melted at 179-180°. Schönberg and Sina report the melting point of norkhellin as 182°. Unfortunately, the yield of final product was so low that no material was available for analysis. It may be safely assumed, however, that the product obtained by the above method was identical with norkhellin described by Schönberg and Sina.

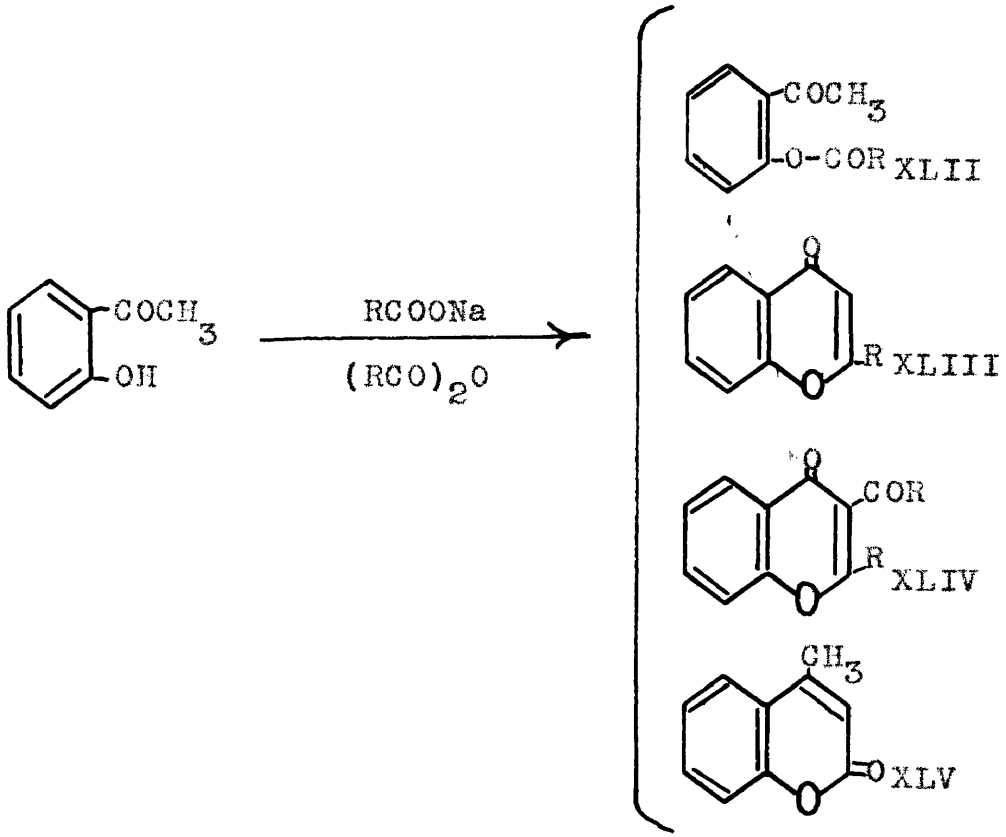
For the synthesis of norkhellin (XXXIX), the method of Mentzer and Meunier (40) proved to be most satisfactory. In this procedure khellinone (IV) was dissolved in excess ethyl formate and powdered sodium added. The mixture was allowed to stand for three days at room temperature, with occasional shaking. The formyl derivative (XLI), was isolated and converted by boiling with alcoholic hydrochloric acid into norkhellin (XXXIX). Schönberg and Sina carried out the same reaction under modified conditions and obtained norkhellin. The product thus prepared melted at 182° and exhibited the same properties as those of a specimen prepared during this investigation.



IV XLI

Preparation and Properties of 2-Alkylchromones.- Of the various methods that are available for the synthesis of 2-alkyl chromones (38), only two appear to be applicable to khellinone: the Kostanecki reaction (32) and the condensation of ortho-hydroxyacetophenones with ethyl esters in the presence of sodium, followed by ring closure of the resulting diketone (24,25,41-46).

In the Kostanecki reaction, ortho-hydroxyacetophenones, or their substituted derivatives, are heated with the anhydride and the sodium salt of an aliphatic or aromatic carboxylic acid to produce chromones substituted in the 2-position (32). Unfortunately, however, the Kostanecki reaction does not invariably lead to the formation of a 2-alkyl chromone. The action of an acid anhydride and the sodium salt of an acid on a phenolic ketone may produce the acyl derivative of the ketone (XLII), a chromone (XLIII), a 3-acylated chromone (XLIV), or a coumarin (XLV).



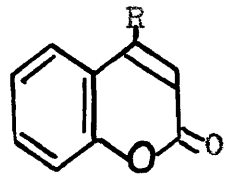
The mechanism of the Kostanecki reaction has been extensively studied (33,43,45,47,48,65-68), but the production of a chromone or a coumarin or a mixture of both depends on the structure of the acid and ketone used as well as the reaction conditions (49). The 3-acyl chromones (XLIV), form very readily by heating chromones with acid anhydrides (50); and it was shown by Baker (51) that the production of these compounds is a general feature of the Kostanecki reaction. However, owing to the fact that the whole reaction product was usually subjected to vigorous alkaline hydrolysis, the 3-acyl group was lost and a chromone unsubstituted in the 3-position (XLIII) was isolated.

Since the Kostanecki reaction may give rise to a number of products, it becomes necessary to devise methods for the detection and separation of chromones and coumarins. The methods used for differentiating these compounds have been reviewed by Kelkar (52), but since these tests were of such importance in the present work, they may be enumerated briefly and supplemented by tests which have been found useful during this investigation.

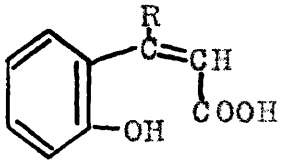
The principle methods employed to differentiate between chromones and coumarins can be divided into two groups; those based upon the hydrolysis of the compound by means of alkaline reagents, and those consisting of the formation of some characteristic derivative.

Hydrolysis of Coumarins.- Since coumarins (XLVI) are lactones, the initial action of alkali is to open the ring

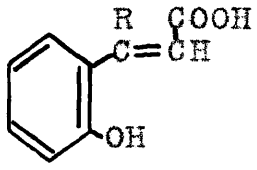
with the formation of a salt of a coumarinic acid (XLVII). Generally, on acidifying, the original coumarin is regenerated. Under certain conditions, however, and especially by the prolonged action of strong alkali, racemization takes place and salts of coumaric acid (XLVIII) are formed (53). The original coumarin cannot be reformed by acidification of these salts. In some cases a stable form of cis-coumarinic acid is formed (54). In the above cases the γ-pyrone ring is simply opened, but in others, complete elimination of the pyrone ring takes place with the formation of a phenol (55,56).



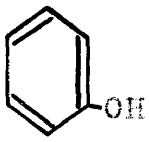
XLVI



XLVII

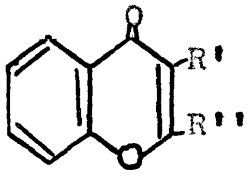


XLVIII

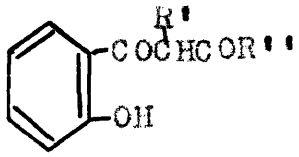


XLIX

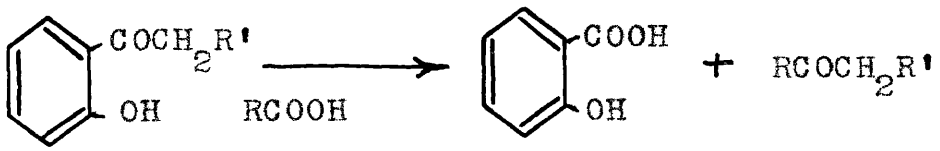
Hydrolysis of Chromones.- According to Simonis (57), the hydrolysis of a chromone (L) occurs through the following stages. One mole of water is taken up and the ring ruptures at the ether linkage, forming a diketone (LI), which is generally further attacked by the alkali to form either a ketone (LII) or an acid (LIII).



L



LI



LII LIII

The hydrolysis of a chromone thus gives rise to an ortho-hydroxyphenyl ketone and an acid, or an ortho-hydroxybenzoic acid and a ketone. The ortho-hydroxybenzoic acid thus formed may lose carbon dioxide to form a phenol (58). Whether the chromone in question undergoes "acid splitting" or "ketone splitting" depends on the nature of the chromone and reaction conditions. There is no way of predicting which reaction will take place.

If a coumarin and a chromone are both produced as products of the Kostanecki reaction, their detection on the basis of the identification of products of alkaline hydrolysis would be extremely difficult because of the variety of products formed, as mentioned above. The interpretation of the results of hydrolysis of benzopyrones by alkalies is by no means simple and requires careful consideration of the various factors involved, especially the nature of the various substituents. The literature contains many examples of coumarins which were thought to be chromones, and vice versa (52).

The Sodium Ethoxide Method for Separating Chromones from Coumarins.- A method based upon the action of sodium ethoxide

on a mixture of a chromone and a coumarin has been devised by Wittig (43). The mixture of chromone and coumarin is treated with cold sodium ethoxide solution, as a result of which both pyrone rings are opened and the substances dissolve. On acidifying, the coumarin ring is regenerated, but the diketone formed from the chromone must be extracted from the solution with aqueous alkali and reformed by treatment with cold concentrated sulfuric acid or hot dilute acid. Canter and Robertson (59) modified this process by carrying out the alkaline hydrolysis in the presence of dimethyl sulfate. The ortho-methoxy cinnamic acid formed thereby could not reform the coumarin when acidified, and thus was easily separated from the chromone.

Formation of Styryl Derivatives from Chromones.- Chromones containing an alkyl group in the 2-position readily condense with aromatic aldehydes to form styryl derivatives (60). This reaction, which will be discussed in detail in another section of this dissertation, is characteristic of 2-alkyl chromones. The corresponding alkyl coumarins do not react.

Acylation in the 3-Position as an Indication of Chromone Formation.- As has been previously mentioned, chromones can be acylated readily in the 3-position when heated with acid anhydrides. Coumarins do not share this property, and this fact is frequently utilized in deciding between chromone and coumarin structures (61).

Formation of Pyroxonium Salts from Chromones.- Chromones form highly colored salts with acids. Picrates, perchlorates,

and hydrochlorides are readily prepared. In the usual procedure, the concentrated or anhydrous acid is allowed to react with the chromone in dry chloroform, from which solvent the acid salts crystallize rapidly. The various structures which have been suggested for these compounds have been discussed in detail (62). Khellin sulfate has been prepared by dissolving khellin in concentrated sulfuric acid and allowing the mixture to stand in a cold place until crystals separated (63). Pyroxonium salts are rapidly hydrolyzed, with regeneration of the starting materials; they cannot be used, therefore, for solubilization of chromone derivatives.

Bromination of Chromones and Coumarins.- Desari (64) has devised a qualitative test for coumarins and chromones based on their reaction with bromine in glacial acetic acid. With chromones, bromine gives an insoluble perdibromide, from which the original chromone is regenerated by treatment with sulfurous acid, while the coumarin invariably gives the soluble 3-bromo derivative. Chromone perbromides resemble pyroxonium salts in their properties.

Synthesis of Khellin Homologs: 2-Ethyl and 2-Propyl-5,8-dimethoxy-6,7,4',5'-furanochromone.- Of the various methods generally used for the synthesis of chromones, only the cyclization of ortho-hydroxyphenyl-β-diketones can be depended upon to lead exclusively to these compounds (24,42,45). These diketones are obtained from ortho-hydroxyacetophenone derivatives by a Claisen-type condensation with ethyl esters

of carboxylic acids in the presence of sodium or sodium hydride (43). In practice, the ortho-hydroxyacetophenone derivative is dissolved in an excess of dry ester and sodium added slowly (sodium powdered under xylene is preferred, but finely sliced sodium can also be used). The reaction is rather vigorous with some compounds and external cooling is often necessary. The reaction mixture is refluxed gently until no further reaction appears to take place. In some cases where the reaction with sodium is sluggish or fails to take place, sodium hydride may be used as a condensing agent (24,43,45). The sodium salt of the enol form of the diketone[1] which separates usually as a yellow mass, is quickly filtered and washed with ether (to remove excess ester) and converted into the free diketone by treatment with dilute acid. An alternative procedure involves pouring the reaction mixture into ice water, acidifying, extracting with ether and recovering the diketone from the ether extract by treatment with aqueous alkali. The diketone, uncontaminated with ester, is recovered by acidifying the alkaline extract. Schönberg and Sina (41) modified the above process by carrying out the condensation in dry ether, thereby avoiding a large excess of ester.

Ortho-hydroxyphenyl-β-diketones can be cyclized to chromones under a variety of conditions, but no general

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[1] These sodium salts can be readily alkylated, and Heilbron, Hay and Lowe have used this method for the synthesis of 2,3-dialkylchromones.

method appears to be useful for all types of chromones. Some compounds cyclize very readily, e.g., ω-acetylkhellinone cyclizes to khellin when heated for a few minutes in alcohol containing only a trace of hydrochloric acid (25). Other compounds require more drastic treatment, such as refluxing with concentrated hydriodic acid for long periods of time. In the khellin series, however, this reagent cannot be used, since it causes cleavage of methoxyl groups and opening of the furane ring followed by recyclization to form isokhellin (25). Sulfuric acid, sulfuric acid in alcohol (10-30% H_2SO_4) (26,33,41), glacial acetic acid containing a small amount of hydrochloric acid (45), and glacial acetic acid saturated with hydrogen bromide (45) have also been used to effect cyclization.

The equations for reactions described above have previously been given (IV→XXI→I), p. 12.

Cyclization of the diketones prepared according to the preceding methods proved to be the most difficult phase in the preparation of homologs of khellin. Whereas ω-acetylkhellinone cyclized very readily under the influence of a trace of hydrochloric acid in alcohol to form khellin (25), the cyclization of ω-propionylkhellinone to homokhellin ("2-ethylkhellin") required 10 percent hydrochloric acid in alcohol, and ω-butyrylkhellinone could only be cyclized to bis-homokhellin ("2-propylkhellin") with 30 percent sulfuric acid in alcohol (41). The attempted cyclization of ω-propionylkhellinone using concentrated sulfuric acid led to the formation of a crystalline substance of unknown

composition.

Attempts were made to prepare 2-butyl and 2-amyl khellin homologs from khellinone and ethyl valerate and ethyl caproate, respectively, via the diketone. The condensation appeared to proceed quite normally when either sodium of sodium hydride was used as condensing agent, yellow crystalline masses being obtained in both cases; but attempts to cyclize these higher ω-acylkhellinones under various conditions led only to the formation of intractable tars. It is probably significant that no unreacted khellinone could be isolated from these tarry products, indicating that the condensation apparently took place as expected, but that polymerization occurred under the influence of acid. The fact that diketones of this type polymerize so readily may account for the observation that higher 2-alkylchromones have not previously been reported.

Attempts to purify ω-propionylkhellinone by vacuum distillation led to the formation of a yellow crystalline product which failed to cyclize to norokhellin. Although there were no visible signs of decomposition during the distillation, decomposition apparently took place, since the analysis of the yellow material did not correspond to that of any expected product.

PREPARATION OF CHALCONES FROM KHELLINONE

Kostanecki (69,70) first applied the term "chalkone" (Gk., bronze or bronze-like) to compounds obtained by condensation of acetophenone or acetophenone derivatives with aromatic

aldehydes. Some of these compounds exhibit beautiful metallic lusters and vary in color from pale yellow to deep red, depending on the substituents present on either ring. The simplest member of the series, benzylidene acetophenone, is known as "chalcone"[1] and other members are named as derivatives thereof. Many chalcones are found in nature as constituents of plant pigments, where they occur free or as glycosides.

Chalcones may be prepared in a number of ways (71,72), using either acid or base catalyzed reactions, but condensation in the presence of alkalies is the most generally used procedure. Kostanecki's original procedure (69) required the use of a large excess of concentrated potassium hydroxide in alcohol to bring about the condensation between the aldehyde and acetophenone, but later investigators found that the concentration of alkali needed to effect condensation depended upon the nature and positions of the substituent groups on the aldehyde and ketone. Schraufstätter and Deutsch (73) recently published the findings of an extensive investigation on the synthesis of chalcones. Extensive work in this field has also been reported by Wheeler and coworkers (74), Monti (75), Honig (76), Geissman and coworkers (77) and many others. Many nitrochalcones have been studied by Tanasescu and Baciu (79). Furfurylidene acetophenones have also been prepared (70,73,80,81).

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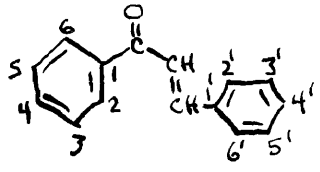
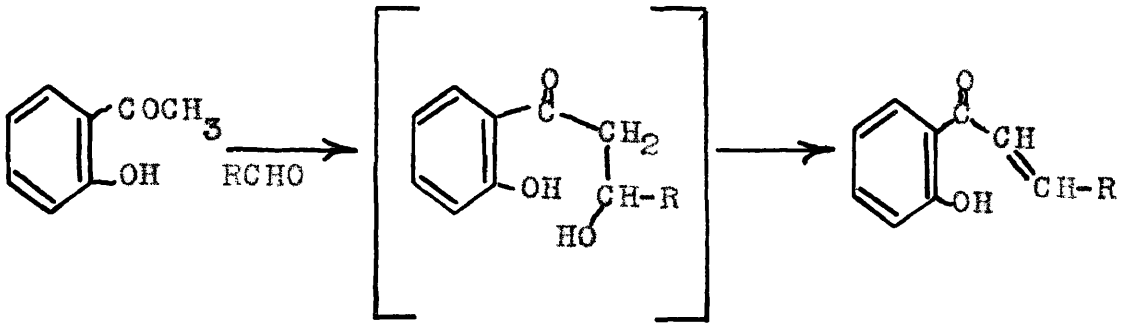
[1] Chalcones are numbered as follows:



Chalcones of pharmaceutical interest have previously been discussed, p. 6.

The condensation of acetophenone derivatives with aldehydes proceeds by way of the intermediate aldol (LIV) which readily loses water to form the chalcone (LV). Aldols have not been isolated in the course of this investigation, but previous workers (78) were successful in isolating these intermediates.



LIV LV

Furanochalcones have been prepared from khellinone by Clarke and Robertson (25) and Schönberg and Sina (41). These workers used an excess of 50 percent aqueous sodium hydroxide (2 gm. for each gram of khellinone) to effect condensation, and it has been found during the course of this investigation that this quantity (or a slight excess) was quite sufficient for all condensations attempted. Clarke and Robertson used piperonal and anisaldehyde as aldehyde components, and, in addition to these, Schönberg and Sina employed vanillin and para-dimethylaminobenzaldehyde. These four aldehydes were also used in this investigation, in addition to a number of other aromatic and heterocyclic aldehydes.

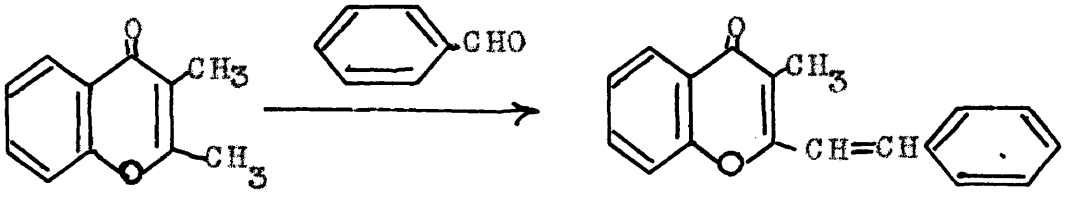
Clarke and Robertson (25) have synthesized the corresponding flavones from the chalcones mentioned above, using phosphoric acid in alcohol as catalyst. It might also be mentioned that cyclization of chalcones to flavones can also be accomplished under alkaline conditions, and flavones are sometimes produced as by-products in the preparation of chalcones (73). The preparation of chalcones from khellinone and flavones from chalcones is illustrated by equations (IV→XXXIII→XXXIIIA), p. 17. Comments on individual compounds prepared during this study will be found in the experimental section of this dissertation.

PREPARATION OF STYRYL DERIVATIVES OF KHELLIN

In 1925 Robinson and Shinoda (82), in a paper on the synthesis of 2-styrylchromonol derivatives, called attention to the interesting fact that while the difference in composition of successive members of naturally occurring fatty acids is C_2H_4, the increment most common among aromatic plant products is C_2H_2. As examples, these authors cite the following facts: benzoic acid and cinnamic acid are frequently found together in many plants, and even piperic acid, the next member of the series, is of quite common occurrence. Moreover, methyl-, propenyl-and allylbenzene derivatives are widely distributed among plant products, but it is unusual to encounter derivatives of ethyl- or propylbenzene among the constituents of plants. These authors recognized, of course, that exceptions to this generalization are known, but most of the ethylbenzene

derivatives of natural origin are believed to be derived from more complex substances; e.g., hordenine, epinephrine and mescaline are known to be formed from phenylalanine derivatives by decarboxylation. On the basis of these assumptions, Robinson and Shinoda considered it probable that representatives of the styrylchromones occur in nature, and mentioned several compounds which they thought might eventually be shown to be of this class. Later workers, however, have either shown that the compounds believed by Robinson and Shinoda to be 2-styrylchromones are differently constituted or have expressed skepticism of the evidence presented (83,84). So far as the present investigators are aware, no definite proof has been offered for the existence of styrylchromones in nature.

In 1923 Heilbron, Barnes and Morton (60) made the interesting observation that the 2-methyl group in 2,3-dimethylchromone (LVI) is conjugated with a carbonyl group through an olefinic double bond.

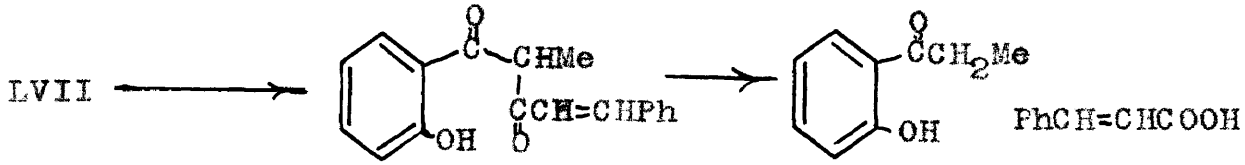


LVI LVII

Accordingly, this methyl group should possess activity similar to the methyl group in crotonaldehyde, ethyl crotonate or quinaldine and should be capable of undergoing condensation with aromatic aldehydes. Indeed, these workers

were able to demonstrate the extraordinary activity of this methyl group by carrying out a number of condensations with various aromatic aldehydes in methanol, using sodium methylate as catalyst, to form styryl derivatives, of type (LVII) shown above. Various aromatic aldehydes were used by these workers, and the condensation was found to take place with a wide variety of substances such as piperonal, benzaldehyde, para-dimethylaminobenzaldehyde, cinnamaldehyde, methoxy-benzaldehydes, and others. Furfuraldehyde was also found to condense readily.

That the condensation actually involved the 2-methyl group was proved by the hydrolysis of 2-styryl-3-methylchromones according to the method of Petschek and Simonis (36), when cinnamic acid was obtained as one of the products (LVII → LIX).



LVIII LIX

Heilbron, Barnes and Morton also postulated, on the basis of the formerly widely-accepted theory of "neutralization of partial valency forces", that 2,3-dimethylchromones substituted in the 7-position should not form 2-styryl derivatives with aromatic aldehydes. They prepared a compound which they regarded as 7-methoxy-2,3-dimethylchromone and found that this compound would not condense with aromatic

aldehydes in the presence of sodium ethylate, even though vigorous reaction conditions were employed. It was later shown, however, that the compound these workers had prepared was in reality 7-methoxy-3,4-dimethylcoumarin and that an authentic specimen of 7-methoxy-2,3-dimethylchromone, does, in fact, condense readily with aromatic aldehydes to form 2-styryl derivatives (61). The compound prepared by Heilbron, Barnes and Morton was another example of the mistaking of a coumarin, prepared by the Kostanecki reaction, for a chromone. Later workers have shown that the formation of styryl derivatives is a characteristic reaction of 2-methyl and 2-ethyl chromones, regardless of the substituents present in any position, and that substituents in the 3-position are not necessary for condensations involving the 2-methyl group (47,83,85). One exception appears to be the 7-benzyloxychromones, however, since Venkatraman and coworkers (86) were unable to prepare styryl derivatives of these compounds.

Clarke and Robertson (25) and Schönberg and Sina (41) demonstrated that the 2-methyl group of khellin also condenses with aromatic aldehydes to form styryl derivatives. These workers used piperonal and anisaldehyde, respectively. During this investigation a series of compounds has been prepared in which the number of aldehydes used has been greatly expanded to include methoxy-, hydroxy-, bromo-, and nitrobenzaldehydes. Furfuraldehyde, α-thiophenealdehyde, and α-pyrrolealdehyde have also been successfully employed;

cinnamic aldehyde and phenylacetaldehyde gave only poor yields and para-dimethylaminobenzaldehyde and 5-nitrofurfuraldehyde produced only tars. It is interesting to note that styryl derivatives of khellin, prepared as described above, are vinylogs of the parent compound.

The general procedure followed in the preparation of styrylkhellin derivatives was as follows: khellin (1 mole) was added to a warm solution of sodium methylate (2 moles) in dry methanol. When the khellin had completely dissolved, the aldehyde (1 mole) was added and the solution warmed on the steam bath for a few minutes. Some sensitive aldehydes required no heating, while others required more vigorous conditions to bring about reaction. The mixture was allowed to stand at room temperature for at least twenty-four hours, at the end of which time the styryl derivative was separated by filtration before or after dilution of the reaction mixture with water. The derivative was then recrystallized from an appropriate solvent.

All of the styryl derivatives prepared during this investigation exhibited marked halochromic properties, highly colored hydrochlorides being instantly formed by the addition of dry hydrogen chloride to solutions of the parent compound in dry chloroform. The colors of the various halochromic salts prepared from styrylkhellin derivatives exhibited no specially marked differences in shade, varying only between reddish-orange and crimson.

MISCELLANEOUS COMPOUNDS RELATED TO KHELLIN

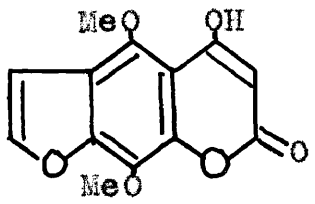
In addition to the compounds previously discussed, a number of miscellaneous compounds were prepared which possess some feature in common with the khellin molecule. These compounds were synthesized to determine, if possible, whether or not simpler compounds having some structural feature in common with khellin also possess some of the physiological properties of khellin. It was also of interest to prepare a khellin analog in which the γ-pyrone ring is replaced by an α-pyrone ring (a coumarin derivative). The following compounds have been prepared:

2-Methylchromone: This compound was prepared from ortho-hydroxyacetophenone and ethyl acetate according to the directions of Wittig (43).

2-Benzylchromone: The procedure of Chadha, Mahal and Venkataraman (33) for the preparation of this compound from ortho-hydroxyacetophenone and ethyl phenylacetate was found satisfactory.

3-Hydroxy-2-acetyl-5,6,4',5'-furanobenzoquinone: This compound was prepared by the oxidation of khellinone with fuming nitric acid in dry ether, according to the procedure of Späth and Gruber (4).

4-Hydroxy-5,8-dimethoxy-6,7,4',5'-furanocoumarin (IX): This compound was prepared by the condensation of diethyl carbonate with khellinone in the presence of sodium, following the procedure described by Jones, Mackenzie and Robertson (87) for the synthesis of 4-hydroxy-6,7-dimethoxycoumarin.



LX

An interesting observation was made by Arndt (88,89) who observed that two products were obtained when 4-hydroxycoumarin was methylated with diazomethane,- a mixture of the expected 4-methoxycoumarin and the isomeric 2-methoxychromone, indicating that 4-hydroxycoumarin is capable of existing in a tautomeric form which gives rise to a chromone when stabilized by methylation.

An attempt was made to prepare 4-hydroxy-2,5,8-trimethoxy-6,7,4',5'-furanocoumarin under conditions similar to those employed by Arndt, but only the 4-methoxycoumarin derivative was obtained, indicating that a tautomeric form of this compound probably does not exist under the conditions used during this experiment.

EXPERIMENTAL

All melting points are uncorrected. Aldehydes used, unless otherwise stated, were Eastman Practical Grades, freshly distilled just before use. Khellin was purchased from S. B. Penick and Company, New York.

Preparation of Khellinone.- Khellinone was prepared according to the procedure of Späth and Gruber (4), modified as follows: Twenty-five grams of khellin was added to

2 liters of boiling 2 percent potassium hydroxide solution contained in a 3-L. three-necked flask equipped with a reflux condenser and a gas inlet tube reaching nearly to the bottom of the flask. Nitrogen was slowly bubbled through the solution during the entire operation. The solution was refluxed until all the khellin had dissolved, about one hour being required. The clear lemon-yellow solution was cooled under the cold water tap and 1 liter of 4 percent sulfuric acid was added. The yellow crystalline precipitate which settled was filtered and recrystallized from dilute methanol. Yellow needles, m.p. 100°. Yield 23 g. (97%).

Preparation of Norkhellin. Method A- Using Diethyl Oxalate.- Three grams of dry khellinone was dissolved in 40 ml. of boiling diethyl oxalate, which had previously been dried with "Drierite" and freshly distilled. Three grams of sodium in thin slices was added, one piece at a time through the condenser, while the solution was gently refluxed. The solution turned deep-red and then brown. Refluxing was continued for about one hour at the end of which time all sodium appeared to have reacted. The mixture was cooled, a small amount of methanol added to decompose any unreacted sodium, and poured onto 200 g. of ice. The reddish-brown solution was carefully acidified with 10 percent acetic acid and an oil separated. The mixture was extracted with three 100 ml. portions of ether and the ether and excess diethyl oxalate evaporated off on the steam bath, finally under reduced pressure. The dark-brown oil which

remained was dissolved in a mixture of 25 ml. of ethanol and 5 ml. of concentrated hydrochloric acid and refluxed gently for one hour.

The tarry material which remained after removal of solvent was dissolved in 150 ml. of alcohol and decolorized by heating with norite, several 3-g. portions being required. When the solution was nearly colorless, the alcohol was evaporated until only a very small volume remained, but no crystalline material separated. After evaporating to dryness a small residue remained (ca. 50 mg.). This residue was dried and placed in a small test tube, the neck of which was drawn out to a fine capillary and bent in the shape of a small retort. On heating the test tube gently with a soft flame, gas was evolved and the material melted. The gas was identified as carbon dioxide by passage through lime water. A white precipitate of calcium carbonate formed which evolved carbon dioxide when a drop of dilute acid was added. When gas was no longer evolved, the test tube was cooled and carefully cut open. Addition of a few drops of ethanol followed by gentle warming caused the residue to dissolve. Treatment of the alcoholic solution with a small amount of norite, filtering and evaporating, followed by the addition of a few drops of water caused colorless crystals to separate on cooling in ice. Yield about 10 mg., m.p. 179-80°. This compound appears to be identical with norkhellin prepared by Schönberg and Sina (41), m.p. 182°.

Preparation of Norkhellin. Method B- Using Ethyl Formate.- Two grams of dry khellinone was dissolved in 30 ml. of ethyl formate, which had previously been dried with "Drierite" and freshly distilled. Two grams of thinly sliced sodium was added in small portions and the flask stoppered with a tube containing calcium chloride and soda lime. The sodium reacted slowly and the next day a yellowish-brown solid had separated. One gram more of sodium was added and the flask was allowed to stand at room temperature for an additional forty-eight hours, with occasional shaking. At the end of this time, a few ml. of methanol was added to destroy unreacted sodium and the mixture was evaporated to dryness on the steam bath in a current of illuminating gas. The residue was dissolved in 100 ml. of water and carefully acidified with 10 percent acetic acid. The oily solution was extracted with three 100 ml. portions of ether, the ether evaporated off on the steam bath and the residue dissolved in 50 ml. of ethanol. Treatment with norite followed by evaporation to a small volume resulted in the formation of almost colorless needles, m.p. 165.5°. Yield, about 50 mg.

The formyl derivative was dissolved in 25 ml. of ethanol, 5 ml. of hydrochloric acid was added and the solution refluxed for three hours. Colorless crystals, m.p. 181°, separated on evaporating and cooling. Yield, about 20 mg.

This compound gave no color with alcoholic ferric chloride, a yellow color with concentrated hydrochloric acid, and an orange red color with concentrated sulfuric acid.

Preparation of Homokhellin ("2-Ethylkhellin").- The success of this preparation depends partly on the use of dry reagents. Khellinone was dried over phosphorous pentoxide and the ethyl propionate was also dried with this reagent before distilling.

Two grams of khellinone was dissolved in 25 ml. of boiling ethyl propionate and 2 g. of powdered sodium was added in several portions through the condenser. The initial reaction was vigorous and cooling was necessary to control the reaction. After the reaction had subsided 20 ml. more of ethyl propionate was added and the yellow solution was gently refluxed for two hours, during which time a yellow solid separated. Ten ml. of methanol was added to destroy excess sodium. The mixture was cooled and poured into 200 ml. of ice-cold water and the yellow solid material dissolved slowly on standing. After carefully acidifying with 10 percent acetic acid, the solution was extracted with three 250 ml. portions of petroleum ether. Attempts to separate the diketone by crystallization from petroleum ether failed, but an orange-yellow solid mass remained when the solvent was removed under reduced pressure. The solid material was dissolved in 40 ml. of ethanol, 10 ml. of hydrochloric acid added and the solution refluxed on the steam bath for one hour. After decolorizing with norite and removal of most of the alcohol, colorless crystals separated from the residual liquor after standing in the refrigerator over night. The material was recrystallized from a small amount of dilute alcohol producing tiny

colorless crystals, m.p. 125°. Yield 0.2 g. (8.6%). Anal. calc. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.14. Found: C, 64.81, H, 5.11

Concentrated hydrochloric acid produced a lemon-yellow color, concentrated sulfuric acid a deep yellow, and iodine-potassium iodide solution a deep blue. Ferric chloride in alcohol gave no color.

Attempts to separate the intermediate ω-propionyl-khellinone from the residue left after removal of petroleum ether by distillation under reduced pressure resulted in the formation of a yellow crystalline substance, b.p. 190-210°/1 mm., m.p. 153° (from ethanol), which could not be cyclized to "ethyl khellin" by refluxing with 10 percent hydrochloric acid in methanol, 50 percent hydrogen bromide in glacial acetic acid, 10 percent sulfuric acid in ethanol for six hours, or 50 percent sulfuric acid in ethanol on the steam bath for thirty minutes. The material dissolved readily in concentrated sulfuric acid; and, after standing for twenty-four hours in contact with this reagent, followed by dilution with water, filtration, and crystallization from ether, a colorless crystalline substance, m.p. 230-231° was produced. The yellow crystalline material, m.p. 153°, gave an intense green color with alcoholic ferric chloride, pale yellow with concentrated hydrochloric acid, and orange-yellow with concentrated sulfuric acid. Analysis showed 64.76 percent carbon and 4.86 percent hydrogen.

These values do not correspond with those calculated for the diketone, khellin or homokhellin.

The above procedure was used successfully on three occasions for the synthesis of homokhellin; however, in three other trials, no homokhellin was obtained. The greatest difficulty was always encountered in the final separation of homokhellin from the oily products remaining after cyclization. Yields varied from 0.2 g. to 0.5 g. from 2 g. of khellinone. Loss of product was attributed to adsorption by the decolorizing carbon.

The sodium hydride condensation described by Wittig (43), when applied to the above reagents, resulted only in the formation of tars from which nothing could be isolated.

Schönberg and Sina (41) prepared homokhellin and found the melting point to be 126°.

Preparation of bis-Homokhellin ("2-Propylkhellin"). Two grams of dry khellinone was dissolved in 25 ml. of dry freshly distilled ethyl butyrate. Two grams of sodium in the form of thin slices was gradually added to the gently refluxing solution. The sodium reacted slowly and, after fifteen minutes, a yellow solid began to separate. After refluxing for one hour, an additional gram of sodium and 5 ml. of ethyl butyrate were added and the mixture allowed to reflux for an additional five hours. The mixture was cooled, 5 ml. of methanol added to destroy excess sodium, and the brownish-yellow mass was poured into 150 ml. of cold water. When the solid had completely dissolved, the

excess ethyl butyrate (top layer) was separated and the aqueous layer acidified with 10 percent acetic acid. A brownish-yellow oil formed. The mixture was extracted with ether and the ether and unchanged ethyl butyrate were removed by distillation under reduced pressure on the steam bath. Twenty-five ml. of methanol and 10 ml. of concentrated hydrochloric acid were added to the residue and the solution refluxed for thirty minutes. After treating with norite, evaporating the solution to a small volume and cooling in ice, colorless crystals separated. Yield 50 mg., m.p. 175°.

Upon treating the oily residue obtained from the hydrochloric acid cyclization reaction, as described above, with 30 percent sulfuric acid in alcohol (41), decolorizing and crystallizing from dilute alcohol, a few milligrams of material, m.p. 175° was obtained, presumably identical with that recently reported by Schönberg and Sina (41).

This substance gave a yellow color with concentrated hydrochloric acid, orange with concentrated sulfuric acid, and no color with alcoholic ferric chloride.

General Procedure for the Condensation of Khellin with Aromatic Aldehydes.- Sodium methylate solution was prepared by dissolving 0.6 g. (.025 equivalent) of sodium in 40 ml. of methanol. To this solution was added 2 g. of khellin (.008 equivalent); and, when the khellin had completely dissolved, an equivalent amount of the aldehyde was

introduced in one portion. The mixture was refluxed on a steam bath for ten minutes and the flask was then tightly stoppered and allowed to stand at room temperature for twenty-four hours. In most cases the condensation product separated during this period; if not, the contents of the flask was poured into 200 ml. of cold water and the precipitate allowed to settle. The mixture was filtered and the precipitate washed well with cold water and pressed dry. The styryl derivative was recrystallized from acetic acid or ethanol, with the use of norite, if necessary, for decolorizing, and dried in air. Several compounds appeared to undergo change when dried under a heat lamp. It is recommended, therefore, that this treatment be avoided.

By use of the above general procedure, the following compounds have been prepared. Any modifications of the general procedure are given in the description of each compound.

Preparation of 2-Styrylkhellin.- From khellin and benzaldehyde. Lemon yellow needles from dilute acetic acid, m.p. 196-196.5°. Yield, 48%. Gives yellow-orange color with concentrated sulfuric acid, reddish-orange with dry hydrogen chloride in chloroform, and no color with alcoholic ferric chloride.

Anal. Calc. for $C_{21}H_{16}O_5$: C, 72.3; H, 4.62. Found: C, 72.16, 72.14; H, 4.77, 4.75

Preparation of 2-(4-bromostyryl)-khellin.- From khellin and p-bromobenzaldehyde. Lemon yellow needles from dilute

acetic acid, m.p. 191-192°. Yield: 95%. Gives orange-red color turning to black with concentrated sulfuric acid, crimson with dry hydrogen chloride in dry chloroform, and no color with alcoholic ferric chloride.

Preparation of 2-(4-hydroxystyryl)-khellin.- From khellin and p-hydroxybenzaldehyde. Lemon yellow tiny clusters from petroleum either, m.p. 116-117°. Yield: 15%. Gives yellowish-orange color with concentrated sulfuric acid and deep-green with alcoholic ferric chloride.

Preparation of 2-(2-hydroxystyryl)-khellin.- From khellin and salicylaldehyde. This synthesis must be carried out under nitrogen to prevent oxidation of the phenolic aldehyde. A yellow precipitate formed instantly when the reactants were mixed. The solid was removed by rapid filtration, suspended in alcohol and cautiously neutralized with concentrated hydrochloric acid. The sodium chloride which formed was removed by filtration, the solution was diluted with water, and the styryl derivative allowed to crystallize. Recrystallization from dilute alcohol gave yellow needles, m.p. 152-153°. Yield: 15%. Gives no color with aqueous or alcoholic ferric chloride, and an intense orange-yellow with concentrated sulfuric acid.

Preparation of 2-(4-methoxystyryl)-khellin.- From khellin and anisaldehyde. Yellow needles from dilute acetic acid, m.p. 170-171°. Yield: 65%. Gives orange-brown color with concentrated sulfuric acid, intense red with dry hydrogen chloride in chloroform, and no color with alcoholic

ferric chloride.

Anal. calc. for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76. Found: C, 69.71, H, 5.10.

This compound has recently been synthesized by Schönberg and Sina (41), who reported a melting point of 171°.

Preparation of 2-(2-methoxystyryl)-khellin.- From khellin and o-methoxybenzaldehyde. Yellow flakes from dilute acetic acid, m.p. 164-165°. Yield: 50%. Gives a bright orange color with concentrated sulfuric acid, faint brown with alcoholic ferric chloride, and a deep orange-red with dry hydrogen chloride in chloroform.

Anal. calc. for $C_{22}H_{18}O_6$: C, 69.7; H, 4.80. Found: C, 68.34; H, 4.80. (Note: Analyst reported "sparks" during combustion).

Preparation of 2-(3-methoxy-4-hydroxystyryl)-khellin.- From khellin and vanillin. Yellow needles from ethanol, m.p. 101-102°. Yield: 53%. Gives an orange-red color with concentrated sulfuric acid, reddish-orange with dry hydrogen chloride in chloroform, and no color with alcoholic ferric chloride.

Preparation of 2-(3,4-dimethoxystyryl)-khellin.- From khellin and veratraldehyde. Lemon yellow needles from dilute acetic acid, m.p. 185°. Yield: 55%. Gives orange-red color with concentrated sulfuric acid, reddish-orange with dry hydrogen chloride in chloroform, and no color with alcoholic ferric chloride.

Anal. calc. for $C_{23}H_{20}O_7$: C, 67.7; H, 4.93. Found: C, 67.31, 67.73; H, 4.95, 5.21.

Preparation of 2-(2,3-dimethoxystyryl)-khellin.- From khellin and 2,3-dimethoxybenzaldehyde. Lemon yellow needles from dilute acetic acid, m.p. 183-184°. Yield: 62%. Gives bright orange color with concentrated sulfuric acid, orange-red with dry hydrogen chloride in chloroform, and no color with alcoholic ferric chloride.

Anal. calc. for $C_{23}H_{20}O_7$: C, 67.7; H, 4.93. Found: C, 66.66; H, 5.12.

Preparation of 2-(3,4-methylenedioxystyryl)-khellin.- From khellin and piperonal. Very fine yellow needles from dilute acetic acid, m.p. 238°. Yield: 40%. Gives orange-red color with concentrated sulfuric acid and no color with alcoholic ferric chloride.

This compound has previously been reported by Clarke and Robertson (25) who reported a melting point of 239°.

Preparation of 2-(3-nitrostyryl)-khellin.- From khellin and m-nitrobenzaldehyde. Brownish-yellow needles from dilute acetic acid, m.p. 253-254°. Gives orange-red color with concentrated sulfuric acid and no color with alcoholic ferric chloride.

Anal. calc. for $C_{21}H_{15}O_7N$: C, 64.1; H, 3.84. Found: C, 63.90; H, 4.19.

Preparation of 2-(2-nitrostyryl)-khellin.- From khellin and o-nitrobenzaldehyde. Lemon yellow needles from dilute acetic acid, m.p. 236°. Yield: 25%. Gives an orange-red color with concentrated sulfuric acid and no color with alcoholic ferric chloride.

Anal. calc. for $C_{21}H_{15}O_7N$: C, 64.1; H, 3.84. Found: C, 64.28, 64.58; H, 4.00, 4.06, 4.09.

Preparation of 2-α-thienylkhellin.- Sodium methylate solution was prepared by dissolving 0.6 g. of sodium in 50 ml. of dry methanol. Two grams of khellin was added and dissolved by warming the mixture. After allowing the solution to cool slightly, 2 g. of freshly distilled α-thiophene aldehyde was added dropwise with constant stirring. The solution turned dark green and then brown after standing for a few minutes at room temperature. Since no further reaction was apparent after standing for several hours, the solution was gently refluxed for thirty minutes. On cooling slightly, the contents of the flask solidified. After standing for two days, the mixture was filtered and the yellow crystalline solid recrystallized from dilute acetic acid. Yellow flakes, m.p. 186°. Yield: 45%. Gives an orange-red color with concentrated sulfuric acid and no color with alcoholic ferric chloride.

Anal. calc. for $C_{19}H_{14}O_5S$. C, 64.4; H, 3.98. Found: C, 64.35; H, 4.07.

Preparation of 2-α-furylkhellin.- Sodium methylate solution was prepared by dissolving 0.6 g. of sodium in 50 ml. of methanol. Two grams of khellin was added and dissolved by warming. To this solution was added 2 g. of freshly distilled furfuraldehyde dropwise and with constant shaking. The solution was gently warmed on the steam bath several times during the addition of the aldehyde. After

the solution had stood for a few minutes, it solidified to a cream colored mass. The mixture was filtered, the precipitate washed with cold water and recrystallized from dilute acetic acid. Cream colored flakes, m.p. 204.5°. Yield: 81%. Gives deep brown color with concentrated sulfuric acid and no color with alcoholic ferric chloride. Anal. calc. for $C_{19}H_{14}O_6$: C, 67.45; H, 4.17. Found: C, 66.96; H, 4.58.

Preparation of 2- α-pyrrylkhellin.- Sodium methylate solution was prepared by dissolving 0.6 g. of sodium in 40 ml. of dry methanol. Two grams of khellin was added and dissolved by warming the mixture. To this solution was added 2 g. of α-pyrrole aldehyde, freshly crystallized from petroleum ether. The mixture was warmed gently for fifteen minutes and allowed to stand tightly-stoppered over night. The solution went through a series of color changes from lemon yellow, to ruby red, to deep brown. The next morning the solution was poured into 250 ml. of cold water. Five percent acetic acid was added with constant stirring until the solution was just acid to congo red. A brown-gummy precipitate formed and was filtered, dissolved in alcohol, decolorized with norite, and re-crystallized from dilute alcohol. Golden yellow needles, m.p. 145°. Yield: 50%.

An excess of norite must be avoided when decolorizing this solution, since the compound appears to be strongly adsorbed by carbon. One batch of material was completely

lost by adsorption on norite. It is best to use the carbon in quantities of about 1 g. suspended in a large volume of alcohol.

General Procedure for the Condensation of Khellinone with Aromatic Aldehydes.- Two grams of khellinone was dissolved in 50 ml. of warm alcohol and an equivalent amount of the aldehyde added. When the aldehyde had completely dissolved, 5 g. of 50% potassium hydroxide solution was added and the mixture refluxed on a steam bath for fifteen minutes to one hour. During this time the mixture underwent a series of color changes and solids usually separated on the side of the flask. The reaction flask was stoppered and let stand over night at room temperature. The mixture was then poured into 100 ml. of cold water and carefully acidified to litmus or congo red with 2 N hydrochloric acid solution. If the precipitated material did not settle immediately, the mixture was allowed to stand in the refrigerator until it congealed. Some compounds separated as oils but crystallized on standing in the cold. The crystalline material was removed by filtration, washed with several small portions of cold water and recrystallized from methanol, ethanol, or acetic acid.

By use of the above general procedure, the following compounds have been prepared. Any modifications of the general procedure are given in the description of each compound.

Preparation of 6-hydroxy-4,7-dimethoxy-5-cinnamoylcoumarone.- From khellinone and benzaldehyde. Orange-yellow plates from dilute methanol, m.p. 125-126°. Yield: 50%. Gives brownish-red color with concentrated sulfuric acid and deep green with alcoholic ferric chloride.

Anal. calc. for $C_{19}H_{16}O_5$: C, 70.4; H, 4.97. Found: C, 70.73; H, 5.24.

Preparation of 6-hydroxy-4,7-dimethoxy-4'-bromo-5-cinnamoylcoumarone.- From khellinone and p-bromobenzaldehyde. Deep orange crystals from dilute methanol, m.p. 147-148°. Yield: 95%. Gives deep-brown color with concentrated sulfuric acid and yellowish-green with alcoholic ferric chloride.

Anal. calc. for $C_{19}H_{15}O_5Br$: C, 56.59; H, 3.75. Found: C, 56.56; H, 4.11.

Preparation of 6-hydroxy-4,7-dimethoxy-4'-(dimethylamino)-5-cinnamoylcoumarone.- From khellinone and p-dimethylaminobenzaldehyde. Reaction mixture was kept in cold-room for twenty-four hours before pouring into water and making just acid with dilute hydrochloric acid. Ruby red crystals from dilute methanol, m.p. 147-148°. Yield: 75%.

Anal. calc. for $C_{21}H_{21}O_5N$: C, 68.65; H, 5.76. Found: C, 68.39; H, 5.87.

Schönberg and Sina (41) report a melting point of 145°.

Preparation of 6-hydroxy-4,7,2'-trimethoxy-5-cinnamoylcoumarone.- From khellinone and o-methoxybenzaldehyde. Ruby red crystals from ethanol, m.p. 124°. Yield: 67%.

Gives orange-red color with concentrated sulfuric acid and brownish-yellow with alcoholic ferric chloride.

Anal. calc. for $C_{20}H_{18}O_6$: C, 67.7; H, 5.12. Found: C, 68.12; H, 5.32.

Preparation of 6,4'-dihydroxy-4,7,3'-trimethoxy-5-cinnamoylcoumarone.- From khellinone and vanillin. Orange crystals from dilute methanol, m.p. 136°. Yield: 86%. Gives orange color with concentrated sulfuric acid and deep green with alcoholic ferric chloride.

Schönberg and Sina (41) report a melting point of 136°.

Preparation of 6-hydroxy-4,7,3',4'-tetramethoxy-5-cinnamoylcoumarone.- From khellinone and veratraldehyde. Golden-bronze colored flakes from methanol, m.p. 155-156°. Yield: 68%. Gives deep orange color with concentrated sulfuric acid and pale yellow with alcoholic ferric chloride.

Preparation of 4',6-dihydroxy-4,7-dimethoxy-5-cinnamoylcoumarone.- From khellinone and p-hydroxybenzaldehyde. Orange-yellow tiny needles from dilute methanol, m.p. 101°. Yield: 45%. Gives a crimson color with concentrated sulfuric acid and intense green with alcoholic ferric chloride.

Preparation of 2',6-dihydroxy-4,7-dimethoxy-5-cinnamoylcoumarone.- From khellinone and o-hydroxybenzaldehyde. Brownish-orange needles from dilute acetic acid, m.p. 147.5°. Yield: 80%. Gives brownish-red color with concentrated sulfuric acid and brownish-green with alcoholic ferric chloride.

Anal. calc. for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74. Found: C, 67.30; H, 5.00.

Preparation of 6-hydroxy-4,7,4'-trimethoxy-5-cinnamoylcoumarone.- From khellinone and anisaldehyde. Yellowish-orange fluffy crystalline material from dilute methanol, m.p. 138-139°. Yield: 55%. Gives bright orange color with concentrated sulfuric acid and brown with alcoholic ferric chloride.

Schönberg and Sina (41) and Clarke and Robertson (25) report a melting point of 137°.

Preparation of 6-hydroxy-4,7,2',3'-tetramethoxy-5-cinnamoylcoumarone.- From khellinone and 2,3-dimethoxybenzaldehyde. Deep red tiny crystals from dilute methanol, m.p. 113°. Yield: 60%. Gives deep brown color with concentrated sulfuric acid and brown with alcoholic ferric chloride.

Preparation of 6-hydroxy-4,7-dimethoxy-3',4'-methylenedioxy-5-cinnamoylcoumarone.- From khellinone and piperonal. Deep red crystals from dilute methanol, m.p. 153°. Yield: 75%. Gives brownish-purple color with concentrated sulfuric acid and deep brown with alcoholic ferric chloride.

Schönberg and Sina (41) and Clarke and Robertson (25) report a melting point of 154°.

Condensation of Khellinone with Furfuraldehyde, α-Pyrrolealdehyde and α-Thiophene aldehyde.- The same quantities of materials as given in the previous procedure were employed in these preparations, but the aldehyde was added slowly dropwise, to the well-stirred warm alkaline solution of

khellinone. This was done to prevent side reactions of the aldehydes (especially furfuraldehyde) and the excessive formation of highly colored by-products. The mixture was then allowed to stand in the tightly-stoppered flask for forty-eight hours at room temperature, after which time it was poured into 100 ml. of cold water and carefully acidified with 10 percent acetic acid, using congo red. The crystalline product was recrystallized from ethanol after careful decolorization with small quantities of norite.

Preparation of 6-hydroxy-4,7-dimethoxy-5-furfurylidene-coumarone.- From khellinone and furfuraldehyde. Rust colored very fine crystals from dilute ethanol, m.p. 132°. Yield: 15%. Gives brownish-red color with concentrated sulfuric acid and brownish-green with alcoholic ferric chloride.

Anal. calc. for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49. Found: C, 64.40: H, 4.68.

Preparation of 6-hydroxy-4,7-dimethoxy-5-pyrrylidene-coumarone.- From khellinone and α-pyrrole aldehyde. Tiny yellowish-brown crystals from dilute ethanol, m.p. 100-100.5°. Yield: 25%. Gives yellowish-brown color with concentrated sulfuric acid and deep green with alcoholic ferric chloride.

Preparation of 6-hydroxy-4,7-dimethoxy-5-thienylidene-coumarone.- From khellinone and α-thiophene aldehyde. Reflux one hour. Copper-bronze needles from dilute ethanol, m.p. 125-126°. Yield: 58%. Gives brownish-orange color with concentrated sulfuric acid and greenish-brown with alcoholic ferric chloride.

Anal. calc. for $C_{17}H_{14}O_5S$: C, 61.80; H, 4.27. Found: C, 62.30; H, 4.45.

Preparation of Intermediates.

α-Thiophene aldehyde.- This compound was prepared by the method of Liberg (90) given in "Organic Synthesis".

α-Pyrrole aldehyde.- The method of Fischer and Orth (91), employing the Reimer-Tiemann synthesis, was found most convenient for the preparation of this compound. Attempts to prepare this aldehyde by the Gatterman reaction led only to the formation of tars.

Preparation of Miscellaneous Compounds Related to Khellin.

Preparation of 4-hydroxy-5,8-dimethoxy-6,7-furanocoumarin.- One gram of dry khellinone was dissolved in 20 ml. of freshly distilled ethyl carbonate and the mixture warmed on the steam bath. Four-tenths of a gram of sodium in the form of thin slices was added and the mixture warmed for an additional thirty minutes. The light brown solid which separated was added to 200 ml. of ether, and a tan flocculent precipitate formed. The mixture was filtered and the precipitate dissolved in 200 ml. of hot water. One gram of norite was added and the mixture heated on the steam bath for fifteen minutes. The mixture was filtered and carefully acidified with dilute hydrochloric acid. The cream colored solid which separated was washed with cold water and dried in a desiccator, m.p. 201°. Yield: 0.65 g. (68%)

Anal. calc. for $C_{13}H_{10}O_6$: C, 59.2; H, 3.89. Found: C, 59.77, 59.57, 59.92; H, 4.12, 3.96, 4.10.

This compound gave a pale yellow color with concentrated sulfuric acid, pale yellow with concentrated hydrochloric acid, no color with 50 percent potassium hydroxide solution, no color with alcoholic or aqueous ferric chloride solutions, and no color with a pellet of sodium hydroxide and a drop of water. It was instantly soluble in 10 percent sodium hydroxide solution and was reprecipitated when the alkaline solution was acidified. The precipitate redissolved in 10 percent alkali. On the basis of these tests, the compound was assumed to be a coumarin.

When the compound was methylated with an excess of diazomethane in ether, nitrogen was evolved and a white crystalline substance separated upon standing in the refrigerator over night. Recrystallized from ethanol, colorless plates, m.p. 209°. Insoluble in sodium hydroxide (10%).

Preparation of 2-methylchromone.- This compound was prepared according to the directions of Wittig (43), from o-hydroxyacetophenone and ethyl acetate. Colorless needles from benzene, m.p. 91°. Yield: 65%.

Preparation of 2-benzylchromone.- This compound was prepared according to the procedure of Chedha, Mahal and Venkataraman (33) from o-hydroxyacetophenone and ethyl phenylacetate. Pale yellow needles from petroleum ether, m.p. 86°. Yield: 10%.

Preparation of 3-hydroxy-2-acetyl-5,6,3',4'-furano-benzoquinone.- This compound was prepared by oxidation of khellinone in dry ether with fuming nitric acid, according to the procedure of Späth and Gruber (4). Yellow tiny needles from alcohol, m.p. 172°. Yield: 15%.

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