THE SYNTHESIS AND STRUCTURE OF BENZOPYRYLIUM (CHROMYLIUM) SALTS

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CONTENTS

I. SYNTHESIS

A. Introduction

Benzopyrylium salts are salts of the basic benzopyranols (I), usually with mineral acids, which may be isolated as such or as double salts with, for example, ferric chloride. They are represented in this review by the general formula II, except in the discussion of their structure, and the numbering of the substituents is as shown. The salts usually possess a


I   II
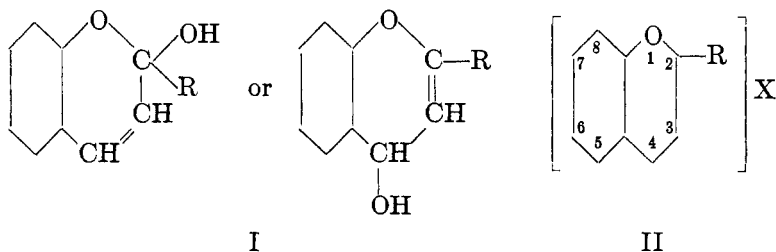
substituent in the 2-position, although unsubstituted salts have been described, as for example, the 3-isopropylbenzopyrylium salts of Decker and Fellenberg (30). When the 2-substituent is a phenyl group the salts are usually referred to as flavylium salts, following the nomenclature of flavones in the chromone series, and Robinson and Walker (103) have recently suggested that, on the same basis, the term "benzopyrylium" should be replaced by "chromylium."

The history of the synthetic salts commences with the conversion by Feuerstein and Kostanecki (40) of salicylidenediacetophenone into 4-phenacylideneflavene, the anhydro base of the 4-phenacylflavylium salts. The first actual salts were prepared by Bulow and Wagner (18), although their existence had been predicted by Hewitt in the previous year (62). Since their discovery these salts have assumed importance owing to, first, the theoretical speculations they have given rise to with respect to their structure and, second, the researches of Willstätter which established their relationship to the natural anthocyanins. The latter has led to a considerable extension of synthetic methods, notably by Robinson and his collaborators. Reviews of the natural products have already been given by Robinson (98, 99, 100), and it is not proposed to deal with them here except insofar as they affect either the synthetic methods for the production of benzopyrylium salts or the problem of their structure.

B. The condensation of diketones (or hydroxymethylene ketones) with reactive phenols

This synthesis was introduced by Bulow and his collaborators in an attempt to prepare representatives of the reduction products of the ketone group in chromones (15, 16, 17, 18, 19). They found that the condensation of 1,3-diketones or of 1,3-aldehydoketones with phenols in the presence of a dehydrating agent led to derivatives of substituted 1,4-benzopyranols. The following scheme represents the course of the reaction between acetylacetone and resorcinol in the presence of hydrogen chloride. Similar compounds were also prepared from phloroglucinol and pyrogallol.
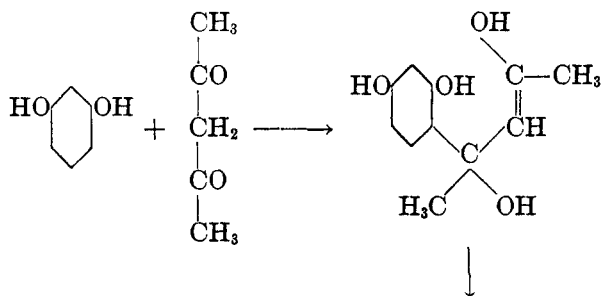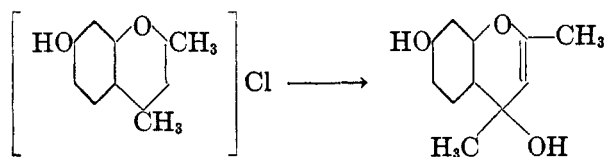
According to Bulow and Wagner (19) the condensation of resorcinol and benzoylacetone in glacial acetic acid solution by means of hydrogen chloride leads to the formation of 4-methyl-7-hydroxyflavylium chloride, which they described as a yellow crystalline solid having one molecule of water of crystallization attached to it. A brownish-yellow, less soluble modification also mentioned was not further investigated. It is apparent that in the case of an unsymmetrical diketone like benzoylacetone two possible products may be formed, namely, 4-methyl-7-hydroxyflavylium chloride and 2-methyl-4-phenyl-7-hydroxybenzopyrylium chloride. Bulow and Wagner established the constitution of their compound by alkaline hydrolysis to acetophenone and resacetophenone. Buck and Heilbron (14), repeating this preparation, found that the product agreeing with that described by Bulow and Wagner contained 0.5 mole of resorcinol so firmly attached that it was not removed by repeated crystallizations. They modified the procedure by replacing the glacial acetic acid by 80 per cent formic acid and thus obtained the salt either anhydrous or containing one mole of water. The difference depended on very small modifications of the procedure. The latter compound, they suggest, may not be a true pyrylium salt but the hydrochloride of the open chain unsaturated ketone (III).
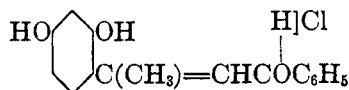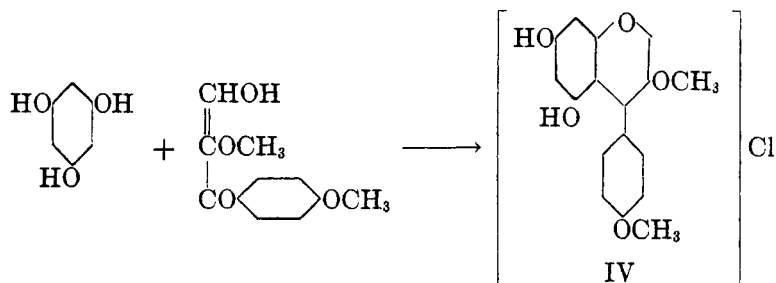

III

In utilizing the reaction for the synthesis of 3,5,7,4'-tetrahydroxyflavylium chloride by the condensation of phloroglucinol and anisyl α-methoxy-β-hydroxyvinyl ketone
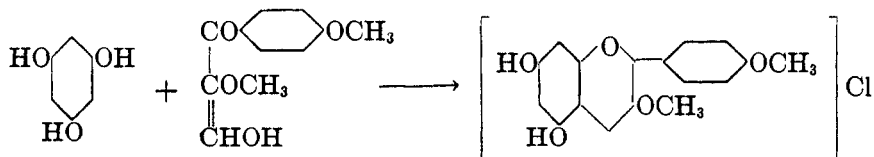
Malkin and Robinson (80) found evidence of what they termed *epi-*

pelargonidin chloride dimethyl ether (IV) formed by condensation as follows.

A further illustration of the caution which must be exercised in the use of this reaction is afforded by a recent paper of Robinson and Walker (102), who found that the condensation of resorcinol and benzoylanisoyl-methane results in the formation of a difficultly separable mixture of salts (V and VI).
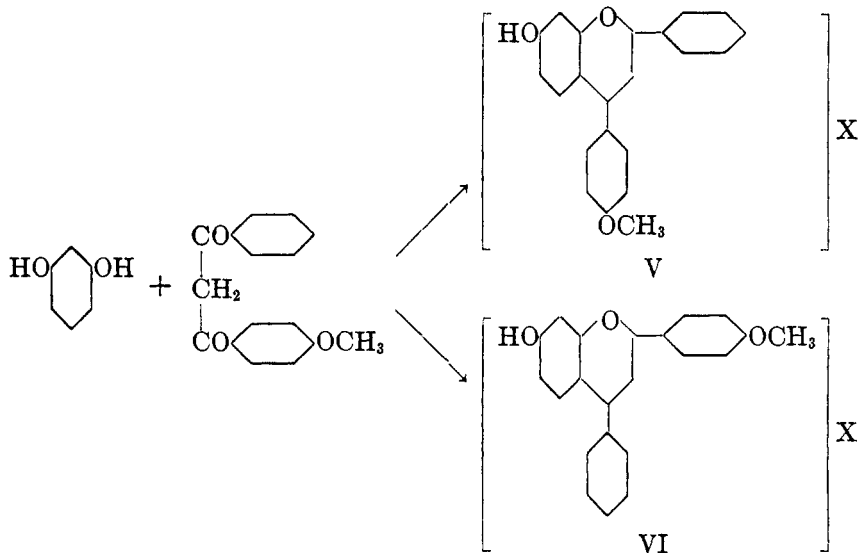
A reaction which may be considered as an extension of Bulow's synthesis was described by Weidel and Wenzel (108). It consists in the condensation of an o-hydroxybenzaldehyde with a reactive phenol under the influence of hydrogen chloride to form a xanthylium salt.
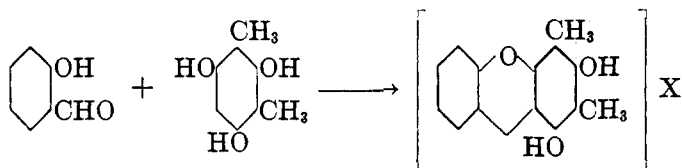
C. The condensation of o-hydroxy aldehydes with ketones

This method for the preparation of benzopyrylium salts was outlined in notes by Decker (26) and Perkin and Robinson (87) and was more fully described in the following years by Decker and Fellenberg (28, 29) and Perkin, Robinson, and Turner (88). It has proved to be one of the most widely used synthetic methods and many modifications of the original synthesis have been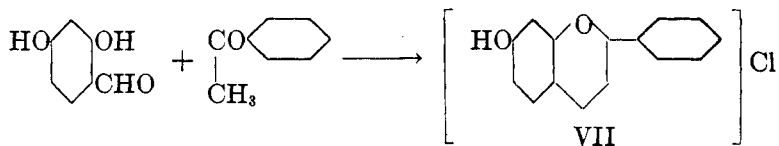 introduced. The reaction is typified by the following scheme of the condensation between resorcylic aldehyde and acetophenone which, in the presence of hydrogen chloride, results in the formation of 7-hydroxyflavylium chloride (VII).

Although it breaks down in the case of the simplest flavylium salt, the reaction is capable of very wide application. Both the aldehyde and the ketone appear to be variable at will. As instances of its wide utility may be cited the preparation of such compounds as 8-methoxy-2,3-indeno(1, 2)benzopyrylium ferrichloride (VIII) (101) and 8-methoxy-β-naphtha-coumarano-(β,α,2,3)benzopyrylium ferrichloride (IX) (95).

VIII   IX
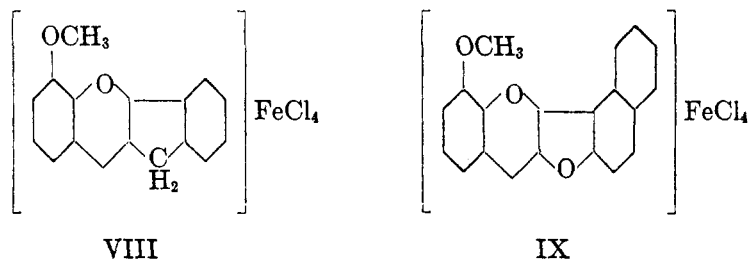
By the employment of ω-substituted acetophenones Robinson and his collaborators have succeeded in preparing numerous 3-substituted flavylium salts related to the naturally occurring anthocyanidins. The vigor of the reaction may be judged from the fact that 7-hydroxy-3,5,4'-tri-

methoxyflavylium chloride (X), which is prepared normally from 2-methyl-phloroglucinaldehyde, may also be obtained by the same procedure from 2,6-dimethylphloroglucinaldehyde, the latter reaction involving the elimination of the o-methyl group.

$$HO\text{-}OH,\ CHO,\ CH_3O\quad +\quad CO\text{-}OCH_3,\ CH_2OCH_3$$

$$HO\text{-}OCH_3,\ CHO,\ CH_3O\quad +\quad CO\text{-}OCH_3,\ CH_2OCH_3$$

$$\left[HO\text{-}O\text{-}OCH_3,\ OCH_3,\ CH_3O \right] Cl \qquad X$$
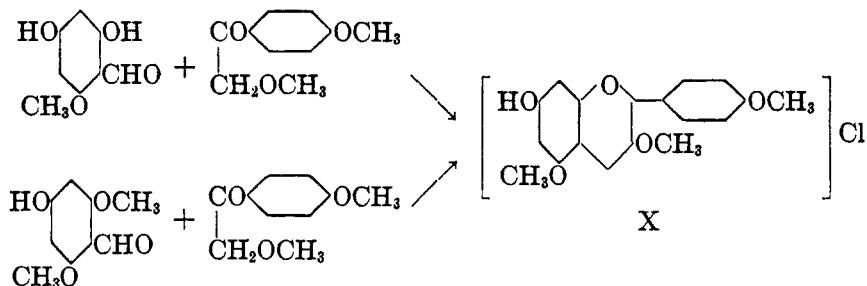
The method is not without its difficulties however. The polyhydroxy-benzaldehydes are not easily condensed, and in their earlier synthetic work Pratt and Robinson (92, 93) used t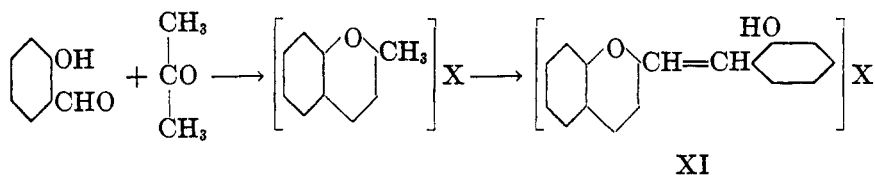he methylated aldehydes and demethylated the subsequent flavylium salts. This procedure had its drawbacks and a search was made for groups that would afford the maximum of protection to the hydroxyl groups combined with the minimum difficulty in their removal. This led to the introduction first of the acetyl derivatives and later of the benzoyl derivatives (see references 95, 96).

A further difficulty arises in the preparation of the 2-methylbenzopy-rylium salts by this method. In this case the desired salt may be accompanied by appreciable quantities of the 2-vinyl derivative (XI) as a result of further condensation between the aldehyde and the reactive 2-methyl group (30, 31, 32, 76).

$$\bigcirc\text{-}OH,\ CHO\quad +\quad CH_3\text{-}CO\text{-}CH_3\quad \longrightarrow\quad \left[\bigcirc\text{-}O\text{-}CH_3\right] X\quad \longrightarrow\quad \left[\bigcirc\text{-}O\text{-}CH=CH\text{-}\bigcirc\text{-}HO\right] X \qquad XI$$

The latter compounds readily pass over into the corresponding *spiro* pyrans (XII) which, in some instances, may form the sole product of the reaction (30, 32, 104).

$$\left[\bigcirc\text{-}O\text{-}CH=CH\text{-}\bigcirc\text{-}HO\right] X\quad \longrightarrow\quad \bigcirc\text{-}O\text{-}O\text{-}\bigcirc \qquad XII$$
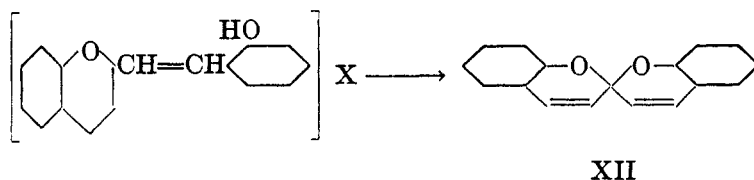
As in the case of Bulow's method the reaction may, when the ketone contains both a methyl and a methylene group, proceed in either of two directions. It has generally been accepted that the former or the latter will be reactive towards aldehydes according to whether the condensation is carried out in alkali or acid (6, 46, 47, 55, 56). Thus a ketone of type CH_3COCH_2R would lead to either 2-methyl-3-R- or 2-R-methylbenzopyrylium salts (XIII and XIV) depending on whether it was condensed directly by acid to the salt or indirectly by alkali through the chalcone (see later).
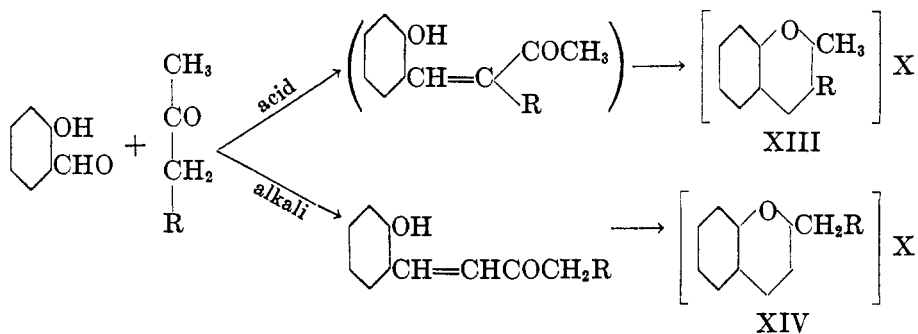

In conformity with this, Decker and Fellenberg (30) prepared 2,3-dimethylbenzopyrylium chloride by direct condensation of methyl ethyl ketone and salicylaldehyde with acid and 2-ethylbenzopyrylium chloride from the same starting materials via the chalcone prepared in alkali.

The generalization cannot be accepted too literally, however, since exceptions to it have been recorded by Stoermer and Wehln (106), Gheorghiu and Arwentiew (45), Lovett and Roberts (78), and Heilbron and Irving (60).

Reference has been made to the preparation of the salts by preliminary condensation of *o*-hydroxy aldehydes and ketones to chalcones which undergo ring closure in the presence of acids. This modification was generalized by Pratt and Robinson (90), and its importance will be apparent from the preceding paragraphs. It provides a method for the isolation in a state of purity of intermediate compounds which can hardly give rise to ambiguous results. Its importance is enhanced by the many solvents which have been suggested for the original condensation with acids. The condensation, which does not invariably proceed smoothly, has often been assisted by a change of solvent. Hence the reaction has been carried out in the absence of solvent, by condensation with concentrated aqueous acids either in the cold or with heating, and in a variety of solvents such as alcohol, ether, glacial acetic acid, formic acid, acetyl
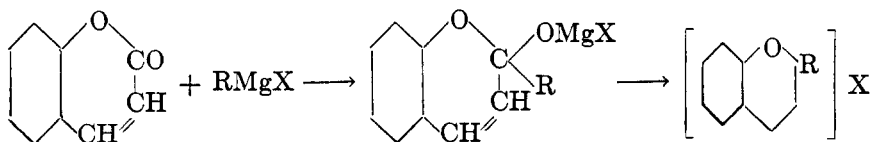
chloride, and ethyl acetate. Of these the most usually employed is glacial acetic acid. The use of some of the others is attended by uncertainties as to the part that they may play in the reaction. Pratt and Robinson (91) found that formic acid, for example, might enter into the condensation, and its use was later generalized for the production of xanthylium salts (57).
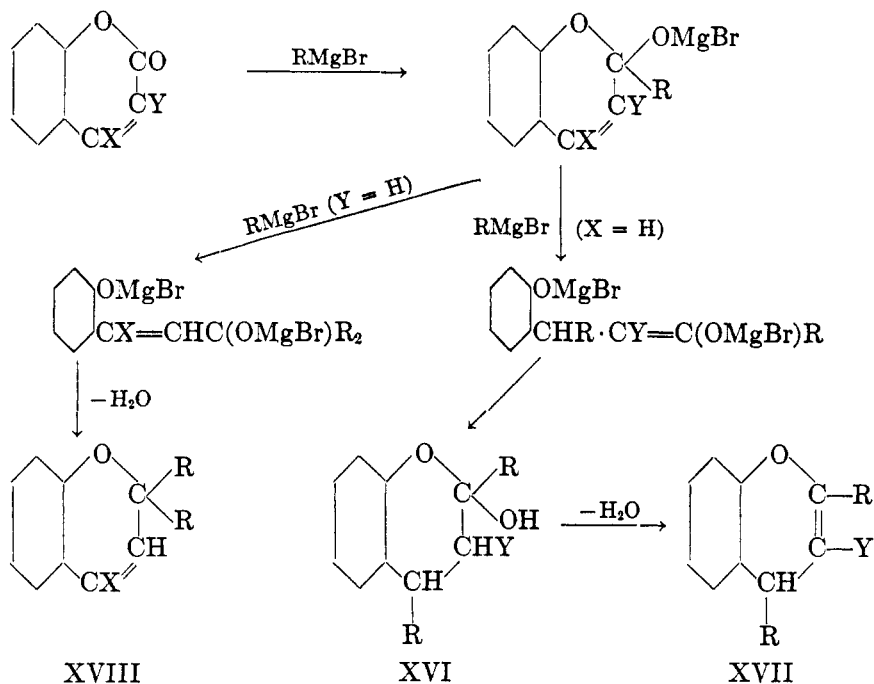
The preparation of the chalcones is often accompanied by the formation of o-hydroxybenzylidenediketones, and by slight modifications of the procedure the latter can be made the principal products of the reaction (23, 31, 40, 64, 69). Since similar benzylidenediketones without an o-hydroxy group can be prepared by the agency of hydrogen chloride (12, 105), it is evident that the condensation of o-hydroxy aldehydes and ketones to give benzopyrylium salts may result in the formation of appreciable quantities of the corresponding diketones. Besides diminishing the yield of the desired product, these compounds are capable of forming 4-phenacyl-flavylium salts (XV), which may contaminate the final product (65). This has actually been shown by Hill and Melhuish (66) to occur in the case of the condensation of salicylaldehyde and p-methoxyacetophenone in ethereal solution, and the formation of such 4-substituted salts as by-products of the direct condensation cannot therefore be overlooked.

XV
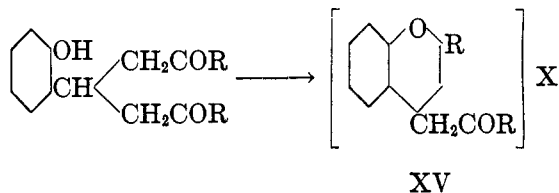
D. The Grignard reaction with benzopyrones

Like the last-described synthesis this procedure was first introduced by Decker (26). Bunzly and Decker (20) had previously found that the action of alkylmagnesium halides on xanthone led to xanthylium salts; the reaction was extended to coumarins and described by Decker and Fellenberg (28, 29) who, by its use, prepared both 2-alkyl- and 2-aryl-benzopyrylium salts. The reaction, generalized in the following scheme, was used by Willstätter for the synthesis of anthocyanidins from 3-methoxycoumarins (113, 114, 115).

In 1926 Heilbron and Zaki (61) published an extension of the reaction to the preparation of 4-substituted benzopyrylium salts by the interaction of phenylmagnesium bromide and 2,3-dimethyl-7-methoxychromone.

A careful study of this reaction has been made by Löwenbein (75) and by Heilbron and Hill (58). According to Houben (68) the interaction of alkylmagnesium halides and coumarin led to the formation of 2,2-dialkyl-Δ^3-chromenes, while phenylmagnesium bromide gave rise to a diphenyl-o-hydroxystyrylcarbinol. Löwenbein showed that the supposed carbinol of Houben was in reality 2,4-diphenylchroman-2-ol, which can be converted easily by the action of glacial acetic acid into 2,4-diphenyl-Δ^2-chromene. He also obtained a 2,2-diphenyl-Δ^3-chromene. Heilbron and Hill then established the conditions under which these compounds were formed. They found that 3-methyl- and 3-phenyl-coumarin both yielded, on treatment with an excess of phenylmagnesium bromide in the hot, the corresponding chromanols (XVI), which were readily dehydrated on heating with glacial acetic acid to the Δ^2-chromenes (XVII). 4-Methyl- and 4-methoxy-coumarins, on the other hand, yielded under the same conditions 2,2-diphenyl-Δ^3-chromenes (XVIII), the constitution of which was established by alkaline hydrolysis. These results led to the conclusion that the primary reaction of the Grignard compound followed a common course, the ultimate formation of Δ^2- or Δ^3-chromenes being influenced solely by the position of the substituent in the pyrone ring.

In none of these reactions were benzopyrylium salts isolated, and it was later shown by Heilbron, Hill, and Walls (59) that their production is dependent on the conditions of the experiment and to some extent at least on the nature as well as the position of the substituents. It is necessary to carry out the reaction in dilute solution at room temperature, and under these conditions 3-substituted coumarins are converted smoothly and in good yields into the corresponding 3-substituted flavylium salts. 4-Substituted coumarins under the same conditions give only small quantities of the desired flavylium salts, much of the coumarin being recovered unchanged. Attempts to increase the yield of flavylium salts by employing more concentrated solutions result only in the formation of diaryl-Δ^3-chromenes without an increase in amount of the monoaryl derivatives. The effect was particularly marked in the cases of 4-methoxy- and 4,7-dimethoxy-coumarins, neither of which could be induced to give a flavyl-

XVIII   XVI   XVII

ium salt. Reaction either failed to occur or, under more drastic conditions, resulted solely in the production of substituted Δ^3-chromenes.

E. The reduction of flavones

In 1914 Everest (39) claimed to have synthesized several anthocyanidins by the reduction of flavones with zinc dust and hydrochloric acid. The experiments were qualitative only and in no instance was the salt isolated, so that the first synthesis of an anthocyanidin must be credited to Willstätter and Mallison (111), who reduced quercetin in methyl alcoholic hydrochloric acid to cyanidin chloride (XIX), using magnesium, zinc dust, or sodium amalgam as the source of hydrogen. The yield was exceedingly small and the product was difficult to isolate.

XIX
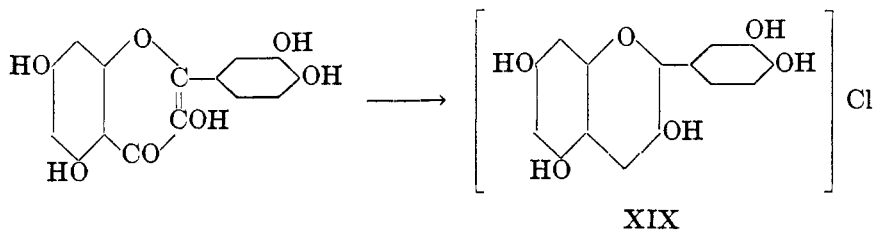
A similar reduction was reported by Robertson and Robinson (97), who acetylated and reduced rhamnetin by zinc dust in boiling acetic anhydride solution. The product of the reaction was hydrolyzed by alcoholic hydrochloric acid with the formation of rhamnetidin chloride. The yield was again poor and other substances were formed as by-products.

The method has been criticized by Malkin and Nierenstein (79) on the ground that the reduction of other ketonic compounds in acid solution leads to the formation of dimolecular products. They repeated the work of Willstätter and Mallison and of Robertson and Robinson, and claimed that the products described by these authors as flavylium chlorides were, respectively, quercetylene chloride (XX) and 7,7-dimethylquercetylene chloride (XXI), formed according to the scheme on page 38.

No such difference of opinion can hold for the alkaline reductions described by Asahina and Inubuse (3, 4) and Asahina, Nakagome, and Inubuse (5). These authors reduced the flavones apigenin and acacetin, and the flavanones naringenin, sakuranetin, hesperitin, eriodictyol, and homoeriodictyol. The reduction was carried out by suspending the flavone or flavanone in water and treating it with sodium amalgam. After the removal of the mercury the products gave with hydrochloric acid the expected flavylium chlorides, e.g., apigenidin chloride from apigenin, acacetinidin chloride from acacetin etc.

They were unable to reduce quercetin itself by this means, although they succeeded in converting pentamethylquercetin into pentamethylcyanidin chloride. The lack of success with quercetin they attributed to the presence of the free pyrone hydroxyl group. To test this they treated rutin (quercetin rhamnoside with the sugar attached to the pyrone hydroxyl) in the same way and obtained a product which after hydrolysis with boiling hydrochloric acid yielded cyanidin chloride.

F. Oxidation reactions

It will be realized from what has gone before that the successful production of benzopyrylium salts depends on the state of oxidation of the pyrone ring. Similar compounds of a higher state of oxidation (e.g., flavones) may be reduced to the correct state, while in the condensation reactions first described, the reactants are already in the right state of oxidation so that only the elimination of the elements of water is necessary. It is apparent that compounds such as chromans are in a lower state of oxidation than the benzopyrylium salts, and it might be anticipated that a number of syntheses should be reported involving the oxidation of such compounds. The procedure has not been systematically investigated to the same extent as the previously described methods, a number of isolated and apparently unrelated syntheses alone being recorded.

XX and XXI
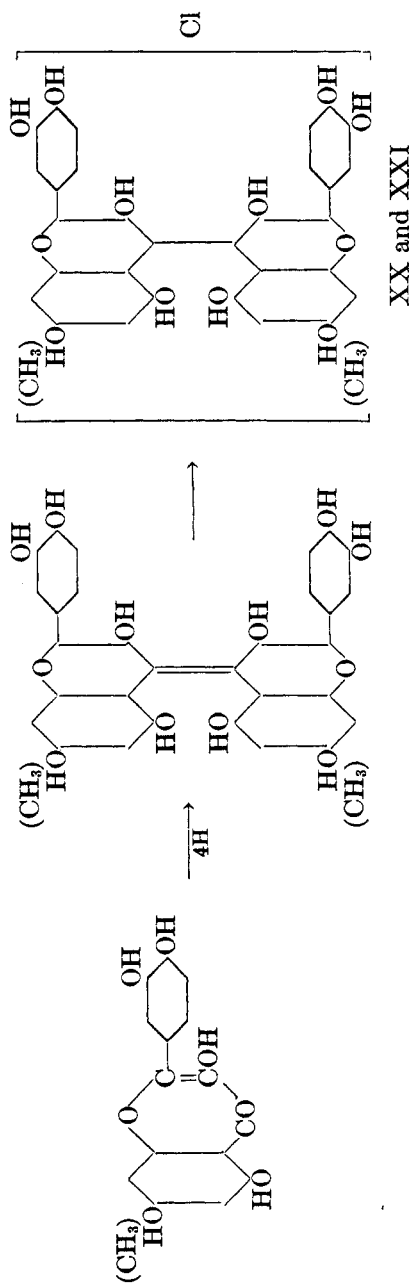
Löwenbein (75) found that the isomeric 2,4-diphenyl-Δ^2- and Δ^3-chromenes could be oxidized by ferric chloride (or phosphorus pentachloride or iodine) in acetic anhydride to the same 4-phenylflavylium salt;
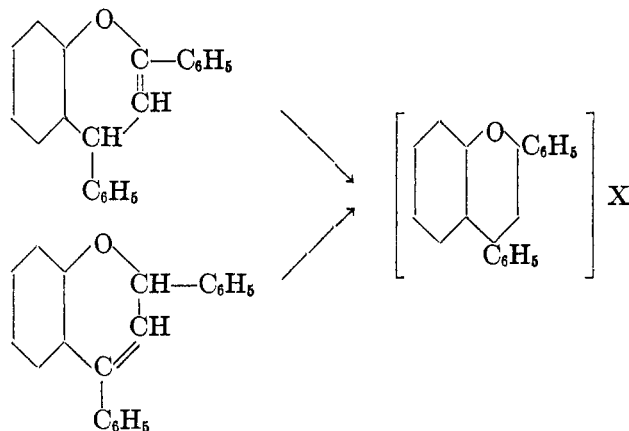

similar oxidations were reported by Löwenbein and Rosenbaum (78). Dilthey (33, 34) has used ferric chloride extensively as an oxidation agent for the preparation of substituted pyrylium salts, and Hill (66), using the same reaction with salicylidenediketones, has found that by slight variations in the conditions, either substituted pyrylium salts or flavylium salts resulted. In the same communication Hill also reported the preparation from 4-phenacylflavenes of flavylium salts and 4-phenacylflavylium salts, both of which were formed by oxidation reactions by a mechanism which is still obscure. The anhydro bases of the latter compounds are formed in 50 per cent yield by the action of glacial acetic acid on the diketones, the remainder of the diketone being converted into dihydrochalcone. In this case, therefore, chalcone acts as the oxidizing agent. Two recent reactions which have resulted in the production of pyrylium salts are of interest in this connection. In the preparation of *sym*-trianisylbenzene by the condensation of *p*-methoxyacetophenone under the influence of a mixture of concentrated sulfuric acid and potassium pyrosulfate, Davis and Armstrong (25) found that a part of the product consisted of a 2,4,6-trianisylpyrylium salt. Similarly, Dovey and Robinson (38) found that acetophenone was converted to 2,4,6-triphenylpyrylium borofluoride in the presence of boron trifluoride. In both of these cases there is a loss of a methyl group, although in neither case could methane or its oxidation products be detected.

Another oxidation reaction in which ferric chloride was used as the oxidizing agent was described by Perkin, Ray, and Robinson (86), who found

that 7-methoxy-3-veratrylidenechromanone (XXII) could be oxidized and condensed by ferric chloride in acetic anhydride to form 6,7-dimethoxy-2,3-[7'-methoxychromano-(4',3')]benzopyrylium ferrichloride (XXIII), the constitution of which was later confirmed by its synthesis in the usual manner from 4,5-dimethoxysalicylaldehyde and 7-methoxychromanone (73).
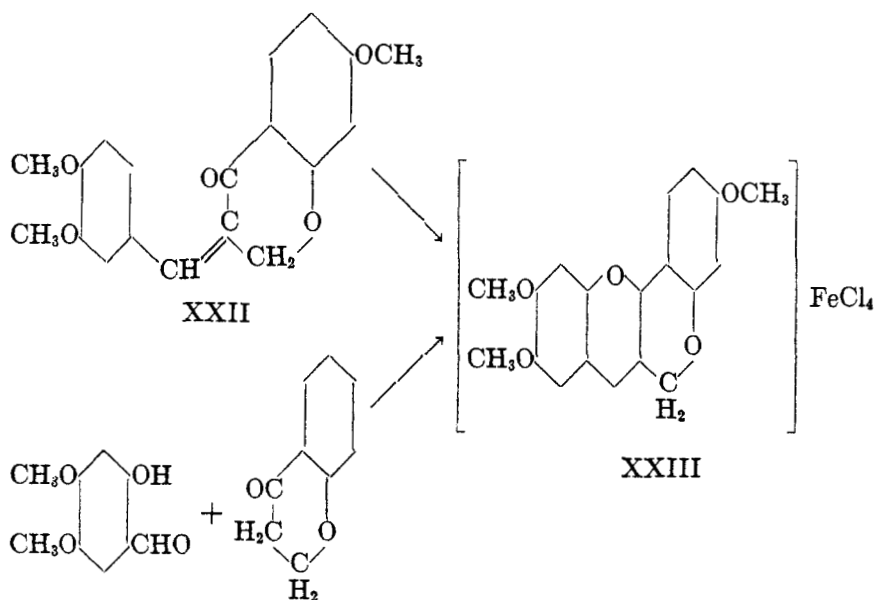

A recent oxidation method which may be regarded as an extension of Bulow's synthesis has been described by Robinson and Walker (102). It involves the condensation of a reactive phenol with an unsaturated aldehyde or ketone in acid solution and in the presence of an oxidizing agent. The particular agent employed was chloranil, and the authors showed that the unsaturated ketone used does not orient itself in both of
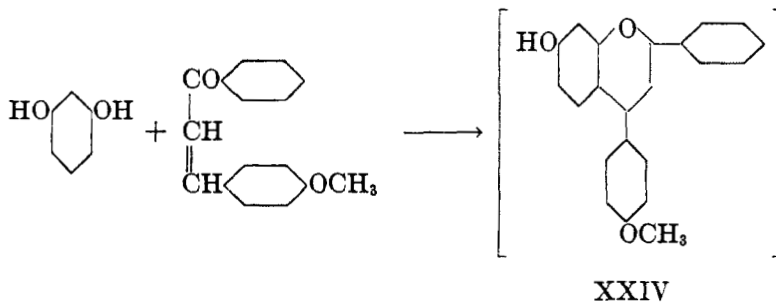
the possible ways but gives one product only. Thus, anisylideneaceto-phenone and resorcinol yielded only 7-hydroxy-4-anisylflavylium chloride (XXIV). In this respect it differs markedly from the Bulow synthesis and should prove a valuable acquisition to the synthetic methods. Its wide applicability was demonstrated by the preparation of many different types of benzopyrylium salts.

Chloranil was also used in conjunction with phosphoryl chloride in an oxidative synthesis described by Miller and Robinson (82). They prepared 2-methyl-5,6-naphtha(1,2)benzopyrylium ferrichloride (XXV) by the ring closure and oxidation of β-(2-hydroxy-1-naphthyl)ethyl methyl ketone followed by conversion into the ferrichloride.

XXV
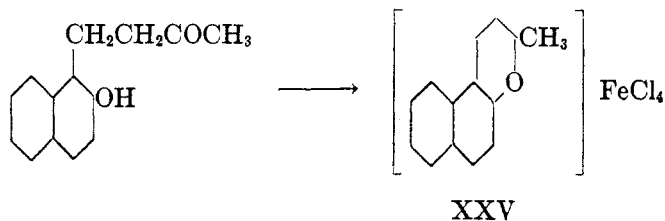
A recent oxidation reaction described by Appel and Robinson (1) converts d-catechin, dissolved in technical dioxane, into a bromocyanidin tetramethylether bromide by means of bromine.

The use of phosphorus oxychloride was advocated by Goswami and Chakravarti (51, 52) for the condensation of phenols and coumarins to form benzopyrylium salts, but their results are not conclusive, the compounds obtained not always agreeing with previously described salts of the same constitution.

II. STRUCTURE

A. Introduction

The skeleton of the benzopyrylium salts as used so far in this review has long been regarded as established. Werner (109) and Decker and Fellenberg (29) both postulated the existence of the oxygen heterocyclic ring on the basis of their analytical results, and the synthetic methods employed have supported this view. Conclusive proof of this skeleton was, however, afforded only recently by the oxidation reactions of Dilthey and Quint (94) and Dilthey and Hoeschen (36), who obtained recognizable degradation products from which no part of the original carbon skeleton had been lost. Thus, 3-methoxyflavylium perchlorate was oxidized by hydrogen peroxide in glacial acetic acid to the benzoate of methyl o-hydroxyphenylacetate (XXVI).

$$\left[\underset{OCH_3}{\overset{O}{\bigbrace}} \right] ClO_4 \xrightarrow{\ H_2O_2\ } \underset{CH_2COOCH_3}{\overset{O \cdot CO \cdot C_6H_5}{\bigbrace}}$$
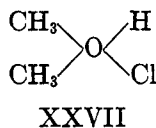
$$XXVI$$
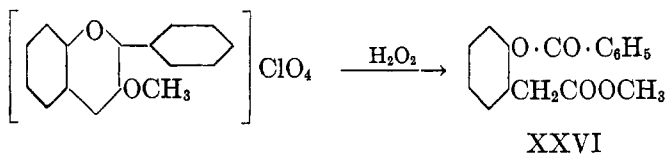
The real interest of the constitution of this group has since rested in the fine structure of the oxygen ring and in the mode of attachment of the acid radical. These two considerations have given rise to much speculation, and a number of different formulas have been proposed for the salts. These fall into three groups depending on whether the anion is regarded as attached to the oxygen (the oxonium theory), to the organic complex as a whole (the centric theories), or to one of the carbons of the oxygen ring (the carbonium and carbenium theories).

B. The oxonium theory

In their first communication on benzopyrylium salts in 1901, Bulow and Wagner (18) considered the compounds to be carbonium salts, but in later papers in the same year they viewed the acid as attached to a quadrivalent oxygen. Werner (109), in the same year, concluded that the xanthylium salts which he had prepared by reducing xanthones with zinc dust and alcoholic alkali and subsequent treatment of the resulting xanthydrols with acids, were anhydro compounds with the anion attached to the oxygen of the heterocyclic ring.

The possible quadrivalence of oxygen was suggested as early as 1864 by Naquet (83, 84), but it was not until 1875 that Friedel (43, 44) obtained a methyl ether hydrochloride to which the following constitution

$$\underset{CH_3}{\overset{CH_3}{\diagdown}} O \underset{Cl}{\overset{H}{\diagup}}$$

$$XXVII$$

(XXVII) was given. Heyes, in 1888, in order to explain the differences between certain inorganic peroxides, suggested that oxygen might have a valency greater than two (63). In the same year Meldola (81) suggested that the oxygen atom in the azo-β-naphthols might be quadrivalent, and in 1897 Bruhl (13) advocated the quadrivalence of oxygen in hydrogen peroxide. In the meantime compounds of organic substances and acids had been prepared by Baeyer (7), Dale and Schorlemmer (24), Wallach and Gildemeister (107), and Perkin (85). All these authors explained their results on the basis of the accepted valency theory, but in 1899 Collie and Tickle (22) published a paper on the salts of dimethylpyrone and

quadrivalent oxygen, in which they rejected formulas **XXVIII** and **XXIX** in favor of a formula (**XXX**) resembling that for dimethylpyridone
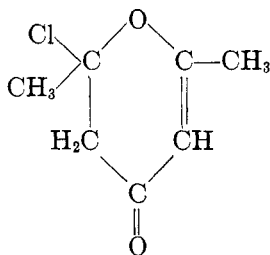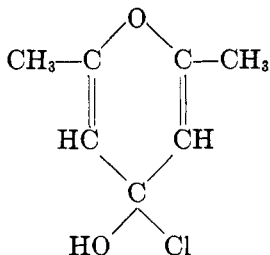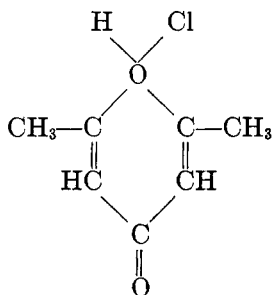

XXVIII   and   XXIX
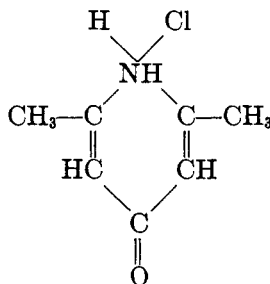
hydrochloride (**XXXI**).   Their views were strengthened by the fact that


XXX   XXXI

the salts were highly colored, and the new formula allowed the adoption of a quinonoid structure in line with the theory of color just then coming into prominence.   In their view the third and fourth bonds of the oxygen would be very weak, but according to Baeyer and Villiger this is not necessarily true (9, 10, 11).   In the year following Collie and Tickle (22), Hewitt (62) extended their views to account for the fluorescence of some compounds in acid solution and suggested that diphenylpyrone should be represented either by the quinonoidal quadrivalent oxygen compound (**XXXII**) or by the symmetrical oxonium compounds (**XXXIII** and **XXXIV**).

The xanthonium salts of Werner (109) and the benzopyrylium salts of Bulow and Sicherer (16) were therefore represented by formulas **XXXV** and **XXXVI**, respectively, and the latter, by simple loss of the elements of water, is readily obtained as the true anhydro oxonium salt corresponding to formula **XXXV**.

XXXIII   XXXII   XXXIV

XXXV   XXXVI
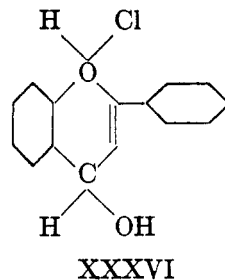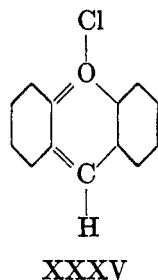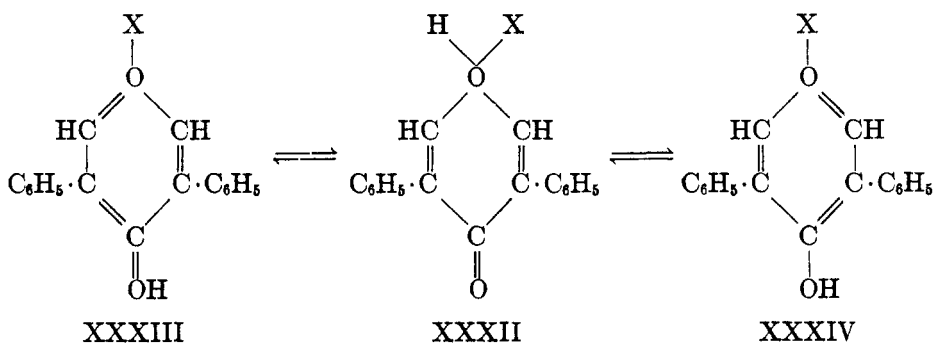
Decker and Fellenberg (28) commenced their investigations on the basis of the oxonium theory, and maintained that the success of their researches was in itself good evidence for the correctness of the theory. As a further point in favor of the oxonium structure they adduced the gradation of stability which they reported finding in the xanthylium, benzopyrylium, and pyrylium salts, which, according to their views based on the series acridine, quinoline, pyridine, was in the expected direction. Their salts were therefore formulated as true oxonium salts. The arguments were expanded in later papers (29, 30, 27), in which they contended that no previous work would explain the basic nature of the compounds without calling in the oxonium theory except the salts of triphenylcarbinol, and these were dismissed from the argument on the ground of the incomparable differences of basicity between the two series.
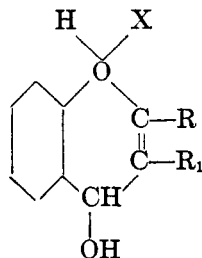
Perkin, Robinson, and Turner (88) retained the quadrivalent oxygen and formulated their salts as pyranol salts of the following constitution, although they were well aware that the water molecule might be present as water of crystallization, in which case the compounds would be, in reality, anhydro salts possessing the oxonium structure.
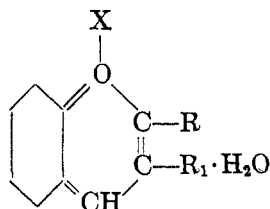

The evidence for or against the anhydro view was not at that time considered conclusive, although the double salts formed with ferric chloride were found to be anhydrous, as Werner had previously found for the xanthylium salts. On the whole, the evidence favored the anhydro formulation and the structure advocated by Decker and Fellenberg was modified, as shown, to include an o-quinonoid structure accounting for the deep color of the salts. Willstätter and Mallison (112), who considered both formulas and also a p-quinonoid formula, finally adopted the o-quinonoid formula of Perkin, Robinson, and Turner, as did also Dilthey (33) for the substituted pyrylium salts.

Fosse (41, 42) utilized the idea of a quadrivalent oxygen in a somewhat different form, and gave the following structure to the dinaphthopyrylium salts which he prepared.
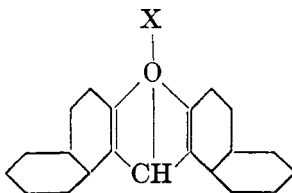

Werner, who first described his xanthylium salts as oxonium compounds (109), later modified his views to a rather similar formula (110) in which the oxygen and the bridge carbon atom were linked by a partial valency with the acid attached in a second sphere; an extension of this has been made by Burawoy (21) to the pyrylium salts by combining the linkage of the oxygen and the 4-carbon atom by a partial valency and uniting the acid radical in an ionized form to the whole positive complex (XXXVII) in the manner developed as described later.
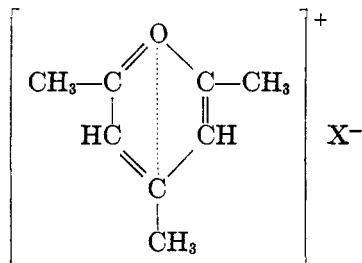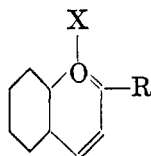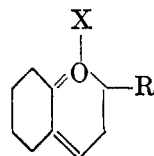
XXXVII

C. The centric theories

Of the formulas utilizing the quadrivalent oxygen so far described, that of Perkin, Robinson, and Turner (XL) is the most satisfactory.
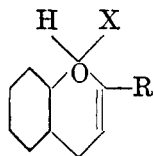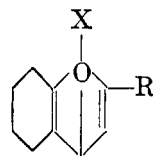

XXXVIII   XXXIX   XL   XLI

The oxonium theory as a whole, however, possesses certain disadvantages. Although the quadrivalency of oxygen may be defended on the basis of the electronic theory of valency, it cannot be regarded as acceptably proved, and it involves, moreover, the consideration that, contrary to its usual state, the oxygen of the pyrone ring is positively charged. Definite evidence on this point in the actual case of a benzopyrylium salt has been afforded by Le Fevre (74), who nitrated flavylium perchlorate and found the resulting compound to be a *m*-nitro derivative. It follows that the oxygen, which is meta-directing, is in the same state as in benzaldehyde and acetophenone. The consideration of Archibald and McIntosh (2) that the third and fourth valencies are amphoteric, being slightly positive as well as slightly negative, cannot be held to be effective in this case, since the acid medium in which the reaction was carried out would stabilize the salt and oxygen would therefore be, on the oxonium theory, positive.

Oxonium salts were regarded by Collie and Tickle as derivatives of a hypothetical oxonium hydroxide, OH_3OH, and by Decker and Fellenberg of a substituted base $R_1R_2R_3 : O \cdot OH$, but the pyranols derived from benzopyrylium salts have never been formulated as oxonium compounds and their formation has therefore always presupposed a rearrangement of valencies to permit the hydroxyl group to be attached to either the 2- or

the 4-carbon atom. The fact that Kehrmann and Bohn (71, 72) have found extremely strong bases to exist in the xanthylium series indicates that such a rearrangement does not occur, but that the acid radical and the basic hydroxyl are located in the same place in the molecule, either attached to the oxygen or at some other point.

In more recent years Löwenbein (75), Löwenbein and Rosenbaum (78), and Popper (89) have investigated the action of the Grignard reagent on benzopyrylium salts and have found that there is a simple interchange between the phenyl group of phenylmagnesium bromide and the anion of the salt, with addition of the phenyl group sometimes to the 2- and sometimes to the 4-carbon atom. Such a reaction is difficult to explain by the oxonium theory for, as Löwenbein says "Bemerkenswert ist, dass bei dieser Austauchreaktion die Phenylgruppe den Platz am 4-C-Atom einnimmt, obgleich der Oxonium-Formulierung nach diesem Kohlenstoffatom keine besondere Funktion bei der Salzbildung zukommt."

The difficulties above were evaded, though not explained, by the adoption of the centric formula of Hantzsch (53, 54), in which the anion is placed in a second, ionizable sphere and regarded as attached to the cation complex as a whole. To indicate this the unused valencies are turned inwards, the oxygen still being considered quadrivalent. He distinguished between true and pseudo salts in the pyrylium series and formulated them respectively as follows.


true   pseudo
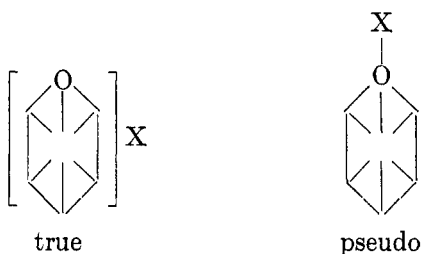
A similar formula was employed by Löwenbein (75).

The centric formula forms a link between the oxonium formula and the carbonium and carbenium formulas, since it may be applied to either. Dilthey, for example, favored for a time a type of centric carbonium formula (35) in which the acid radical was attached to the whole cationoid complex. He advanced arguments against the oxonium theory and based his formula upon the work of Kauffmann (70). The acid radical was again supposed to exist in a second sphere, and the unsaturated valencies of the carbon atoms were turned inwards, as in Hantzsch's formula, to indicate that it was not known which of the carbon atoms was involved in the linkage and to facilitate the migration of the hydroxyl of the pseudo base.

D. The carbonium and carbenium theories

It has already been remarked that Bulow and Wagner (18) formulated their salts at first as carbonium compounds. Werner also modified his original views that they were oxonium salts, and Baeyer (8) extended the modification and formulated the xanthylium salts as carbonium compounds (XLII), in which carbon atom 9 and the acid radical were linked by an ionizable valency. Gomberg and Cone (48, 49) and Gomberg and West (50) expressed both the xanthylium and the benzopyrylium salts as "quino-carbonium" compounds (XLIII).
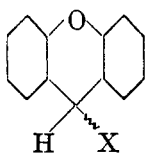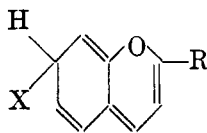

XLII   XLIII

The carbonium formula first proposed by Dilthey (35) did not attempt to define the point of attachment of the acid radical, and in an effort to establish this Quint and Dilthey (94) oxidized xanthylium salts by perhydrol in acid or neutral solution. Oxidation commenced at the heteropolar atom with the formation of a peroxide, and by this means they established that in these salts the *meso*-carbon atom was the heteropolar atom. When the same reaction was applied by Dilthey and Quint (37) and Dilthey and Hoeschen (36) to 3-substituted flavylium salts, the peroxide first formed


XLIV
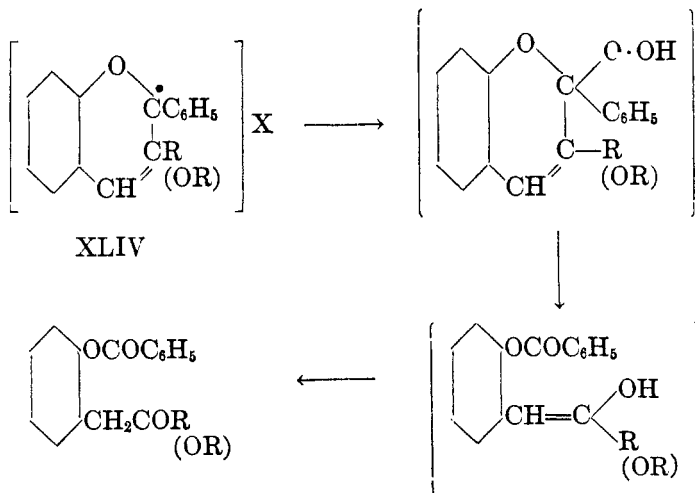
proved to be unstable, and oxidation proceeded further with the formation of benzoyl esters of o-hydroxybenzyl ketones (or o-hydroxyphenylacetic acid) according to the scheme on page 48, which shows conclusively that the 2-carbon atom is the heteropolar atom and that a double bond occurs in the 3,4-position. Had the 4-carbon atom, for example, been the heteropolar atom, the oxidation must have produced flavones.

XLV
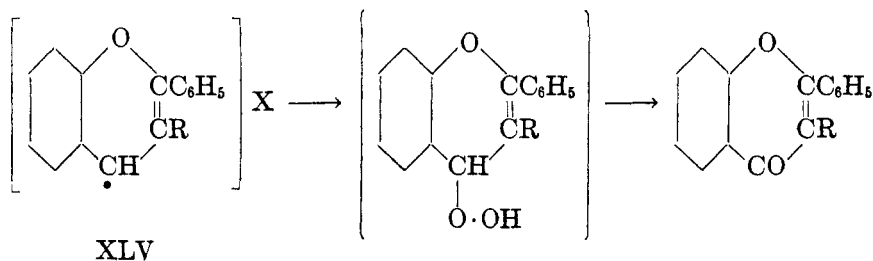
On the basis of these results Dilthey and his collaborators introduced a carbenium formula for the benzopyrylium salts. According to this the anion is linked to the pyrone ring at an ionized coördinatively unsaturated carbon atom, the heteropolar atom being indicated by a point as in formulas XLIV and XLV. The complete absence of flavones in their experiments led Dilthey and Hoeschen (36) to conclude that, when localizable, the heteropolar atom in flavylium salts is the 2-carbon atom.

It was suggested by Hill (65), as a result of experiments with salicylidenediacetophenones and 4-phenacylflavenes, that in some instances the 4-carbon atom might also act as a heteropolar atom. This view receives support from many indications in previous work. Thus, the first benzopyrylium salts prepared by Bulow and Wagner (18) were the 2,4-dimethyl derivatives which yielded, instead of the normal pyranols, 2-methyl-4-methyleneflavenes. In the same connection, Löwenbein and Rosenbaum (78) prepared bis-chromenyls containing a benzyl group in the 4-position (XLVI), which readily underwent a disproportionation with the formation of 4-benzylideneflavenes (XLVII).

A similar unsaturated compound was described by Ziegler and Ochs (116) by the interaction of xanthone and diphenylvinylmagnesium bromide. The resulting compound was not the expected 9-diphenylvinyl-xanthenol (XLIX), but its dehydration product (L). All these unsaturated compounds spontaneously add acids with the formation of benzopyrylium or xanthylium salts (XLVIII or LI). The reaction between the Grignard compound and benzopyrylium salts whereby addition sometimes occurs at the 2-carbon atom and sometimes at the 4-carbon atom has already been commented upon (75, 78, 89).

XLVI → XLVII + (structure)

XLVIII

XLIX → L → LI
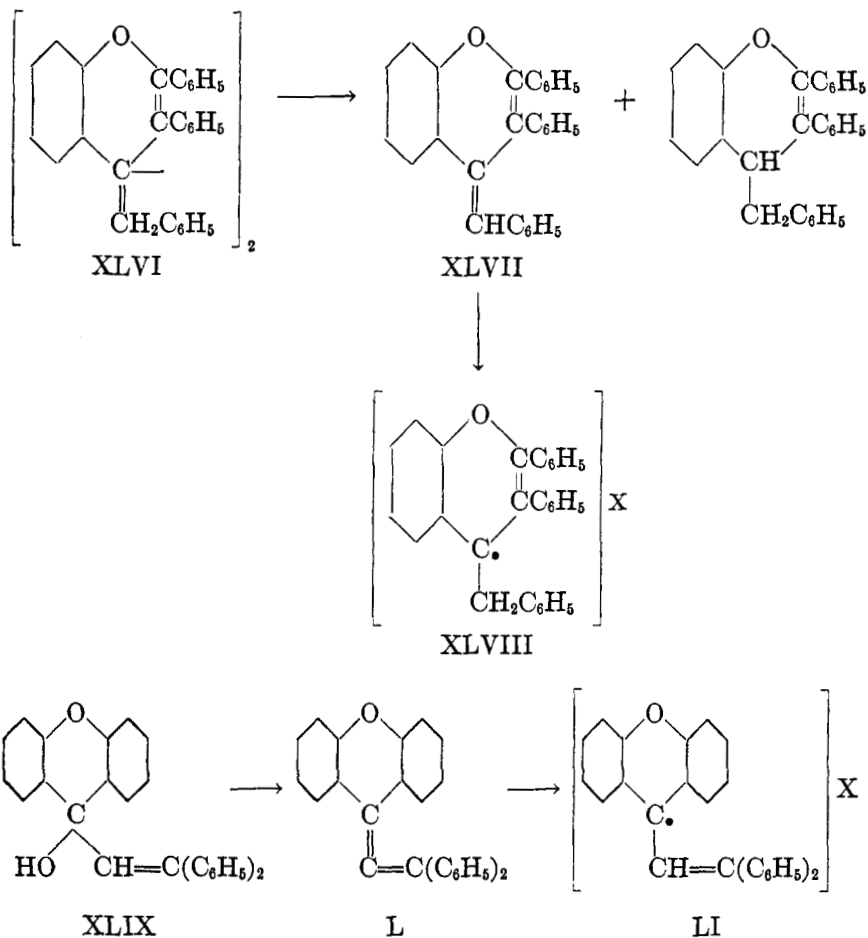
There is therefore considerable indirect evidence for assuming that the 4-carbon atom may be the heteropolar atom under conditions which have not so far been investigated. The strongest evidence for this would be the production of flavones. A recent investigation by Hill and Melhuish (67) has established the formation of two distinct types of flavylium salt, which give rise to two series of pyranols, and one of these has been converted into the corresponding flavones. Treatment of 3-substituted flavylium salts with sodium carbonate or sodium hydroxide at room temperature led to the production of pyranols only, but when the same procedure was applied to flavylium salts unsubstituted in position 3, a mixture of products was obtained from which the corresponding chalcones (LIII) and flavones (LIV) were isolated in each case. The explanation of this difference in behavior lies in the properties of the pyranols derived

from the two series of salts. The pyranols derived from flavylium salts unsubstituted in position 3 are unstable and can only be isolated as their ethyl ethers. Even these ethers are comparatively unstable and are converted by simple heating in aqueous alcohol into their respective chalcones. The pyranols from 3-substituted flavylium salts, on the other hand, are stable and can be isolated in the free state. Neither they nor their ethyl ethers are converted into chalcones by aqueous alcohol.

The formation of flavones from salts unsubstituted in position 3 is sufficient evidence that they are flavylium-4-chlorides (LII), and the instability of their pyranols leads to the following scheme of the changes involved.
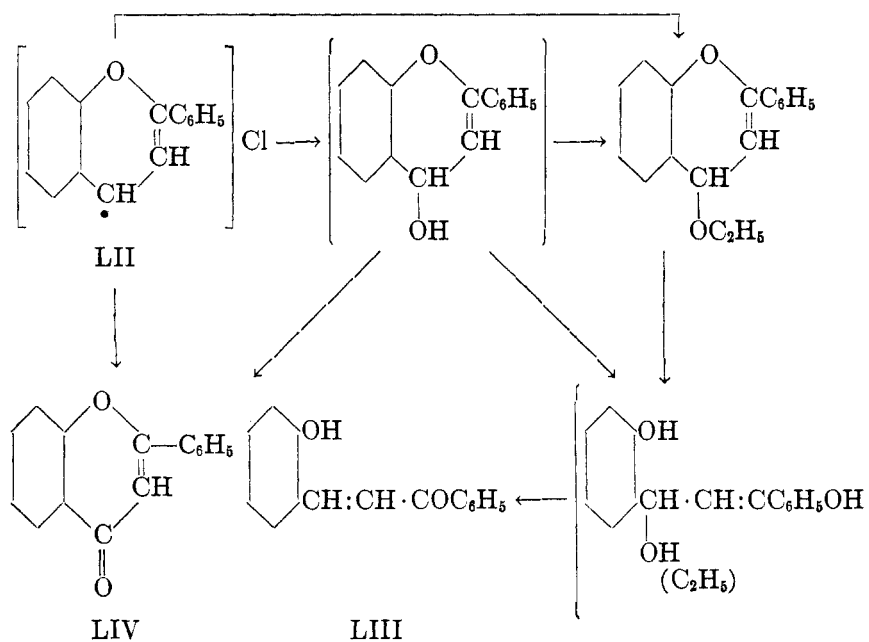
The salts from which stable pyranols were obtained are those which Dilthey and his collaborators have already shown to be flavylium-2-chlorides, and they obviously cannot undergo the reactions outlined above. The fundamental difference exhibited between the two series of pyranols must be reflected in the salts from which they are obtained and this difference is best formulated on the basis of the carbenium theory.

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