AROMATIC CYCLODEHYDRATION

CHARLES K. BRADSHER

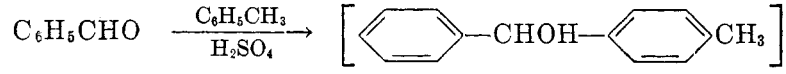
Department of Chemistry, Duke University, Durham, North Carolina

Received August 27, 1945

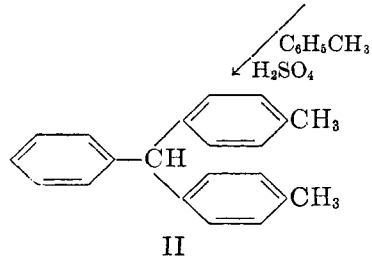
CONTENTS

I. INTRODUCTION

It is well known that the carbonyl groups of aldehydes and, much more rarely, ketones in the presence of acid catalysts may condense with reactive aromatic nuclei. If the condensation is intermolecular in character, the carbonyl oxygen is usually replaced by two such nuclei. Evidently, the first step in this reaction is, in effect, the addition of an aromatic nucleus to a carbonyl linkage and is followed by further reaction with the resulting carbinol. This may be exemplified by the condensation of benzaldehyde with toluene in the presence of sulfuric acid to yield di(*p*-tolyl)phenylmethane (II) (101), the probable intermediate being 4-methylbenzohydrol (I).



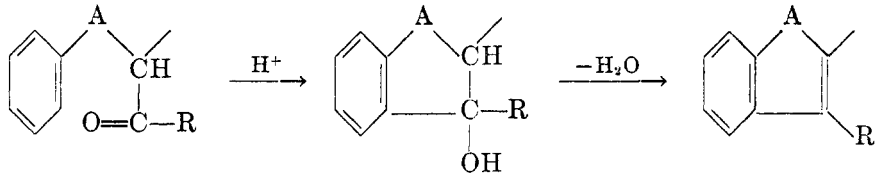
I



II

If the condensation is intramolecular, as illustrated by the general equation below, the cyclic carbinol (IV) first formed usually undergoes dehydration with

General equation



III IV V

(R = alkyl, aryl, or H; A = —C=C—, —O—, —S—, —NH—, —N=C—, —C=N—)

the establishment of a new double bond. If the other component of the new ring is such that it will not stabilize this double bond (e.g., V, A = —CH_2—), the newly formed compound will be prone to undergo further change in the presence of the cyclizing agent. If, on the other hand, the other component is capable of stabilizing the newly created double bond by resonance (e.g., V, A = —CH=CH—), to that extent the new compound will be resistant to further attack and can be said to have aromatic character. This second class of cyclization has been designated as aromatic cyclodehydration (44) and forms the subject of the present review.

In confining this discussion to this second class of cyclizations, we do not seek to imply any difference in mechanism, but rather to correlate and evaluate a general type of cyclization which, in carbocyclic systems at least, is almost unique in its ability to afford a new, fully aromatic ring without resort to dehydrogenation.

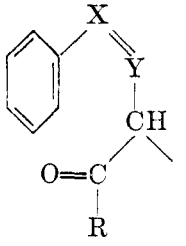
While cyclodehydrations of the aromatic type were applied in the synthesis of many heterocyclic derivatives as early as the end of the last century, it was not until 1935 that its systematic application in the carbocyclic system was initiated by Haworth and Sheldrick (87), working in the naphthalene series. Its use in the phenanthrene (38) and anthracene (11, 27) series is an even more recent development.

This review has been prepared in the hope that correlation and evaluation of the known examples of aromatic cyclodehydration may point the way to further applications of this interesting type of reaction.

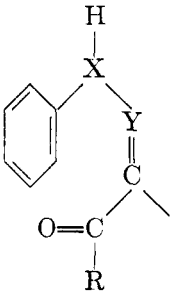
The cyclizations to be considered have been divided into bicyclic and tricyclic, depending on the nature of the final product. Heterocyclic systems have been arranged to follow their carbocyclic counterparts.

Although it has been stated that all of the cyclization products which will be considered possess aromatic character, some are much less resistant to the attack of acid than are others. An example is benzofuran which, because of its tendency to polymerize in acid solution, corresponds more nearly to indene than to naphthalene.

In those cases in which the new ring is to have six members, it is not necessary that the original double bond have the position shown in formula VI. It may be conjugated instead with the carbonyl group (VII). This latter is undoubtedly the structure of the intermediate in the anthracene and acridine syntheses and



VI



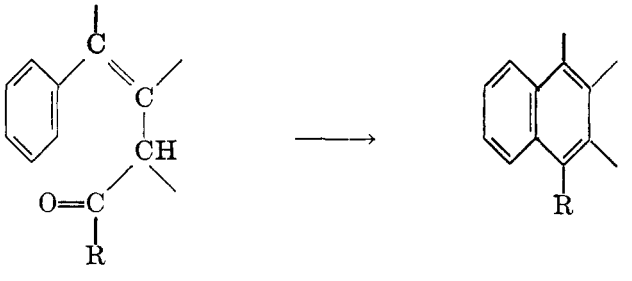
VII

may be as well that involved in the quinoline synthesis. Under such circumstances, the dehydration of the carbinol intermediate is transannullar in character, but in no other way does it differ essentially from the general reaction already discussed. A more complete treatment of this aspect will be found in the section on mechanism.

II. BICYCLIC SYSTEMS

A. Naphthalene system

From the general equation it might be predicted that the cyclization of β-styrylacetaldehyde or β-styrylmethyl ketones (I, R = H, alkyl, or aryl) would yield naphthalene derivatives (II). In actual practice, it will be found that rather severe limitations are put on this cyclization by the presence of a



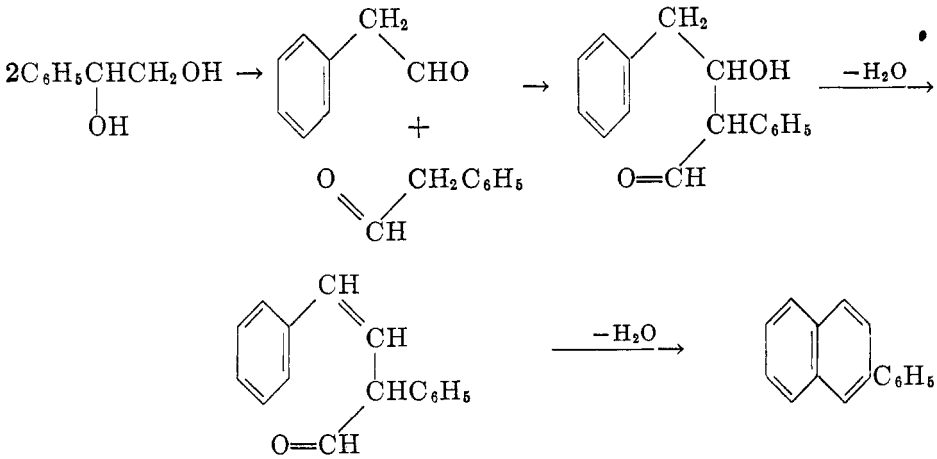
I II

(R = H, alkyl, or aryl)

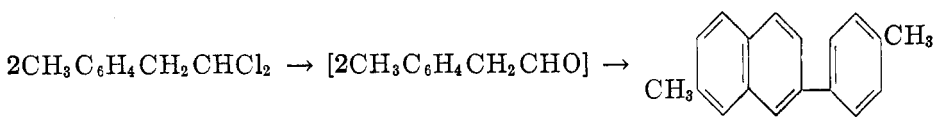
double bond as well as a reactive methylene group, both of which may be affected under conditions employed in the cyclization. An additional complication rising out of the presence of the double bond is the possibility of geometric isomerism, an important factor when only one of the two forms could be expected

to cyclize. Despite these limitations, several instances of the naphthalene type of cyclization have been observed.

Perhaps the first case of aromatic cyclodehydration was encountered in 1884, when Zincke and Breuer (153) observed that phenylglycol or phenylacetaldehyde, in the presence of boiling 50 per cent sulfuric acid, yielded a hydrocarbon which was shown (154) to be β-phenylnaphthalene. Zincke assumed, in the case of the phenylethylene glycol, that the reactions involved are dehydration to phenylacetaldehyde followed by aldol condensation of two molecules of phenylacetaldehyde, dehydration, and finally cyclization.

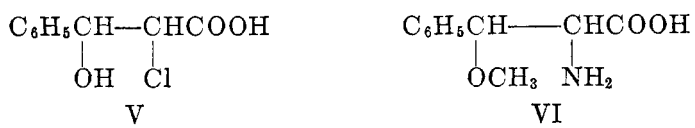


Similarly, a homolog (IV) of β-phenylnaphthalene was produced by von Auwers and Keil (2, 3) by the hydrolysis of *p*-methyl(β,β-dichloroethyl)benzene (III).



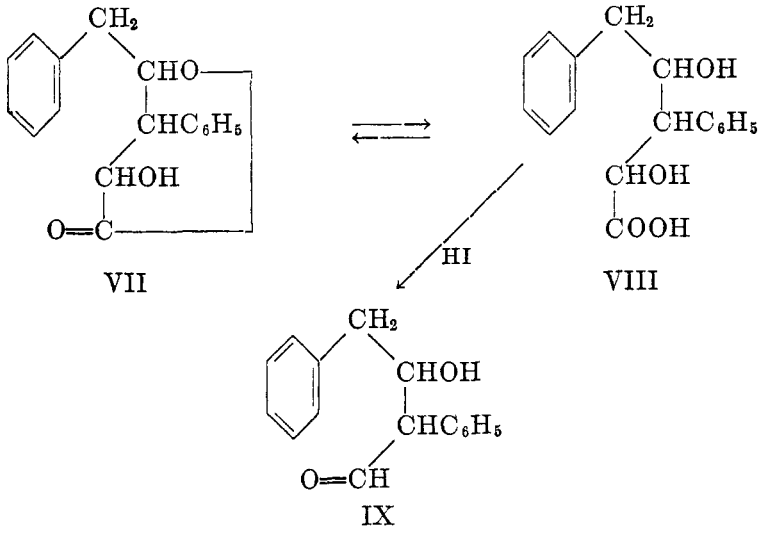
III IV

The formation of β-phenylnaphthalene appears characteristic of all compounds which yield phenylacetaldehyde when refluxed with boiling mineral acids. These include, in addition to phenylethylene glycol, β-phenyl-β-hydroxyethylamine (55), α-chloro-β-hydroxy-β-phenylpropionic acid (V) (3), phenylserine (20a) and its methyl ether (VI) (55). Späth (134) proposed that the conversion of the γ-lactone (VII) of α-hydroxy-β-phenyl-γ-hydroxy-δ-phenyl-



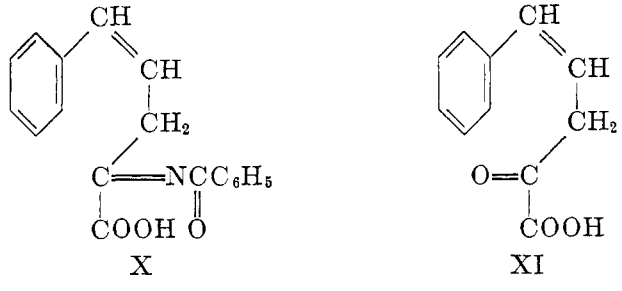
V VI

valeric acid to β-phenylnaphthalene might likewise involve fission into molecules of phenylacetaldehyde, followed by recombination.

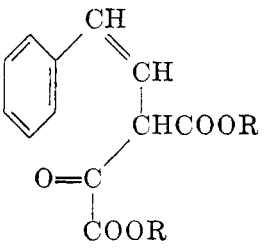


An equally plausible explanation is that the α-hydroxy acid (VIII) merely loses carbon monoxide and water, yielding the hydroxyaldehyde (IX) which is the first intermediate proposed in the Zincke mechanism for phenylacetaldehyde cyclization.

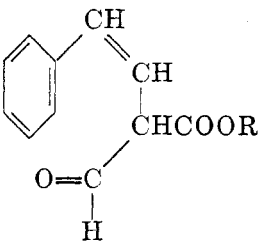
Erlenmeyer and coworkers (62, 63) observed that the α-benzimino-β-(β-styryl)propionic acid (X), upon hydrolysis with hydrochloric acid at 120°C., gave a mixture of naphthalene and α-naphthoic acid. These authors postulated (β-styryl)pyruvic acid (XI) as an intermediate.



The first recorded attempts to prepare a naphthalene derivative directly by cyclization of an unsaturated aldehyde or ketone were made by von Auwers and Möller (5). The condensation products of ethyl oxalate (XII) or ethyl formate (XIII) with ethyl (β-styryl)acetate resisted all attempts at cyclization using sulfuric acid or phosphorus pentoxide. von Auwers and Möller postulated that XII was in the *trans* configuration and showed that XIII polymerized rapidly under the conditions used in the attempted cyclization.

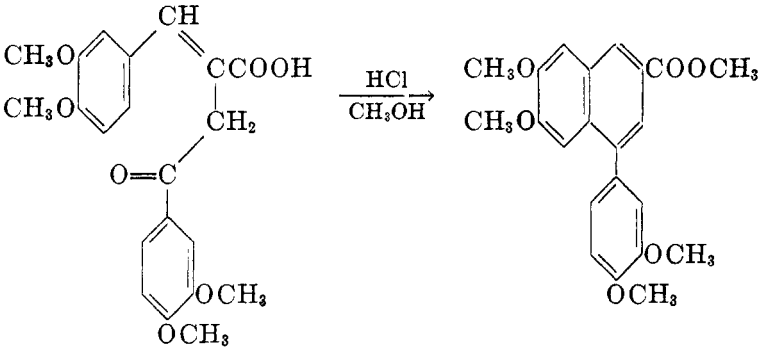


XII



XIII

It remained for Haworth and his students to provide the first clear-cut case of the cyclization of a β-styryl ketone and to make important application of this reaction to the synthesis of phenolic resin derivatives. Haworth and Sheldrick (87) observed that when β-3,4-dimethoxybenzoyl-α-(3′,4′-dimethoxybenzylidene)propionic acid (XIV) was refluxed for 4 hr. with a methyl alcohol solution of hydrogen chloride, the methyl ester (XV) of 6,7-dimethoxy-1-(3′,4′-dimethoxyphenyl)naphthalene-3-carboxylic acid was obtained. When



XIV XV

the lactone of XIV was allowed to stand in a chloroform solution containing iodine, the acid corresponding to XV was obtained.

This type of reaction was reported a little later by Howell and Robertson (92) and finally, Ohmaki (119) made a thorough study of the effect of substituents on the ease of cyclization in such systems. A summary of the results of all these authors is to be found in table 1.

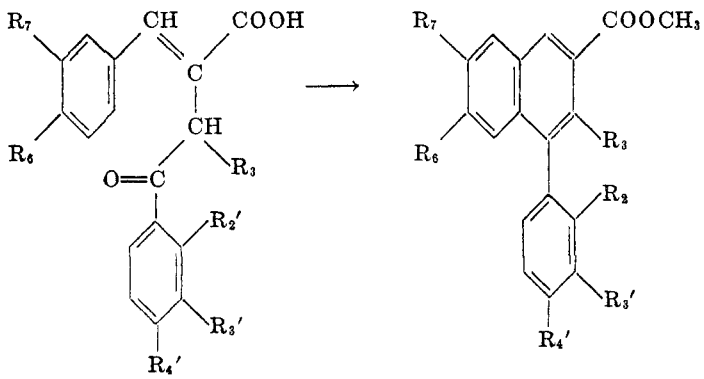
Ohmaki concluded that there must be a hydroxyl or alkoxyl group para to the point at which cyclization is to take place or, in other words, R_7 must be a hydroxyl, alkoxyl, or a terminus of a methylenedioxy group. The ease of cyclization did not appear to be influenced by the nature of the substituents ($R_{2'}$, $R_{3'}$, and $R_{4'}$) in the ring attached to the carbonyl group.

Of the groups capable of activating cyclization, the hydroxyl (R_7 = OH) was the most potent. The α-(*m*-hydroxybenzal)-β-anisylpropionic acid (XVII) as

a consequence could not be prepared from its lactone (XVI), for cyclization took place spontaneously, yielding the α-phenylnaphthalene derivative (XVIII).

TABLE 1

Cyclization experiments with α-benzal-β-benzoylpropionic acids



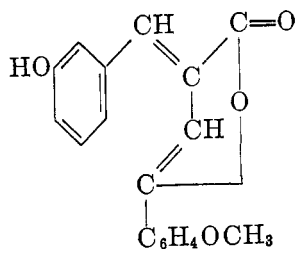
Cyclized

R_3	R_6	R_7	R_2'	R_3'	R_4'	REFERENCES
H	OCH_3	OCH_3	H	H	H	(92, 119)
H	—O—CH_2—O—		H	H	H	(119)
H	OH	OCH_3	H	H	OCH_3	(119)
H	—O—CH_2—O—		H	H	OCH_3	(119)
H	H	OH	H	H	OCH_3	(119)
H	OH	OCH_3	H	OCH_3	OCH_3	(119)
H	OCH_3	OCH_3	H	OCH_3	OCH_3	(87, 119)
CH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	(88)
H	OC_2H_5	OCH_3	H	OCH_3	OCH_3	(119)
H	—O—CH_2—O—		H	OCH_3	OCH_3	(119)
H	OH	OCH_3	OCH_3	H	OCH_3	(119)
H	—O—CH_2—O—		OCH_3	H	OCH_3	(119)

Failed to cyclize
(R_3 and R_2' = H)

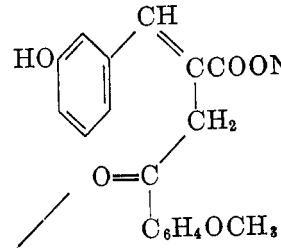
R_6	R_7	R_3'	R_4'	REFERENCES
H	H	H	H	(119)
H	H	H	CH_3O	(92, 119)
CH_3O	H	H	CH_3O	(119)
H	H	CH_3O	CH_3O	(119)
CH_3O	H	CH_3O	CH_3O	(119)
CH_3	H	CH_3O	CH_3O	(119)
H	CH_3	CH_3O	CH_3O	(119)

After the hydroxyl, the alkoxyl groups (R_7 = OR) appear to stand next in activating influence, with yields of the order of 85 per cent being reported (87).

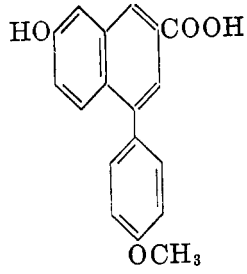


XVI

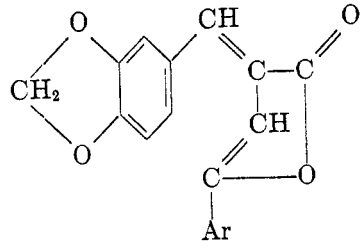
alcoholic NaOH



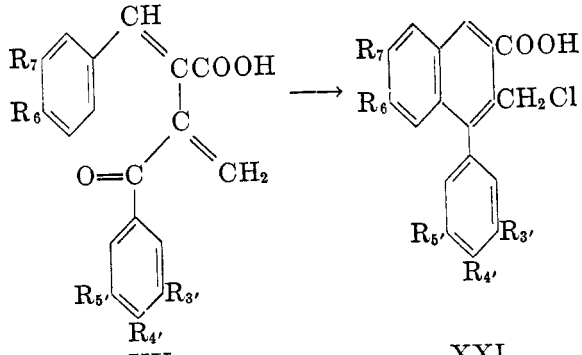
XVII



XVIII



XIX



XX XXI

($R_{3'}$ = H; R_6, R_7, $R_{4'}$, $R_{5'}$ = OCH_3)

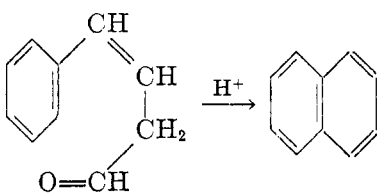
XXII XXIII

($R_{3'}$, $R_{4'}$, $R_{5'}$ = OCH_3; R_6—R_7 = —O—CH_2—O—)

The methylenedioxy group at the same position (R_6 and R_7 = —O—CH_2—O—) is reported to give the poorest results, the yields after 8–15 hr. refluxing being not over 5 to 8 per cent. Ohmaki attributes this to the intermediate formation of the difficultly soluble lactone (XIX).

One other reaction which may be considered in this connection was observed by Haworth, Richardson, and Sheldrick (86), who found that β-3,4-dimethoxybenzoyl-α-(3′,4′-dimethoxybenzylidene)-β-methylenepropionic acid (XX) undergoes cyclization and addition of hydrogen chloride to yield 6,7-dimethoxy-1-(3,4-dimethoxyphenyl)-2-chloromethylnaphthalene-3-carboxylic acid (XXI). This reaction was further extended (XXII→XXIII).

The simplest example of aromatic cyclodehydration in the carbocyclic series and, indeed, one which might be considered the prototype, is the cyclization of β-styrylacetaldehyde (XXIV) to yield naphthalene. The aldehyde was first synthesized by Rinkes (128), who reported that he had certain proof that



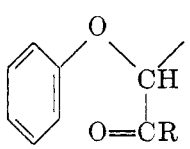
XXIV

it could be converted to naphthalene, although the amount of aldehyde available precluded an investigation of this problem.

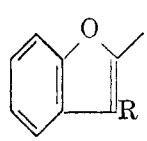
In order to determine whether the cyclization was an acid-catalyzed reaction of the general type under consideration, the author (29) prepared the aldehyde (XXIV) and found that refluxing with hydrobromic and acetic acids gave naphthalene in a yield of 25 per cent.

B. Benzofuran system

The formation of the benzofuran nucleus (XXVI) by aromatic cyclodehydration requires, as a starting material, a phenoxyacetaldehyde or phenoxymethyl ketone (XXV, R = H, alkyl, or aryl). Having no double bond, the aldehyde or ketone is more stable toward acid than its counterpart in the naphthalene system and there is no problem arising from geometric isomerism. The pres-



XXV



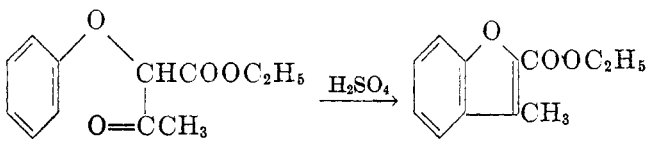
XXVI

(R = H, alkyl, or aryl)

ence of a strong *o–p*-directing ether linkage results in a markedly greater ease of cyclization. This is an important feature, in that the stability of the ben-

zofuran nucleus (XXVI) in acidic media is considerably less than that shown by naphthalene derivatives.

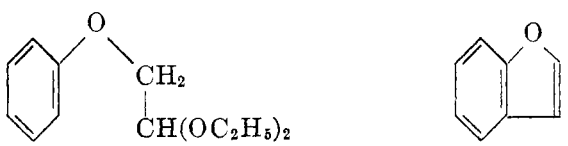
The first application of such a cyclodehydration to the preparation of benzofuran derivatives was made in 1886 by Hantzsch (84, 85), who found that the material produced by condensation of sodium phenoxide with α-chloroacetoacetic ester (presumably α-phenoxyacetoacetic ester (XXVII)) would undergo cyclization in the presence of concentrated sulfuric acid to yield 2-carbethoxy-3-methylbenzofuran (XXVIII). The reaction was extended (85)



XXVII XXVIII

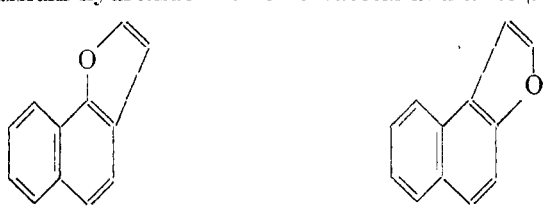
to the corresponding naphthofurans by the use of α- and β-naphthoxyacetoacetic esters.

A few years later, in a paper dealing mainly with sulfur compounds, Autenrieth (1) described the preparation of phenoxyacetal (XXIX) and, citing the analogy to the results of Hantzsch, predicted that it could be cyclized to benzofuran (XXX). His paper gives no indication that this cyclization was actually



XXIX XXX

carried out. Pomeranz (126) reported that all of his attempts to cyclize phenoxyacetal resulted in failure, owing to the easy polymerization of benzofuran in the presence of mineral acids. Hesse (91) likewise failed to cyclize phenoxy- or cresyloxy-acetal, but did succeed in preparing the corresponding α- and β-naphthofurans (XXXI and XXXII) by heating together at 200°C. alcoholic solutions of potassium hydroxide with chloroacetal and α- or β-naphthol.



XXXI XXXII

It is significant that when sodium ethoxide in alcohol was used under the same conditions, no cyclization took place, but formation of naphthoxyacetal was observed.

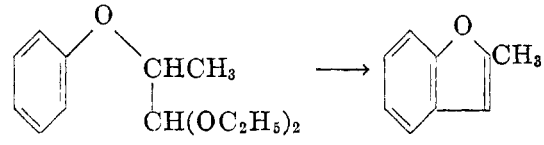
$$C_{10}H_7OH + C_2H_5ONa + ClCH_2CH(OC_2H_5)_2 \rightarrow$$

$$C_{10}H_7OCH_2CH(OC_2H_5)_2 + NaCl + C_2H_5OH$$

It seems probable that, in the cases where cyclization was observed, water acted as a source of protons for the cyclization.

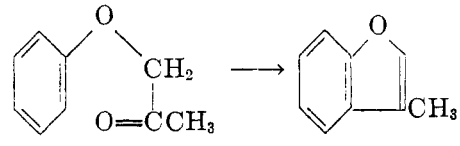
From certain observations (137) which will be discussed later, Stoermer concluded that cyclization of phenoxy- and cresyloxy-acetals and acetaldehydes could be accomplished if a cyclizing agent of the proper strength could be found. He found that an acetic acid solution of zinc chloride functioned very well and was useful for the preparation of naphthofuran, and of benzofuran and its homologs. Owing to the great tendency of the products to undergo polymerization, yields rarely rose above 10 per cent. In the case of the acetal, a good reagent for the cyclization was found to be anhydrous oxalic acid.

This type of cyclization is quite general in its nature. The acetal (XXXIII) of α-phenoxypropionaldehyde cyclizes to yield 1-methylbenzofuran (XXXIV) (138). Stoermer (137) found that the action of sulfuric acid on phenoxy-



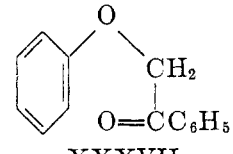
XXXIII XXXIV

acetone (XXXV) yielded the 2-methyl isomer (XXXVI). This reaction could



XXXV XXXVI

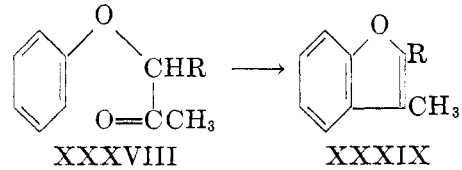
not be extended to the cyclization of α-phenoxyacetophenone (XXXVII) (139).



XXXVII

Benzofurans with two substituents in the five-membered ring (XXXIX) may be made by the use of suitably substituted ketones (XXXVIII) (140, 148).

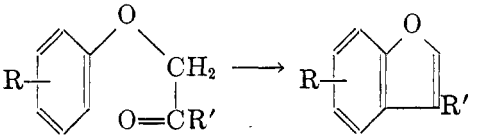
In addition, by varying the aryl groups, many derivatives can be made with



XXXVIII XXXIX

(R = CH_3, $CH_2C_6H_5$)

substituents in the six-membered ring (138). Stoermer (138) concluded that

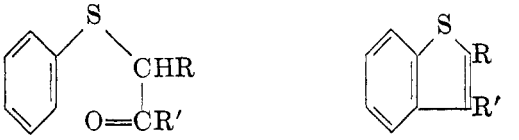


XL XLI

the presence of methyl groups in the aryl ring (XL) facilitated cyclization, while chlorine in the para-position (XL, R = *p*-Cl) greatly inhibited it. A nitro group in the para-position (XL, R = *p*-NO_2) appeared to prevent cyclization altogether.

C. Thianaphthene system

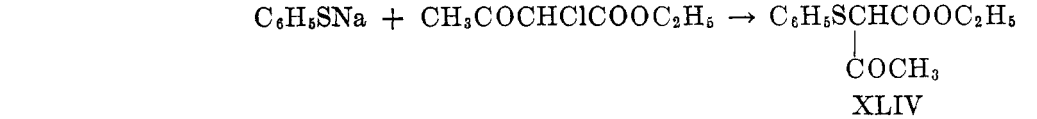
The similarity of the chemistry of sulfur to that of oxygen would suggest that α-phenylsulfhydryl ketones or aldehydes (XLII) might be cyclized to thianaphthene derivatives (XLIII). Such an idea occurred to the earliest workers in the benzofuran series. The almost universal lack of success experienced with the sulfur compounds seems to originate from the instability of the



XLII XLIII

phenylsulfhydryl ketones and aldehydes (XLII), as well as from a low order of ortho activation produced by the thioether group.

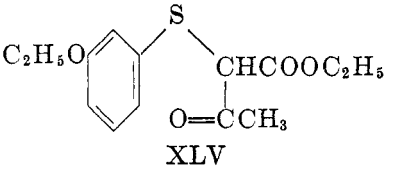
Hantzsch (84) attempted to prepare α-(phenylsulfhydryl)acetoacetic ester (XLIV) by the action of sodium phenylmercaptide with α-chloroacetoacetic ester in the hope that cyclization to 2-carbethoxy-3-methylthianaphthene (XLIII, R = $COOC_2H_5$, R′ = CH_3) might be accomplished. Unfortunately,



XLIV

instead of the sulfhydryl ester, phenyl disulfide was obtained under these conditions.

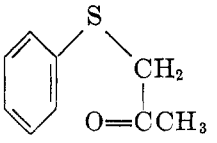
Delisle and Schwalm (61) succeeded in preparing phenylsulfacetoacetic ester (XLIV) and found that it decomposed on heating to yield phenyl disulfide and resisted all attempts at cyclization. The corresponding *m*-ethoxy derivative (XLV), which would be expected to be more likely to cyclize, was likewise



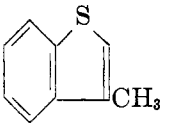
XLV

found to yield *m*-phenetole disulfide very readily, making attempts at cyclization equally futile.

In an earlier paper, Delisle (60) reported the synthesis of phenyl acetonyl sulfide (XLVI) and projected its cyclization to the corresponding 2-methylthianaphthene (XLVII), although no evidence was given that such a cyclization

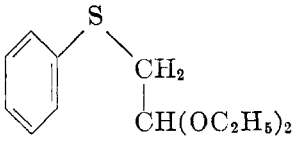


XLVI

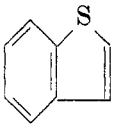


XLVII

was carried out. Essentially the same idea was reported by Autenrieth (1), with no statement that the cyclization experiment had met with any success. Autenrieth likewise prepared thiophenylacetal (XLVIII), but was unable to



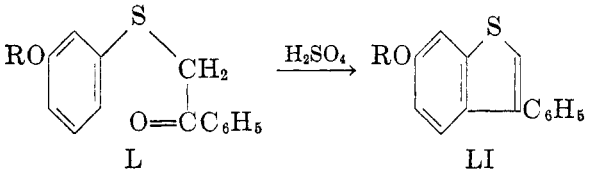
XLVIII



XLIX

effect its cyclization to thianaphthene (XLIX), although a variety of acidic cyclizing agents were tried.

Apparently the only clear-cut case of a cyclization of this type in the thianaphthene series is afforded by the work of Fries and his colleagues (77), who observed that phenacyl 3-hydroxyphenyl sulfide (L, R = H) could be cyclized by concentrated sulfuric acid to yield 3-phenyl-6-hydroxythianaphthene



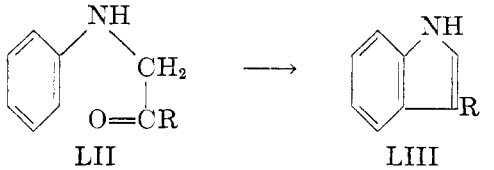
L LI

(R = H or CH_3)

(LI, R = H) in 45 per cent yield. A better yield was obtained using the methyl ether. Investigation of similar activated systems would appear desirable.

D. Indole system

From the cyclizations already considered, it might be predicted that α-anilino ketones or aldehydes (LII) could be cyclized by acidic reagents to yield



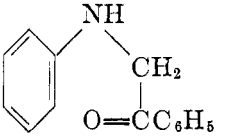
LII LIII

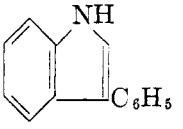
(R = H, alkyl, or aryl)

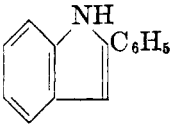
indoles (LIII). Actually, this mode of reaction appears to be more nearly the exception than the rule, cyclization usually being accompanied by real or apparent rearrangement.

The first ketone of this class to receive any extensive study was phenacylaniline (LIV), which Möhlau made by the reaction of phenacyl bromide with aniline (113). This phenylamino ketone, upon refluxing with aniline (113), dry distillation (115), or heating its hydrochloride with phosphorus pentachloride (115), yielded a new compound, m.p. 185°C. On the basis of a molecular-weight determination (114), later admitted to be erroneous (116), Möhlau concluded that the molecular formula was $C_{28}H_{22}N_2$, and the structure could be most adequately described as "diphenylpseudoamphiphenacylnitrile".

A few years later, Wolff (149) expressed the opinion that the dehydration product obtained by Möhlau was 3-phenylindole (LV). It remained for Fischer


LIV

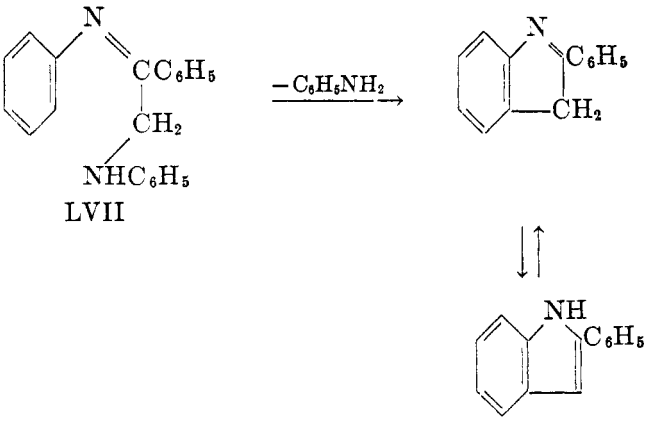

LV


LVI

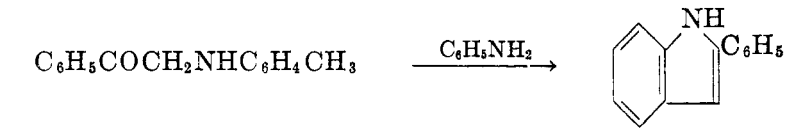
and Schmitt (71) to demonstrate that the product was in reality the isomeric 2-phenylindole (LVI), a compound whose structure had been well established by both synthesis (69, 122) and degradation (123).

While Fischer and Schmitt (72) observed that 3-phenylindole will rearrange to the 2-isomer when heated with zinc chloride, Ince (93), by heating the 3-indole in the presence of aniline hydrochloride at temperatures as high as 230°C., demonstrated fairly well that rearrangement does not occur under the conditions usually used in the indole cyclization.

To this apparent dilemma, Bischler (22) offered an ingenious solution. According to his postulate, the phenacylaniline, first formed in the reaction between phenacyl bromide and aniline, reacts further to yield an anil (LVII) which cyclizes by loss of a molecule of aniline to yield 2-phenylindole. It is the phenyl

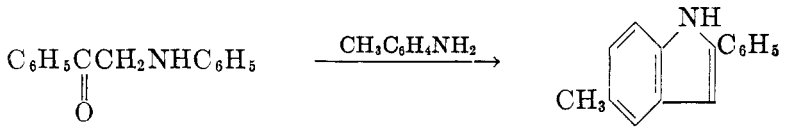


radical of the phenylimino rather than the phenylamino group which becomes part of the indole nucleus. Phenacylamines were refluxed with a variety of aromatic primary amines to demonstrate that the structure of the final indole was independent of the group originally associated with the phenacyl radical, and depended solely on the amine with which it had been refluxed. For example, phenacyl(*p*-toluide) (LVIII), when refluxed with aniline, gave 2-phenylindole,



LVIII

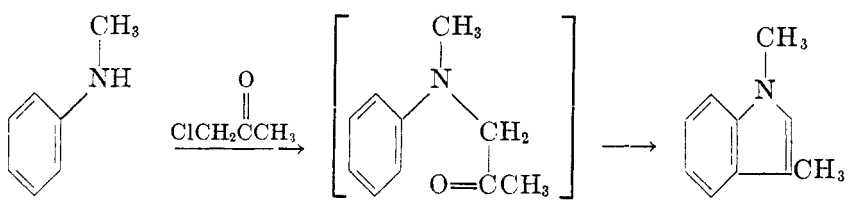
while phenacylaniline, when refluxed with *p*-toluidine, yielded 2-phenyl-5-methylindole (LIX).



LIX

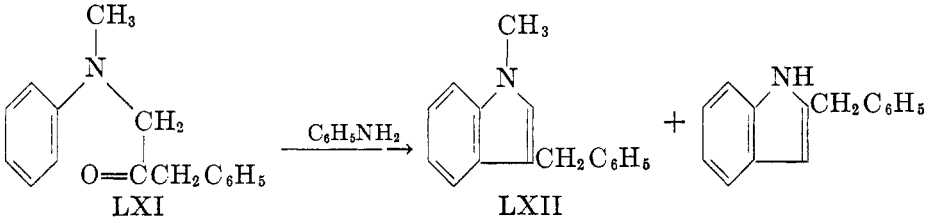
In a great many experiments (e.g., 23, 52, 58, 89, 90, 118, 135) the products actually obtained have been those predicted on the basis of the Bischler theory and it is not surprising that this theory has found almost universal acceptance.

In recent papers calling into question the validity of Bischler's assumption, Verkade and Janetsky (146, 147) have pointed out several examples of indole formation which could be explained on the basis of simple cyclodehydration. Nearly all of these cases involve or are believed to involve a phenylmethylamino ketone as an intermediate. Meisenheimer (111) observed that methylaniline with chloroacetone gave the 1,3-dimethylindole (LX) rather than the 1,2-isomer. Julian and Pikl (100) showed that when 1-phenylmethylamino-3-phenylpropanone-2 (LXI) was heated with aniline, in addition to the 2-ben-



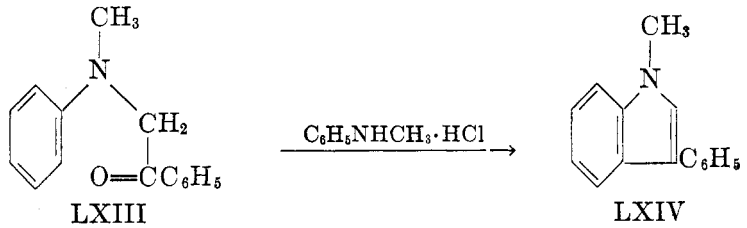
LX

zylindole predicted by the Bischler theory, 1-methyl-3-benzylindole (LXII) was obtained. Verkade and Janetsky showed that both phenylmethylamino-

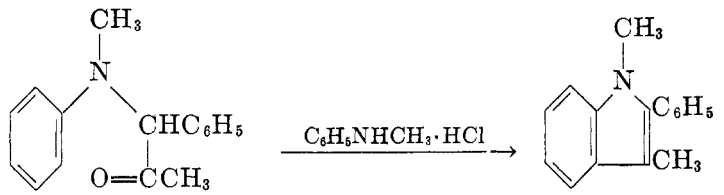


LXI LXII

acetophenone (LXIII) and 1-phenyl-1-phenylmethylaminopropanone-2 (LXV), when heated with *N*-methylaniline hydrochloride, yield the products which would be expected if simple cyclization had taken place,—namely, 1-methyl-3-phenylindole (LXIV) and 1,3-dimethyl-2-phenylindole (LXVI).

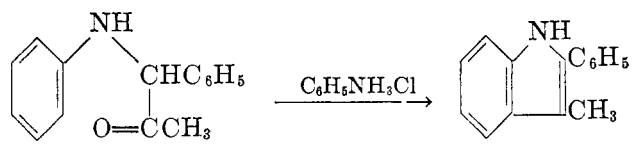


LXIII LXIV



LXV LXVI

While all of the cases considered above have had a methyl group attached to the nitrogen atom, Verkade and Janetsky have shown that indole formation by apparent cyclization is possible without this or any substituent. When 1-phenylamino-1-phenylpropanone-2 (LXVII) is heated with aniline hydrochloride, 2-phenyl-3-methylindole (LXVIII) is obtained in almost quantitative yield. Verkade and Janetsky have also shown that the formation of indoles



LXVII LXVIII

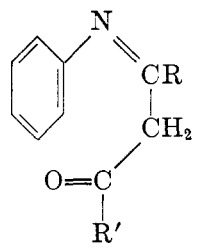
from arylaminoketones is acid-catalyzed and does not occur in the absence of a catalyst. This confirms the earlier observations of Japp and Murray (95).

It may be safely concluded that in a few instances, α-arylaminoketones may undergo the general aromatic cyclodehydration reaction observed in other systems, but usually the reaction is more complicated and is as yet imperfectly understood.[1]

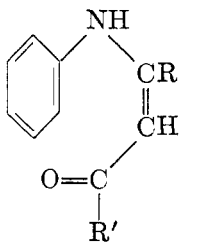
[1]Since this manuscript was completed, Julian, Meyer, Magnani, and Cole (J. Am. Chem. Soc. **67**, 1203 (1945)) have published an excellent paper concerning the indole cyclization.

E. Quinoline system

More readily comparable to the naphthalene than the heterocyclic systems thus far considered, quinoline may be prepared by the acid-catalyzed dehydration of diketone anils (LXIX or LXX). Whether the nitrogen is attached to the chain by an imine (LXIX) or a vinylamine linkage (LXX), it is known that the hydrolysis of the carbon-to-nitrogen bond tends to take place under



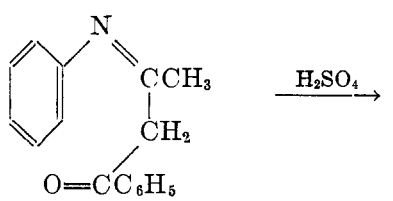
LXIX



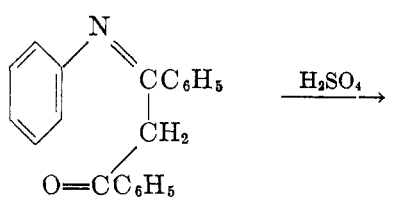
LXX

the conditions used for cyclization. Despite this limitation, the ring closure of diketone anils, in particular those of acetylacetone (the Combes synthesis), constitutes one of the two most important and extensive applications of aromatic cyclodehydration.

The first such cyclization was reported in 1887 by Beyer (21), who found that the anils of benzoylacetone (LXXI) and of dibenzoylmethane (LXXIII) may be cyclized by the action of concentrated sulfuric acid to yield 2-methyl-4-phenyl- and 2,4-diphenyl-quinolines (LXXII and LXXIV).



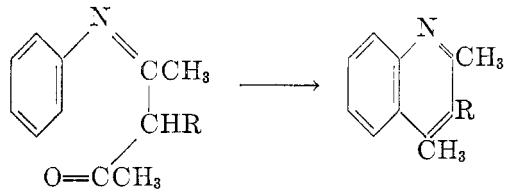
LXXI LXXII



LXXIII LXXIV

Much new evidence pertaining to the mechanism of cyclization has been presented, together with alternate explanations for some of the phenomena observed by Verkade and Janetsky. Julian and his coauthors have summarized as follows: "The experiments recorded in this paper justify on the whole the Bischler hypothesis with modifications. They do not rule out of consideration 'direct' ring closure with loss of water, and until more evidence is obtained we prefer to take the point of view that both reactions may take place, the evidence at present being still predominantly in favor of the Bischler hypothesis of intermediate diamine formation."[?]

The following year, Combes (53, 54) effected a similar cyclization, using the anil of acetylacetone (LXXV, R = H) to produce 2,4-dimethylquinoline (LXXVI, R = H). Similarly, methyl acetylacetone anil (LXXV, R = CH_3)



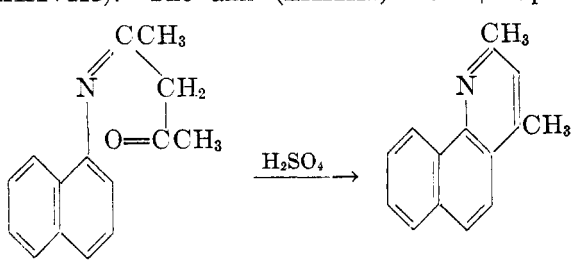
LXXV LXXVI

yields 2,3,4-trimethylquinoline (LXXVI, R = CH_3).

As may be seen from table 2, the Combes synthesis has found many applications. Roberts and Turner (129) have made a thorough study of the factors influencing cyclization. The presence of a methoxyl group meta to the position at which cyclization is expected (R_6 or R_8 = OCH_3) completely inhibits the cyclization. An inhibition of this type has been observed in other cyclizations (66, 83, 94, 98, 112, 150) and is likewise quite characteristic of aromatic cyclodehydration (102, 103, 129, 142). The presence of a chlorine atom meta to the position of cyclization likewise prevents cyclization, but this may be in part due to the general deactivating influence of chlorine on the aromatic ring since the methyl group, which has about the same order of ortho–para-activating influence, shows no such inhibition.

In the case of the inhibition due to a *m*-methoxyl group, the deactivation can be overcome by introduction of a second methoxyl group ortho or para to the position at which cyclization is expected, as when R_7 and R_8 or R_4 and R_8 = OCH_3. In only one case was the same type of action observed in the corresponding dichloro compounds, the anil of 3,4-dichloroaniline (R_6 and R_7 = Cl) being converted, in a single experiment, to the 6,7-dichloroquinoline. A single ortho–para-directive group, ortho or para to the point at which cyclization is expected to occur, increases the ease of cyclization.

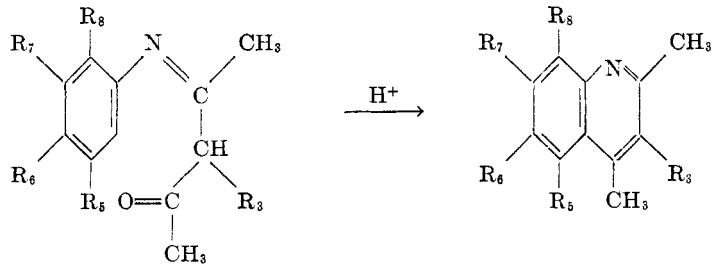
The Combes synthesis has been applied to the synthesis of benzoquinolines (54) starting from naphthylamines. The α-naphthylamine–acetylacetone condensation product (LXXVII) cyclizes readily to yield 2,4-dimethyl-7,8-benzoquinoline (LXXVIII). The anil (LXXIX) from β-naphthylamine gives



LXXVII LXXVIII

TABLE 2

Combes synthesis



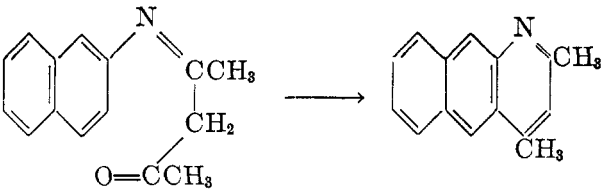
Cyclized

R_7	R_5	R_6	R_7	R_8	REFERENCES
H	H	H	H	H	(53, 54, 74)
CH_3	H	H	H	H	(53, 54)
H	H	CH_3	H	H	(53, 54)
H	H	C_2H_5	H	H	(82)
H	H	H	H	CH_3	(53, 54)
H	H	H	H	C_2H_5	(6)
H	H	H	H	n-C_3H_7	(8)
H	CH_3	H	H	CH_3	(47)
CH_3	H	H	H	CH_3	(7)
CH_3	H	H	H	C_2H_5	(81)
CH_3	H	H	H	n-C_3H_7	(132)
H	H	H	—$(CH_2)_4$—		(47)
H	H	H	OCH_3	OCH_3	(105a)
H	OCH_3	H	H	OCH_3	(105a)
H	H	OCH_3	OCH_3	OCH_3	(105)
H	OCH_3	OCH_3	OCH_3	H	(105)
H	OCH_3	OCH_3	H	Br	(105a)
H	H	H	Cl	H	(129)
H	H	Cl	Cl	H	(129)

Failed to cyclize
(R_3 = H)

R_5	R_6	R_7	R_8	REFERENCES
H	OCH_3	H	H	(103)
H	H	H	OCH_3	(129)
H	H	H	Cl	(129)
H	Cl	H	H	(129)
H	Cl	H	Cl	(129)
Cl	H	H	Cl	(129)
Cl	H	Cl	H	(129)

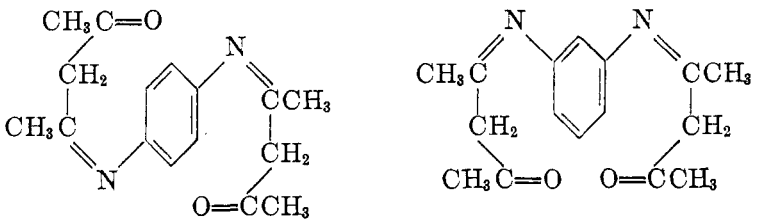
what has recently been shown (99) to be the 6,7-benzoquinoline analog (LXXX). The formation of the linear product is remarkable in that the condensation has



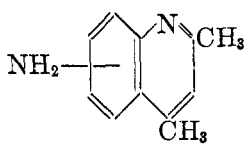
LXXIX LXXX

taken place at what is normally a relatively unreactive beta position, rather than the reactive alpha position.

Marckwald and Schmidt (106) first studied the reactions of the dianils from



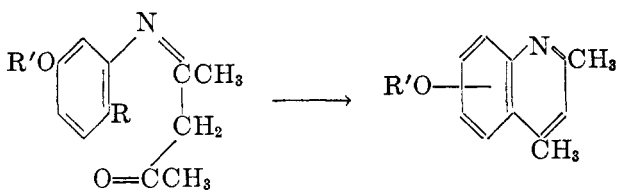
LXXXI LXXXII



LXXXIII

p- and *m*-phenylenediamines. The dianil (LXXXI) from *p*-phenylenediamine simply underwent fission when treated with sulfuric acid, while its *m*-isomer (LXXXII), by a single cyclization and fission, gave what is believed (129) to be the 7-amino-2,4-dimethylquinoline (LXXXIII) rather than its 5-isomer.

The Combes synthesis has been used by Murray and Turner (117) to prepare some diquinolinyl ethers. The anils (LXXXIV) having groups ortho to the nitrogen atom (R = CH_3, OCH_3, OC_2H_5) could not be cyclized, while those



LXXXIV LXXXV

(R = H; R′ = 2-methyl-4-quinolinoxy or 4-methyl-2-quinolinoxy)

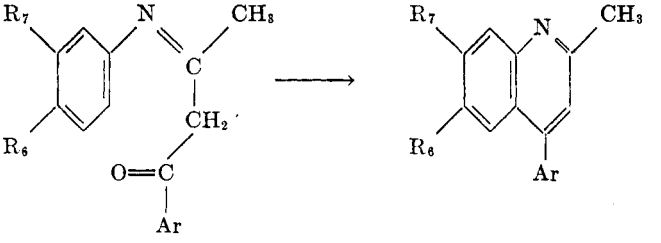
having no such substituent (R = H) yielded the diquinolinyl ethers (LXXXV). The authors did not ascertain whether the quinolinoxy group was at the 7- or the 5-position of the new quinoline nucleus.

The somewhat less extensive data on the cyclization of the anils (LXXI) of benzoylacetone (table 3) suggests that the behavior of these compounds is very similar to that of the acetylacetone anils. In addition, it has been observed (103) that the presence of a methoxyl group meta to the point at which condensation is to be expected (R_6 = OCH_3) causes a complete inhibition of cyclization.

In his original observation, Beyer (21) found that the cyclization of the anil of dibenzoylmethane (LXXXVI, R = H) to 2,4-diphenylquinoline (LXXXVII,

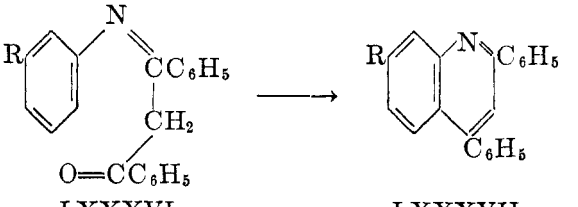
TABLE 3

Preparation of derivatives of 2-methyl-4-phenylquinoline



Ar	R_6	R_7	REFERENCES
C_6H_5	H	H	(21, 74)
C_6H_5	CH_3	H	(74)
o-$CH_3OC_6H_4$	H	H	(18, 20)
m-$CH_3OC_6H_4$	H	H	(18, 20)
p-$CH_3OC_6H_4$	H	H	(18, 20)
o-$C_2H_5OC_6H_4$	H	H	(18)
C_6H_5	H	OH	(49)

R = H) took place with great difficulty. So great is the activation produced by the introduction of a methoxyl group para to the point of expected cycliza-

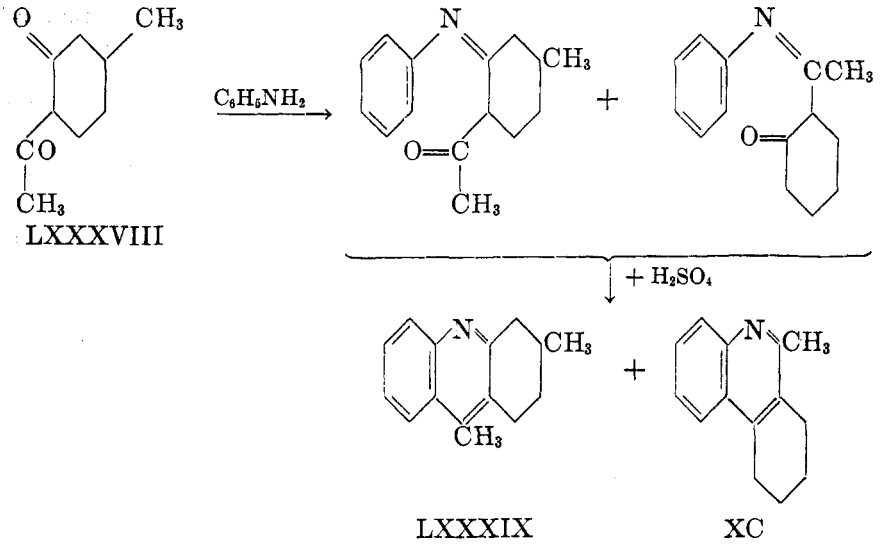


LXXXVI LXXXVII

(R = H, OCH_3)

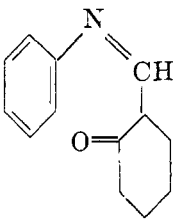
tion, that cyclization under *these* circumstances may be accomplished in very good yield and under very mild conditions (104).

One other type of diketone anil which has been successfully cyclized is that of 5-methyl-2-acetylcyclohexanone (LXXXVIII).



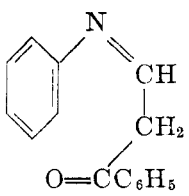
LXXXVIII LXXXIX XC

While this can and does form an anil at either carbonyl, Borsche (24) found that conditions can be so controlled that most of the condensation takes place with the ring carbonyl. The two anils were not separated but were cyclized simultaneously by the action of sulfuric acid to yield a mixture which was 85 per cent 3,10-dimethyl-1,2,3,4-tetrahydroacridine (LXXXIX) and 15 per cent tetrahydromethylphenanthridine (XC). In the same way, by the use of *m*-hydroxyaniline with acetylcyclohexanone, acetylmethylcyclohexanone, and acetylcamphor, the corresponding hydroxytetrahydroacridines were prepared. It is interesting to note that the anil (XCI) derived from 2-formylcyclohexanone cannot be cyclized. This may be a consequence of improper steric configuration.

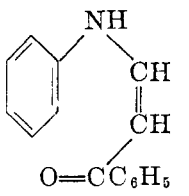


XCI

Several other anils belonging to this general system have failed to cyclize. Claisen and Fischer (50) reported that the anil (XCII) of formylacetophenone gave no quinoline derivatives with concentrated sulfuric acid. Later (51), it

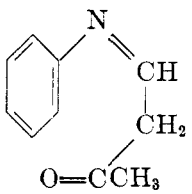


XCII

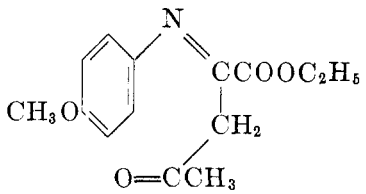


XCIII

was suggested that the condensation product between formylacetophenone and aniline might have the isomeric structure (XCIII), which could be responsible for the failure of the compound to cyclize. Since all of the anils considered here may have a structure analogous to XCIII, it seems more probable that the explanation is to be found either in incorrect steric configuration or in the presence of a phenyl group attached to the carbonyl. At best, the system could be no better than that of dibenzoylmethane anil (LXXXVI, R = H). The failure (142) of the anil (XCIV) of formylacetone to cyclize seems probably a clear-cut case of wrong steric configuration. It is more difficult to agree with Thielepape (142) that the *p*-aniside of acetone-oxalic ester fails to cyclize for



XCIV

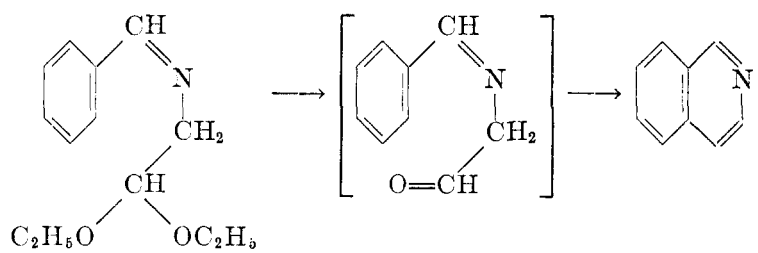


XCV

the same reason, since, in this case, any cyclization must take place meta to a methoxyl group, a situation which is known to represent a very unfavorable arrangement.

F. Isoquinoline system

The application of the general reaction to the synthesis of isoquinoline derivatives appears to be limited to the cyclization of simple derivatives of benzaldiminoacetaldehyde (XCVII). The first reported attempt to prepare isoquinoline by this method was made in 1893 by Fritsch (78), who prepared the benzal derivative (XCVI) of aminoacetal, but failed to find the proper conditions for effecting cyclization. The following year, Pomeranz (124) reported that the



XCVI XCVII XCVIII

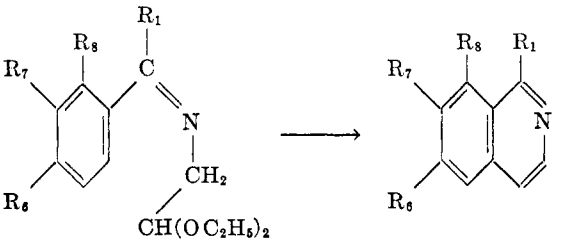
acetal could be cyclized by sulfuric acid to isoquinoline (XCVIII), presumably through the aldehyde (XCVII). The use of this general synthesis in the preparation of isoquinoline derivatives is shown in table 4. If, instead of a benzaldehyde, a phenyl ketone is condensed with aminoacetal, the product yields a small amount of a 1-substituted isoquinoline (table 4, R_1 = alkyl or aryl) upon cyclization. The most important variations have involved effecting a

similar condensation with substituted benzaldehydes to yield, upon ring closure, isoquinolines with substituents in the benzenoid ring.

The presence of a hydroxyl or alkoxyl group para to the point of expected cyclization seems again a favorable influence, although introduction of a second methoxyl group meta to the point of cyclization produces a compound difficult (R_7 and R_8 = OCH_3) (121) or impossible (R_6 and R_7 = OCH_3) (131) to cyclize. The latter appears odd, in view of the ability of the corresponding methylenedioxy derivative (R_6—R_7 = —O—CH_2—O—) to undergo ring closure. More successful application of the Pomeranz–Fritsch synthesis seems to be

TABLE 4

Pomeranz–Fritsch cyclization



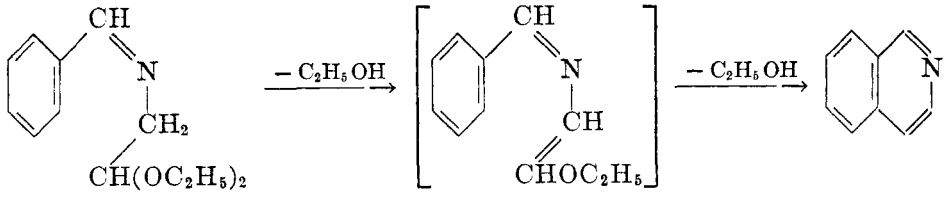
R_1	R_6	R_7	R_8	REFERENCES
H	H	H	H	(124, 125)
CH_3	H	H	H	(125)
H	H	H	CH_3	(127)
H	CH_3	H	H	(127)
H	H	H	Cl	(127)
C_6H_5	H	H	H	(127)
H	H	OH*	H	(79, 152a)
H	H	OCH_3	H	(79)
H	H	OC_2H_5	H	(79)
H	—O—CH_2—O—		H	(79)
H	H	OCH_3	OCH_3	(121)
H	H	H	Br	(143)
H	H	Br*	H	(143)
H	Br	H	H	(143)

* Contained some 5-substituted isoquinoline.

limited by the difficulty of finding conditions sufficiently drastic to hydrolyze the acetal but not the aldimine linkage.

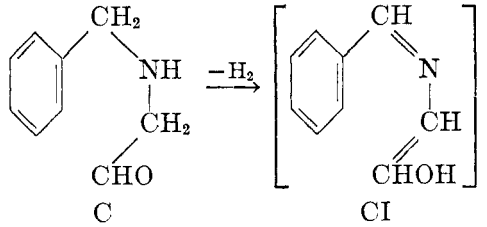
Staub (136) has made a study of several compounds containing the C_6H_5—C—N—C—C grouping and has reached the conclusion that for isoquinoline cyclization, the chain must possess: (*1*) a system of double bonds or the possibility of their formation, (*2*) a hydroxyl or alkoxyl group beta to the nitrogen atom. Staub postulates that the first step in the cyclization of benzaldiminoacetals involves loss of alcohol to give the conjugated system (XCIX). The Fischer (70) cyclization of a benzylaminoacetaldehyde (C) to isoquinoline is

Staub mechanism



XCIX

interpreted as involving preliminary dehydrogenation and formation of the enol (CI).



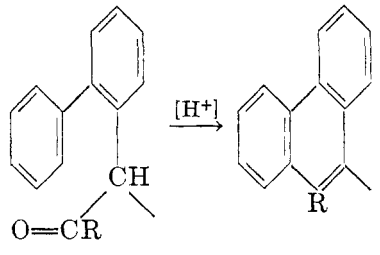
C CI

Without speculation concerning the stage at which dehydrogenation occurs in the Fischer cyclization, it must be conceded that there exists no positive evidence that the Pomeranz–Fritsch synthesis involves direct cyclization of a vinyl ether (XCIX), while every analogy suggests that the intermediate is, as suggested by Pomeranz, benzalaminoacetaldehyde (XCVII), the conjugate acid of which would be expected to cyclize according to the general mechanism.

III. TRICYCLIC SYSTEMS

A. Phenanthrene system

It is possible to conceive of 2-biphenylylacetaldehydes and the corresponding ketones as β-styrylacetaldehydes or methyl ketones in which the double bond



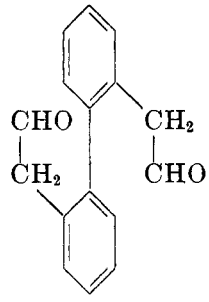
(R = H, alkyl, or aryl)

has been incorporated into a benzene ring. Both systems are similar, in that acid-catalyzed cyclodehydration leads to the formation of an aromatic derivative, but there exists considerable difference between the two with respect to yield. Almost uniformly better results are obtained in the phenanthrene as opposed to the naphthalene system, for the elimination of the double bond not only

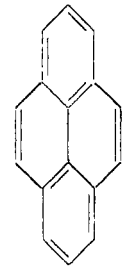
removes a cause for polymerization, but also obviates the possibility of wrong (i.e., *trans*) steric configuration.

Nearly all of the most useful reactions expected to yield 2-biphenylylacetaldehydes or the related ketones involve, as a final step, hydrolysis or rearrangement in the presence of mineral acid. Since these conditions likewise bring about cyclization, in nearly every such experiment, no carbonyl compound is isolated. While this is usually very convenient as applied to synthesis, it does raise questions as to the actual mechanism involved. For the purpose of the present discussion, it will be assumed that a ketone or aldehyde is always involved as an intermediate, and a more complete discussion of the alternative possibilities will be deferred until the subject of mechanism is considered (Part IV).

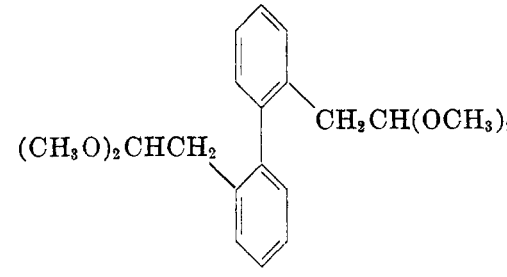
While the preparation of phenanthrene derivatives by this mode of cyclization is a comparatively recent development, the same principle had been applied as early as 1912 by Weitzenbock (151) in an attempt to synthesize pyrene (II). Seeking to prepare the necessary biphenylene-2,2′-diacetaldehyde (I), he hydrolyzed the corresponding acetal (III) with 3 per cent sulfuric acid. Instead



I

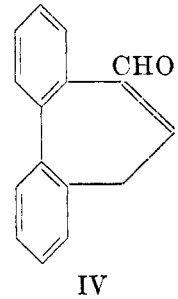


II

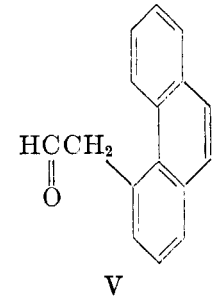


III

of the expected dialdehyde (I) or pyrene (II), he obtained a new aldehyde to which he assigned the structure of 4,5,6,7-dibenzo-Δ-1,4,6-cycloheptatriene-1-aldehyde (IV) rather than that of the partially cyclized product, 4-phenanthrylacetaldehyde (V). This decision was based on the following observations: (*1*) the aldehyde failed to yield pyrene under more energetic treatment with



IV



V

acid; (*2*) it reacted immediately with permanganate solution; (*3*) it reacted readily with bromine to give a stable dibromide (phenanthrene dibromide de-

composes on standing); (4) oxidation yielded phenanthrenequinone instead of a phenanthrenequinone monocarboxylic acid. The evidence cannot be considered as amounting to a demonstration, and any final decision will have to await an independent synthesis of one of these compounds.

In a series of experiments beginning in 1938, the author and his students have investigated the cyclization of compounds of such a structure that they might

TABLE 5

Cyclization of mono ethers of 2-biphenylylethylene glycol (VII)

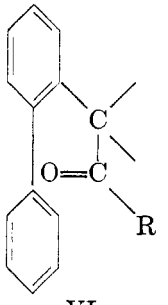
A. Methyl ethers

R	R′	YIELD*	REFERENCES
		per cent	
H	H	46	(44)
CH_3	H	50	(43)
C_2H_5	H	53	(30)
n-C_3H_7	H	51	(30)
n-C_4H_9	H	40	(30)
$C_6H_5CH_2$	H	70	(30)
C_6H_5	H	†	(38)
p-$CH_3C_6H_4$	H	†	(38)
B. Phenyl ethers			
CH_3	H	32*	(43)
C_6H_5	H	84	(38)
C_6H_5	CH_3	72*	(37)
C_6H_5	C_2H_5	70	(37)
C_6H_5	C_6H_5	62*	(37)

* Over-all; carbinol not isolated.

† Not reported.

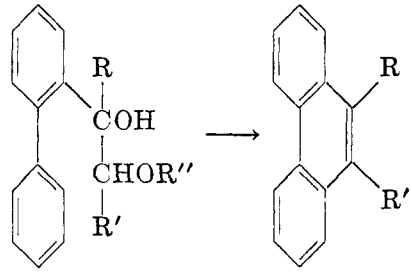
be expected to yield derivatives of 2-biphenylylacetaldehyde or 2-biphenylylmethyl ketones (VI, R = H, alkyl, or aryl) under conditions of the cyclization.



VI

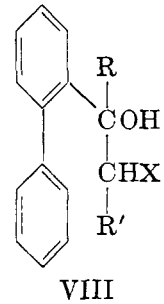
(R = H, alkyl, or aryl)

One such type embraces the monomethyl or phenyl ethers of 2-biphenylylethylene glycol (VII, R″ = CH_3 or C_6H_5). The results are summarized in table 5.



VII

Several other experiments, mostly of an exploratory nature, were tried with the similar systems (VIII) in which the β-carbon atom of the chain contained some group other than methoxyl or phenoxyl. These include the hydroxyl (45), β-naphthoxyl (43), and diethylamino (43) groups, all of which undergo

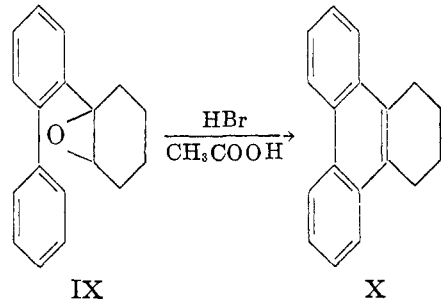


VIII

(X = OH, β-$OC_{10}H_7$, $N(C_2H_5)_2$)

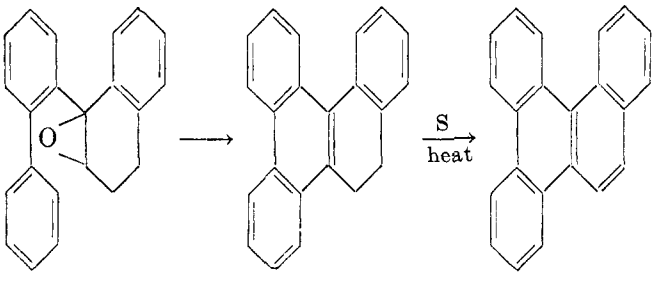
cyclization to some extent.

More important than any of the methods noted is the cyclization of olefin oxides. The first example (26) was the cyclization of the oxide (IX) derived from (2-biphenylyl)cyclohexene-1 to yield 9,10-cyclohexenophenanthrene. This general method has been applied with the oxides of several cycloölefins. The



IX X

cyclization of 1-(2-biphenylyl)-3,4-dihydronaphthalene oxide (XI), for example, affords the most direct route to the carcinogenic 1,2,3,4-dibenzophenanthrene (XII) (34). Other examples will be found in table 6.



XI XII

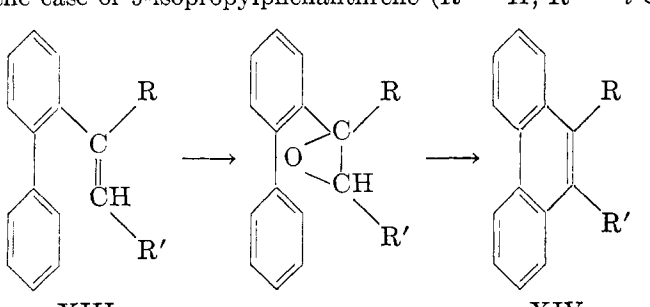
The olefin oxide cyclization is equally applicable to the preparation of alkyl, dialkyl, and alkyl-aryl phenanthrenes, using non-cyclic 2-biphenylyl olefins.

TABLE 6

OXIDE OF 1-(2-BIPHENYLYL)-	CYCLIZATION PRODUCT	YIELD*	REFERENCES
		per cent	
Cyclopentene	9,10-Cyclopentenophenanthrene	16	(26)
Cyclohexene	9,10-Cyclohexenophenanthrene	30, 100	(26, 36)
3,4-Dihydronaphthalene	1,2,3,4-Dibenzo-9,10-dihydronaphthalene	51†	(34)
4-Methyl-3,4-dihydronaphthalene	9-Methyl-9,10-dihydro-1,2,3,4-dibenzophenanthrene	89.5	(35)
3-Methyl-3,4-dihydronaphthalene	10-Methyl-9,10-dihydro-1,2,3,4-dibenzophenanthrene	73	(35)
3,4-Dimethyl-3,4-dihydronaphthalene	9,10-Dimethyl-9,10-dihydro-1,2,3,4-dibenzophenanthrene	‡	(35)

* Unless otherwise noted, all yields are over-all for both oxidation and cyclization.
† Yield of 1,2,3,4-dibenzophenanthrene after dehydrogenation.
‡ Not reported.

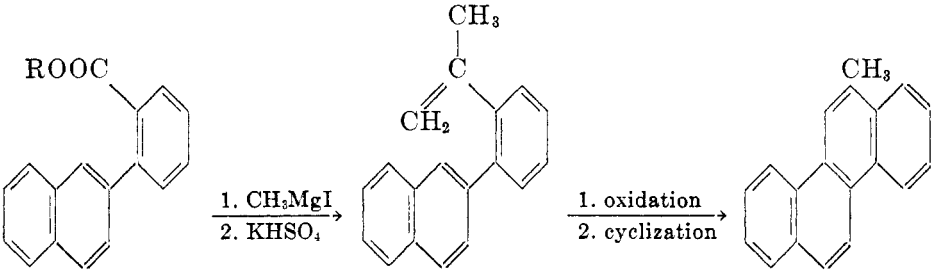
The over-all yield of phenanthrene hydrocarbon (XIV) obtained from the olefin (XIII) varies from 2 per cent in the case of phenanthrene (R and R′ = H) to 69 per cent in the case of 9-isopropylphenanthrene (R = H; R′ = i-C_3H_7). The



XIII XIV

results are summarized in table 7.

This type of cyclization has been applied to the synthesis of 6-methylchrysene (33). When 2'-carbomethoxy-2-phenylnaphthalene (XV) was treated with methylmagnesium iodide and the resulting carbinol dehydrated, the olefin



XV XVI XVII

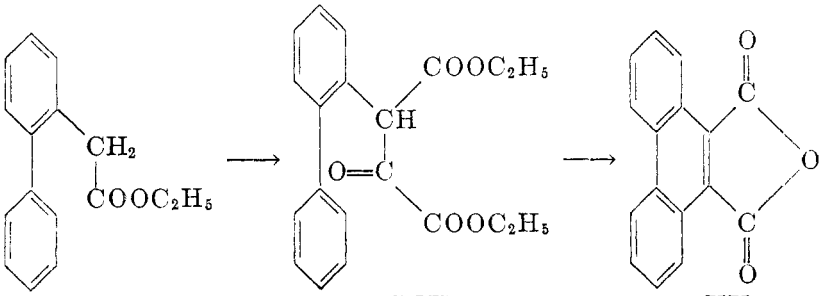
(XVI) which resulted was readily oxidized and cyclized to 6-methylchrysene (XVII).

TABLE 7

Cyclization of simple olefin oxides

R	R'	YIELD FROM OLEFIN	REFERENCES
		per cent	
H	H	2	(44)
H	C_2H_5	43	(30)
H	n-C_3H_7	66	(30)
H	i-C_3H_7	69	(30)
H	n-C_4H_9	34	(30)
H	n-C_5H_{11}	53	(30)
CH_3	H	40	(31)
C_2H_5	CH_3	54	(31)
n-C_3H_7	C_2H_5	44	(31)
n-C_4H_9	n-C_3H_7	67	(31)
n-C_5H_{11}	H	31	(32)
CH_3	CH_3	39	(32)
C_6H_5	n-C_3H_7	64	(32)
C_6H_5	n-$C_{10}H_{21}$	39	(32)

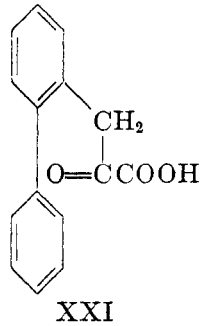
The first report of the successful cyclization of a 2-biphenylylmethyl ketone derivative was that of Schönberg and Warren (133), who found that ethyl α-keto-β-(2-biphenylyl)succinate (XIX), obtained by the condensation of



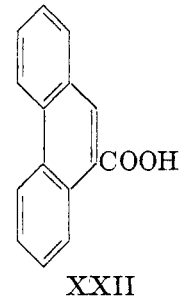
XVIII XIX XX

ethyl oxalate with ethyl biphenylyl-2-acetate (XIX) in the presence of potassium, underwent cyclization in 95 per cent sulfuric acid to give a good yield of phenanthrene-9,10-dicarboxylic anhydride (XX). This is an unusual example of the Bougault reaction (5, 25) in that, instead of a hydroaromatic derivative, a fully aromatic compound is formed directly.

In an independent investigation, Geissmann and Tess (80) observed that the keto ester (XIX) could be cyclized in a boiling mixture of hydrobromic and acetic acids. Under these conditions, a mixture consisting chiefly of phenanthrene-9-carboxylic acid (XXII) together with a small amount of the 9,10-dicarboxylic acid was obtained. The formation of the monocarboxylic acid



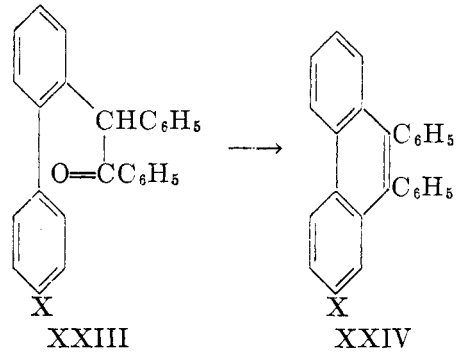
XXI



XXII

(XXII) seems best explained by assuming the formation of an intermediate keto acid (XXI) by hydrolysis and decarboxylation of the oxalyl ester (XIX). A comparable transformation has been observed by Fieser and Holmes in a related system (67, 68).

Finally, the only simple ketones which have been cyclized to phenanthrene



XXIII XXIV

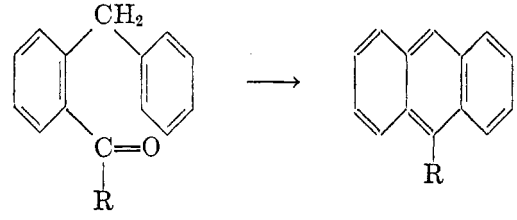
(X = H or Cl)

derivatives are α-(2-biphenylyl)desoxybenzoin (XXIII, X = H) and its 4′-chloro derivative, which are readily cyclized by either sulfuric acid or the usual hydrobromic–acetic acid mixture to yield the corresponding 9,10-diphenylphenanthrenes (XXIV) (46).

B. Anthracene system

The most recently discovered of all aromatic cyclodehydrations is that yielding anthracene derivatives from *o*-benzylphenyl aldehydes and ketones (XXV,

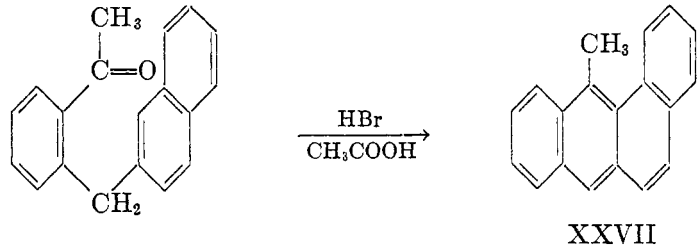
R = H, alkyl, or aryl). As might be predicted from the known stability of aromatic aldehydes and ketones, side reactions are, in general, less important than those encountered in the naphthalene and phenanthrene systems.



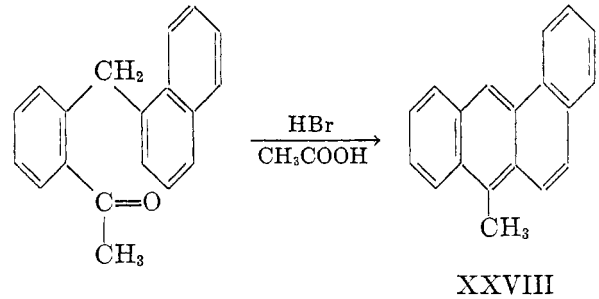
XXV XXVI

The first example of this type of cyclization was observed by Bergmann (11), who found that hydrolysis of the acetal of *o*-benzylbenzaldehyde (XXV, R = H) gave not only the expected aldehyde, but also a small quantity of anthracene.

It was felt (27) that this could not be a modification of the Elbs synthesis, as claimed by Bergmann, but rather an acid-catalyzed cyclodehydration such as those which were already known in the naphthalene and phenanthrene systems. The reaction was extended to *o*-benzylphenyl ketones (XXV, R = alkyl or aryl), resulting in the formation of meso alkyl- and aryl-anthracenes (27). It was pointed out that this reaction might form a useful tool in the introduction of meso alkyl groups into systems containing the anthracene nucleus. This was illustrated by the synthesis of the carcinogenic 9-methyl- and 10-methyl-1, 2-benzanthracenes (XXVII and XXVIII) (28).



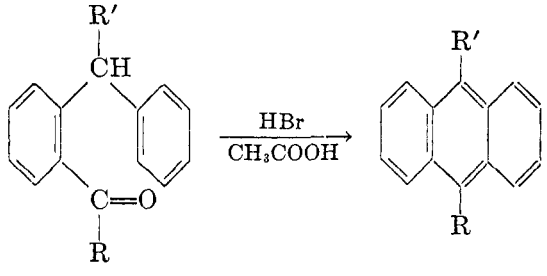
XXVII



XXVIII

Another extension of the synthesis can be effected by introduction of a substituent in the alpha position of the benzyl group of the *o*-benzylphenyl ketone

(XXIX), yielding an anthracene derivative with substituents in both meso-positions (XXX).



XXIX XXX

TABLE 8

Cyclization of o-benzylphenones (XXIX → XXX)

R	R′	TIME	YIELD	REFERENCES
		hours	*per cent*	
H	H	6	0.4*	(11)
CH_3	H	96	80	(27)
C_2H_5	H	96	69	(27)
C_6H_5	H	96	75	(27)
CH_3	C_6H_5	264	50†	(40)
C_2H_5	C_6H_5	264	47.5†	(40)
C_6H_5	C_6H_5	240	81	(40)
CH_3	CH_3			(13)
C_2H_5	CH_3			(13)
n-C_3H_7	CH_3			(13)
n-C_4H_9	CH_3			(13)
n-C_5H_{11}	CH_3			(13)
n-C_6H_{13}	CH_3			(13)
C_6H_5	CH_3			(13)
$C_6H_5CH_2$	CH_3			(13)

* Calculated from acetal. No effort made to carry reaction to completion.

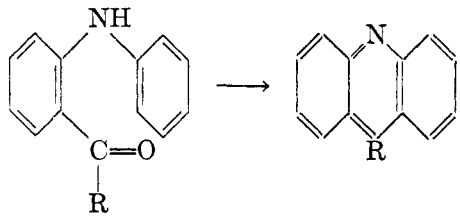
† Over-all yield from nitrile.

9-Phenyl-10-alkyl- and aryl-anthracenes (XXX, R′ = C_6H_5, R = alkyl or aryl) were prepared in this way (40). More recently, Berliner (13) has shown that the reaction can be extended to *o*-(α-phenylethyl)phenyl ketones (XXIX, R′ = CH_3) to yield 9-methyl-10-alkyl- and aryl-anthracenes (XXX, R′ = CH_3, R = alkyl or aryl).

The results of the anthracene cyclization are summarized in table 8.

C. Acridine system

The nitrogen analog of the anthracene synthesis is the cyclization of *o*-anilinobenzaldehydes or *o*-anilinophenyl ketones (XXXI, R = H, alkyl, or aryl) to yield acridine derivatives (XXXII). The older of the two, the acridine synthesis,

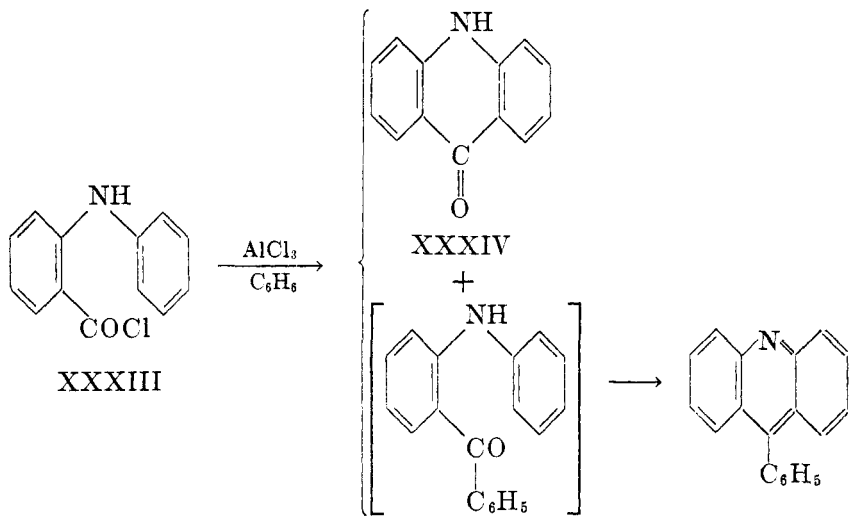


XXXI XXXII

(R = H, alkyl, or aryl)

has proved a versatile tool, and many complex and highly substituted derivatives have been prepared by its use.

The first instances of this reaction, encountered in the anthraquinone series (9, 59), were complex in character and the general nature of the reaction was not appreciated until a few years later (1906), when Ullmann and Ernst (145) came upon an accidental instance of this cyclization. When the acid chloride (XXXIII) of *N*-phenylanthranilic acid in benzene solution was treated with aluminum chloride, not only acridone but also 9-phenylacridine (XXXVI) was

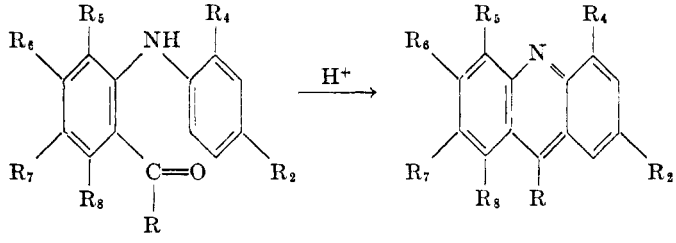


XXXIII XXXIV XXXV XXXVI

obtained. Ullmann and Ernst concluded that the intermediate in the formation of the latter compound was 2-phenylaminobenzophenone (XXXV), and they were able to show that such a cyclization could be effected by the use of sulfuric acid in acetic acid solution. Ullmann and his coworkers prepared many substituted 2-phenylaminobenzophenones containing substituents in either or both nuclei and showed that these ketones could be cyclized. Mayer and coworkers (107, 108, 109), a few years later, showed that the same reaction could be extended to *o*-phenylaminobenzaldehydes. A summary of their results, as well as those of other workers in the field, will be found in table 9.

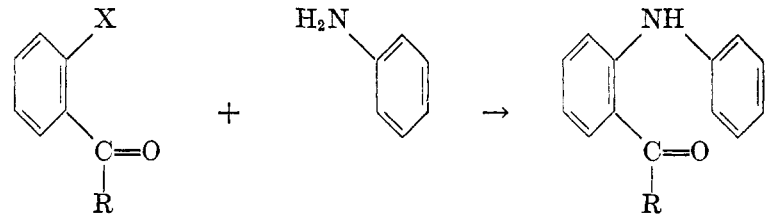
The general methods by which the required phenylamino phenones and benzaldehydes were obtained involved either the condensation of an arylamine

TABLE 9

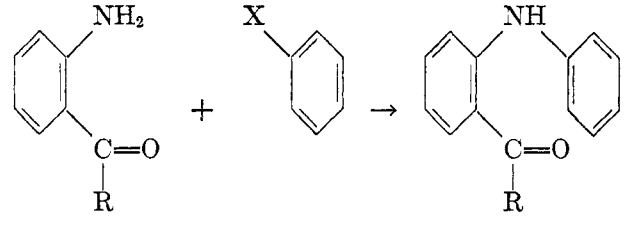


R	R_2	R_4	R_5	R_6	R_7	R_8	REFERENCES
H	CH_3	H	H	H	H	H	(96)
H	H	CH_3	H	H	H	H	(96)
H	OC_2H_5	H	H	H	H	H	(97)
H	H	OCH_2	H	H	H	H	(97)
H	NO_2	H	H	H	H	H	(96)
H	H	NO_2	H	H	H	H	(96, 109)
H	CH_3	NO_2	H	H	H	H	(109)
H	Cl	NO_2	H	H	H	H	(108)
H	NO_2	NO_2	H	H	H	H	(109)
CH_3	CH_3	H	H	H	H	H	(97)
CH_3	NO_2	H	H	H	H	H	(97)
CH_3	H	H	H	H	NO_2	H	(97)
C_6H_5	H	H	H	H	H	H	(107)
C_6H_5	CH_3	H	H	H	H	H	(97)
C_6H_5	OC_2H_5	H	H	H	H	H	(97)
C_6H_5	NO_2	H	H	H	H	H	(97)
C_6H_5	H	NO_2	H	H	H	H	(97)
C_6H_5	H	H	H	NO_2	H	H	(145)
C_6H_5	CH_3	NO_2	H	H	H	H	(107)
C_6H_5	Cl	NO_2	H	H	H	H	(107)
C_6H_5	NO_2	NO_2	H	H	H	H	(107)
C_6H_5	NH_2	H	H	NO_2	H	H	(145)
C_6H_5	H	H	H	NO_2	H	NO_2	(144)
C_6H_5	CH_3	NO_2	H	CH_3	H	H	(107)
C_6H_5	NO_2	NO_2	H	CH_3	H	H	(107)
C_6H_5	NO_2	NO_2	H	H	CH_3	H	(107)
C_6H_5	OCH_3	NO_2	NO_2	H	H	H	(130)
C_6H_5	NH_2	H	H	NO_2	H	NO_2	(144)
C_6H_5	H	OH	H	NO_2	H	NO_2	(144)
p-$CH_3OC_6H_4$	H	H	H	NO_2	H	H	(145)

(XXXVIII) with an *o*-halophenone or *o*-halobenzaldehyde (XXXVII, R = H, alkyl, or aryl) or of a halogen derivative (XL) with an *o*-aminophenone or *o*-aminobenzaldehyde (XXXIX).



XXXVII XXXVIII

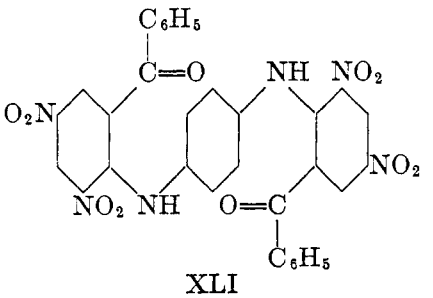


XXXIX XL

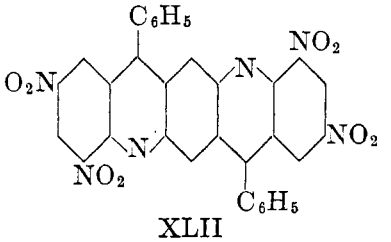
Not infrequently, nitro groups are introduced in positions ortho and/or para to the halogen atoms (XXXVII and XL), greatly increasing the ease of condensation. These condensations are usually brought about by heating the reactants at a reasonably high temperature (150–220°C.), usually in the presence of sodium or potassium carbonate. Under these conditions, it is not uncommon for a small quantity of the arylamino ketone or aldehyde formed to cyclize to the acridine. In the majority of the cases reported, the arylamino ketone or aldehyde was not purified, but used directly in the cyclization. In the absence of the carbonate, more cyclization takes place directly, but the yield of cyclized material is usually not high. If it is desired to bring about condensation and cyclization in a single operation, good yields may be obtained by using sodium acetate. Several instances of this direct cyclization have been recorded, though they are not so noted in the tables, the assumption being made that the ketone is the intermediate in each case. In the great majority of the cases, cyclization was effected as a separate step using sulfuric acid, either concentrated or diluted with acetic acid.

From table 9, it may be seen that ring closure is not prevented by the presence of alkoxyl groups meta to the point of expected cyclization and that acridine derivatives containing a variety of substituents may be prepared by this process. The 1,2- and 3,4-benzacridines prepared by this general method have been listed separately in tables 10 and 11.

In addition to the foregoing, there are several instances of cyclization of this general type which do not lend themselves well to tabular presentation. Ullmann and Broido (144) found that *p*-phenylenediamine could be condensed with 2 moles of 2-chloro-3,5-dinitrobenzophenone to give XLI, which underwent cyclization to yield the pentacyclic derivative (XLII).



XLI

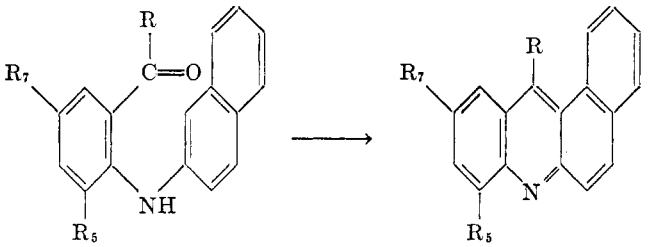


XLII

Stimulated by a desire to prepare substances capable of being used as, or converted to, dyes, investigators have prepared many acridine derivatives from the

TABLE 10

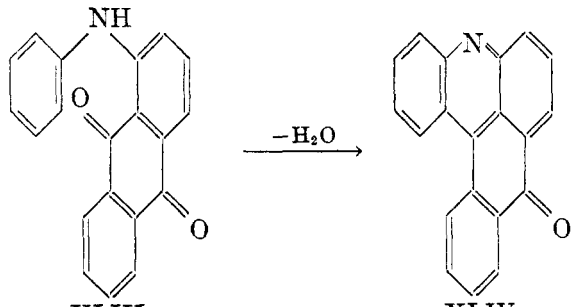
1,2-Benzacridines



R	R_5	R_7	REFERENCES
CH_3	H	H	(12)
C_6H_5	H	H	(107)
C_6H_5	H	NO_2	(145)
C_6H_5	NO_2	NO_2	(144)

anthraquinone nucleus by carbonyl cyclization. These can be divided into two groups: those which involve one or both of the carbonyls of the anthraquinone, and those which do not.

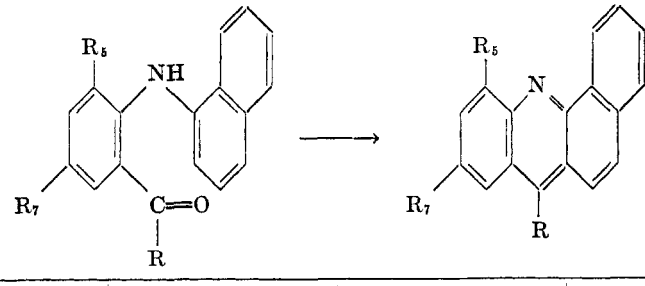
The first recorded instance of the formation of an acridine nucleus by aromatic cyclodehydration belongs to the former type. Damman and Gattermann (59) showed that 1-phenylaminoanthraquinone (XLIII) could be cyclized to yield a compound (XLIV) containing an acridine nucleus. This type of synthesis has been further extended (9, 76).



XLIII XLIV

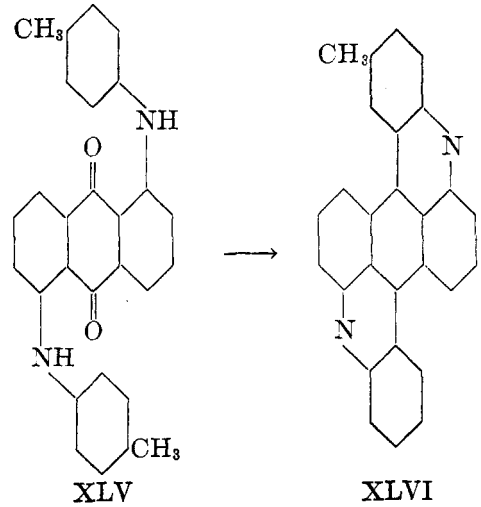
TABLE 11

3,4-Benzacridines



R	R_5	R_7	REFERENCES
CH_3	H	H	(12)
C_6H_5	H	H	(107)
C_6H_5	H	NO_2	(145)
C_6H_5	NO_2	NO_2	(144)

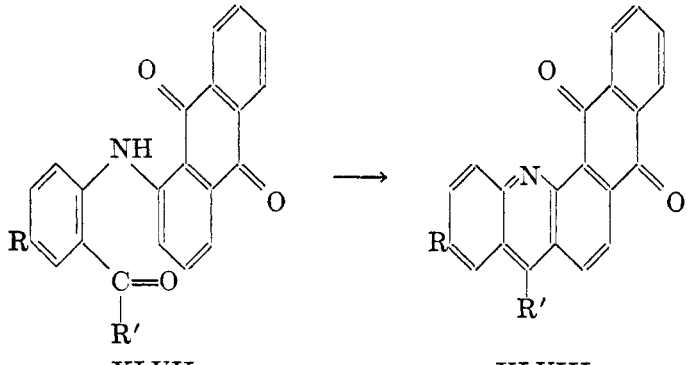
The patent literature reveals claims that both carbonyls of an anthraquinone nucleus can be used in such a cyclization. Thus, 1,5-di(*p*-toluidino)-anthraquinone (XLV) (9) may be cyclized to a compound (XLVI) which



XLV XLVI

contains two acridine nuclei. This is claimed to be general for 1,5-diarylaminoanthraquinones.

The other major class of "acridinated" anthraquinones consists of those in which the carbonyl groups of the quinone do not take part in the cyclization, condensation being effected instead with the terminal nuclei. Mayer and Freund (107) observed that derivatives of 1-(*o*-acylbenzamino)anthraquinones (XLVII) would undergo cyclization to yield acridine derivatives (XLVIII). Even more complex examples (10, 107) based on the same principles have been cited.

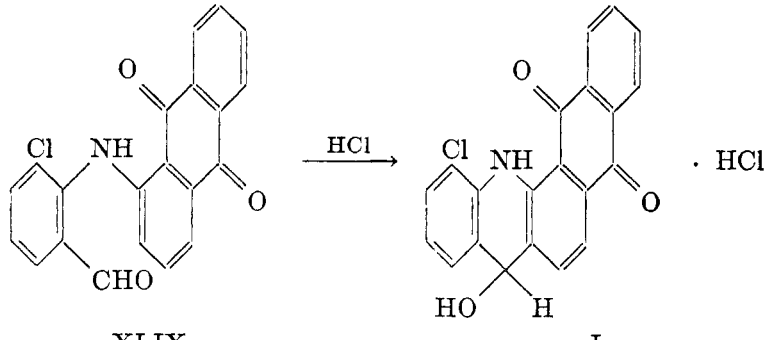


XLVII XLVIII

(R = H; R′ = C_6H_5)

(R = CH_3; R′ = CH_3)

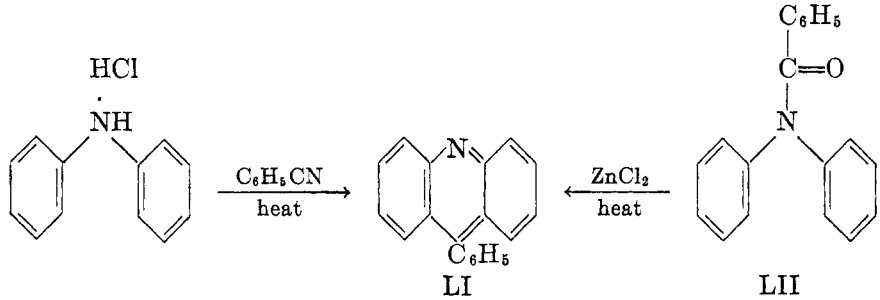
When 1-(*o*-formylbenzamino)anthraquinones (XLIX) are used, the reaction involved does not follow the general pattern, but appears, instead, to be arrested at what might be called an "intermediate" stage to yield 9,10-dihydroacridine derivatives (L) (108, 109). It is probable that all of the acridine cyclizations which have been discussed pass through such a stage, elimination of water being the final step. Berliner (12) has presented an electronic mechanism for the acridine cyclization.



XLIX L

In addition to the acridine synthesis already discussed, there are several others which may involve aromatic cyclodehydration. The first of these is the Bernthsen synthesis. Bernthsen found that heating diphenylamine hydrochloride with benzonitrile (14) or heating *N*-benzoyldiphenylamine (LII) with zinc

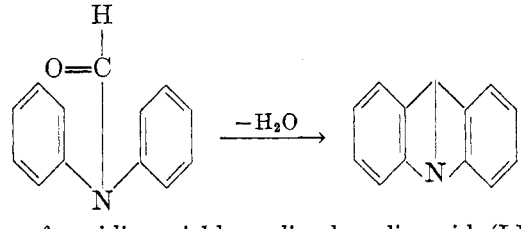
chloride (15) yielded a base which was shown (17) to be 9-phenylacridine (LI). Similar results (17) were obtained by heating diphenylamine with benzoic acid



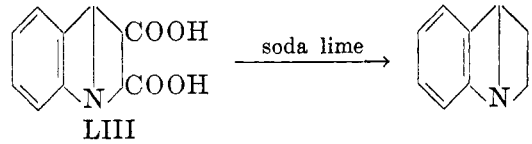
LI LII

and zinc chloride. In the same way, acetic (16, 17, 19, 73) or formic (17) acid with diphenylamine and zinc chloride gave 9-methylacridine and acridine, respectively. The mechanism proposed by Bernthsen and Bender (17) postulates the formation of a para bond.

Bernthsen and Bender mechanism

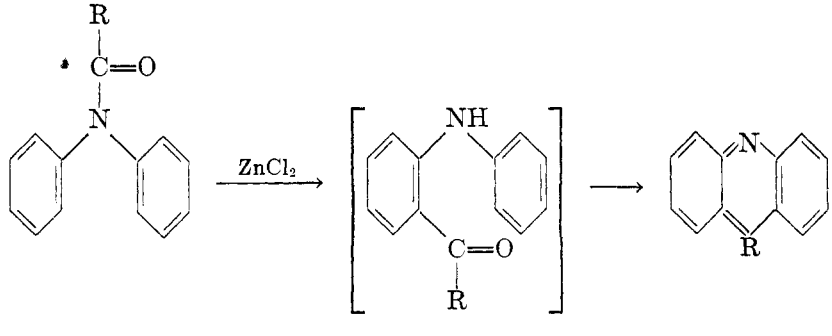


Since oxidation of acridine yields a dicarboxylic acid (LII) which may be decarboxylated to yield quinoline, they were convinced that quinoline likewise had a para bond.

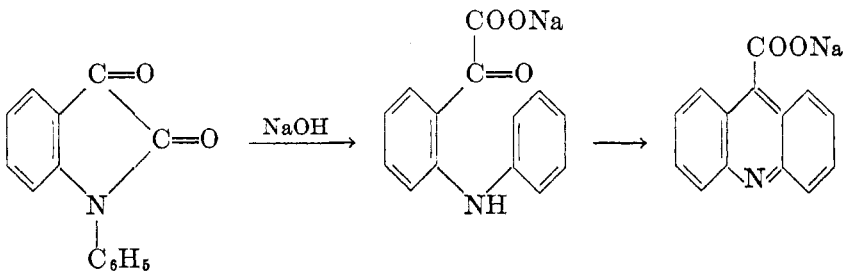


LIII

In view of the evidence (4) that no such bond exists in acridine, a more likely mechanism involves the preliminary migration of the acyl group to the ortho-position of one of the benzene nuclei, followed by aromatic cyclodehydration.



The last type of cyclization which will be considered is that involved when *N*-phenylisatin (LIV) is refluxed with a sodium hydroxide solution (75). The keto acid salt (LV) first formed cyclizes to yield the salt of acridine-9-carboxylic acid (LVI). Stollé (141) has applied this synthesis to the preparation of benz-



LIV LV LVI

and dibenz-acridinecarboxylic acids. If this reaction proceeds by the same mechanism as the acid-catalyzed cyclization previously considered, it may be a consequence of an activating influence of the carboxylate ion which makes possible cyclization at a lower hydrogen-ion concentration than is required in the previous cases.

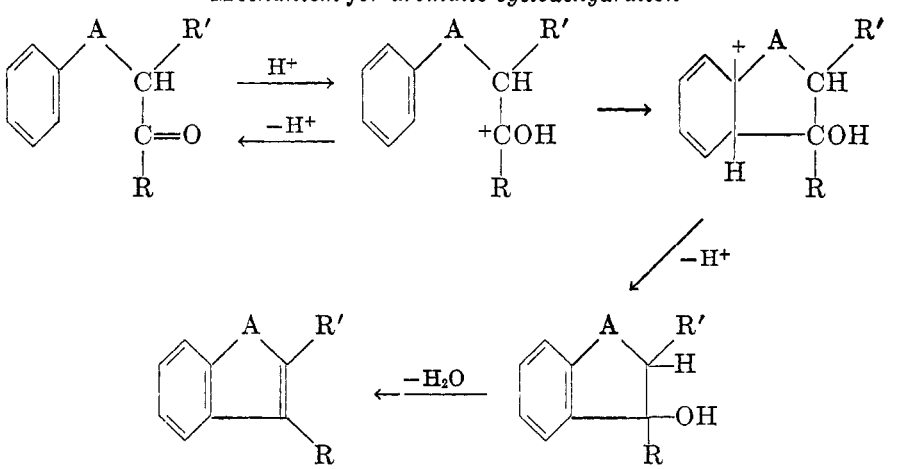
IV. MECHANISM

A. General mechanism

In discussing the mechanism for aromatic cyclodehydration, the general mechanism will be considered first and then two special cases—the phenanthrene and the anthracene cyclizations—considerable justification for their particular mention being found in the amount of pertinent evidence now available.

Turning to the general reaction, the first step probably involves the addition of

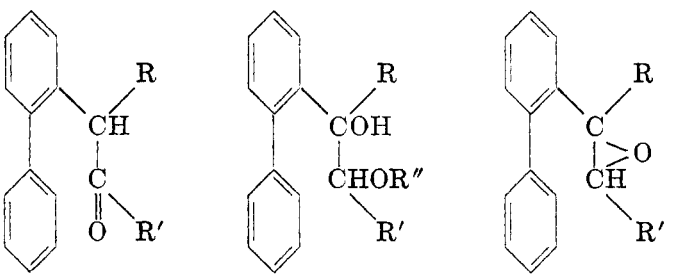
Mechanism for aromatic cyclodehydration



a proton to the carbonyl oxygen, followed by an electrophilic attack upon the benzenoid ring by the positively charged carbon. Following restoration of benzenoid character to the ring by loss of a proton, the carbinol is dehydrated with the creation of a new double bond.

B. Phenanthrene system

The cyclization of 2-biphenylylmethyl ketones (I) raises no problem which cannot be dealt with in terms of the general mechanism. This ability to yield phenanthrene derivatives is shared by two other types of compounds,—namely, 2-biphenylylglycols and their ethers (II) and olefin oxides (III). In view of the



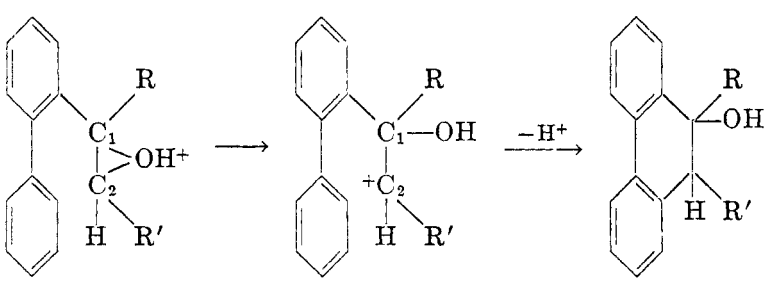
I II III

(R″ = H, alkyl, or aryl)

known ability of glycols and olefin oxides to rearrange to aldehydes and ketones, the mechanism for this transformation might seem too obvious to warrant further discussion, though a detailed analysis of the possibilities will show that these types of cyclization may be a good deal more complex in character. While such an analysis may be made for each of these, attention will be centered on the more important biphenylylolefin oxides (III).

The first step in cyclization is undoubtedly the addition of a proton to the

"Direct" mechanism



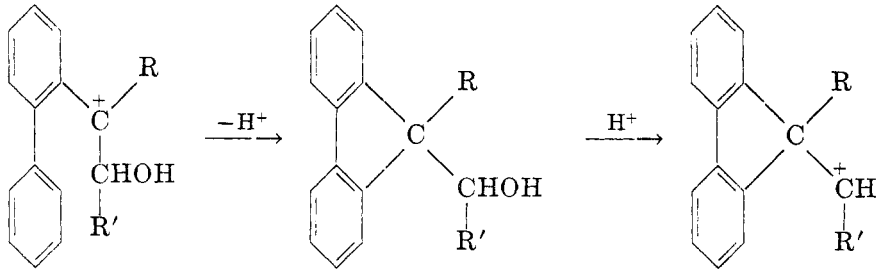
IV V VI

oxygen to yield the conjugate acid (IV). The second step is a scission of the bond between either the C_1 (first) or C_2 (second) carbon atom of the chain and the

oxide oxygen. In the simpler and more improbable case, we can imagine that the C_2-to-oxygen bond has been broken, leaving C_2 with a positive charge (V). This could attack the adjacent benzenoid ring, yielding a 9-hydroxy-9,10-dihydrophenanthrene derivative which could simply lose the elements of water to become fully aromatic. While this "direct" mechanism is appealing in its simplicity, it is probably erroneous since oxides, like glycols, tend to dissolve that carbon-to-oxygen bond which bears the most potent electron-releasing groups (93a), in this case, C_1.

If the hypothesis that it is the C_1-oxygen bond that is broken is accepted, there still remain several plausible routes to the phenanthrene hydrocarbon. The carbonium ion (VII) may stabilize itself in any one of at least three ways. It

"Fluorene carbinol" mechanism



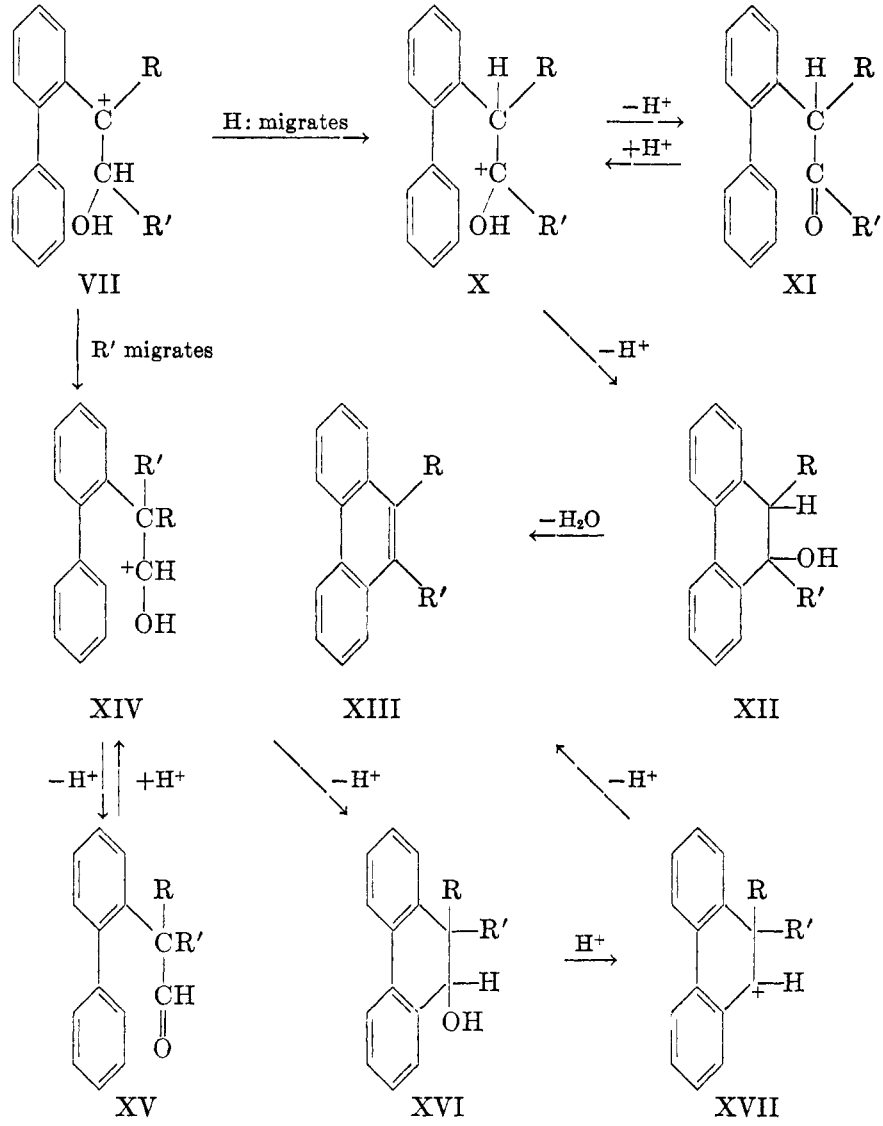
VII VIII IX

may attack the adjacent aromatic ring electrophilically, yielding a "fluorene carbinol" (VIII). Present evidence (48, 110, 152) seems to indicate that fluorene carbinols of type VIII (R = R′), upon dehydration, rearrange to yield phenanthrene derivatives, evidently through the intermediate IX.

Another way in which the carbonium ion (VII) may achieve stability is by rearrangement, the hydrogen or R′ group migrating to C_1. If we assume the migration of the hydrogen atom with an electron pair, the result is the conjugate acid (X) of the ketone (XI). The cyclization of this conjugate acid (X) yields a dihydrophenanthrene derivative (XII), which is immediately dehydrated to the fully aromatic compound (XIII).

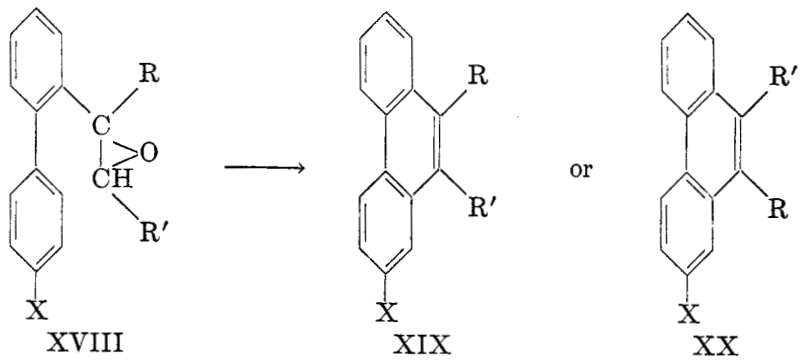
If, instead of hydrogen, the R′ group of the original carbonium ion (VII) migrates with a pair of electrons, the product is the conjugate acid (XIV) of the aldehyde (XV). Cyclization of the conjugate acid (XIV) yields the 9,10-dihydrophenanthrol (XVI), which may be dehydrated, with rearrangement, to yield the phenanthrene hydrocarbon (XIII), the ion (XVII) probably being formed as an intermediate. If R and R′ are different, the group which migrates in the first rearrangement (VII → XIV) may not be that which migrates in the second (XVII → XIII). A forseeable consequence of such a double rearrangement is that in the cyclization of a 2-biphenylylolefin oxide (XVIII) in which the biphenylyl group is unsymmetrically substituted, either or both of two possible phenanthrene cyclization products (XIX or XX) might be obtained.

"Carbonyl" mechanism

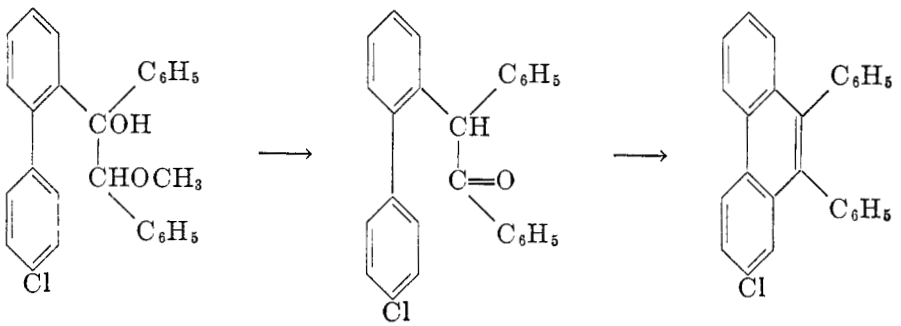


What evidence exists, points to the "carbonyl" mechanism as opposed to the "direct" or "fluorene carbinol" mechanisms. It has been found (46) that the cyclization of 1,2-diphenyl-1-(4-chlorobiphenyl-2-yl)-2-methoxyethanol-1 (XXI) to 2-chloro-9,10-diphenylphenanthrene (XXIII) involves as an intermediate the ketone XXII.

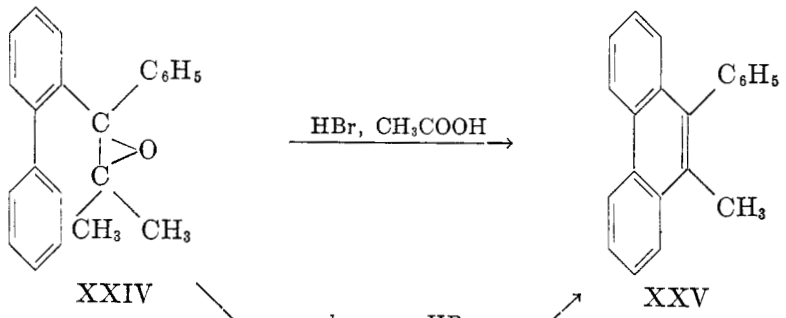
Another observation (36) made in connection with the olefin oxide type of cyclization involves the oxide (XXIV) of 1-phenyl-1-(2-biphenylyl)-2-methylpropene-1, which loses a methyl group when refluxed with hydrobromic and acetic acids, yielding 9-phenyl-10-methylphenanthrene (XXV). With cold



XVIII XIX XX

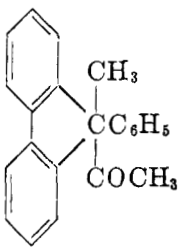


XXI XXII XXXIII



XXIV XXV XXVI

concentrated sulfuric acid, the product is believed to be 9-methyl-9-phenyl-10-methylene-9,10-dihydrophenanthrene (XXVI). This hydrocarbon likewise yields 9-phenyl-10-methylphenanthrene (XXV) when refluxed with boiling hydrobromic and acetic acids. A possible explanation for the formation of XXVI is that in concentrated sulfuric acid, at least, the first reaction is the rearrangement of the oxide to a ketone (XXVII), followed by cyclization and elimination of the elements of water.

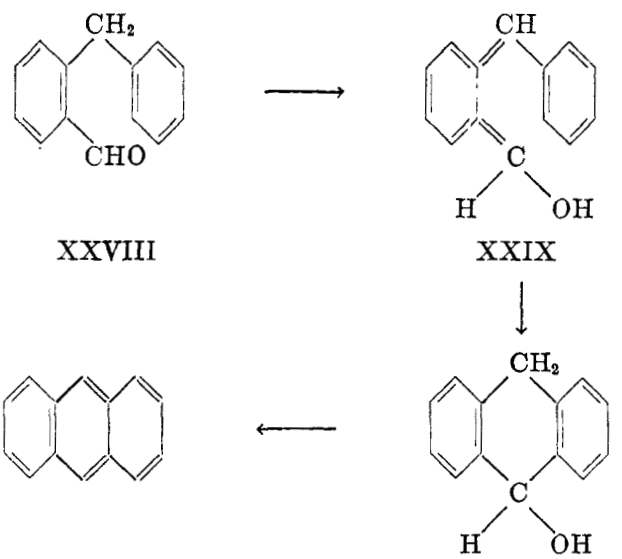


XXVII

C. Anthracene system

In addition to characterizing the cyclization of *o*-benzylbenzaldehyde (XXVIII) as "a modification of the Elbs synthesis of anthracene derivatives," Bergmann (11) proposed a mechanism based on that suggested by Cook (56) for the Elbs reaction.

Bergmann mechanism

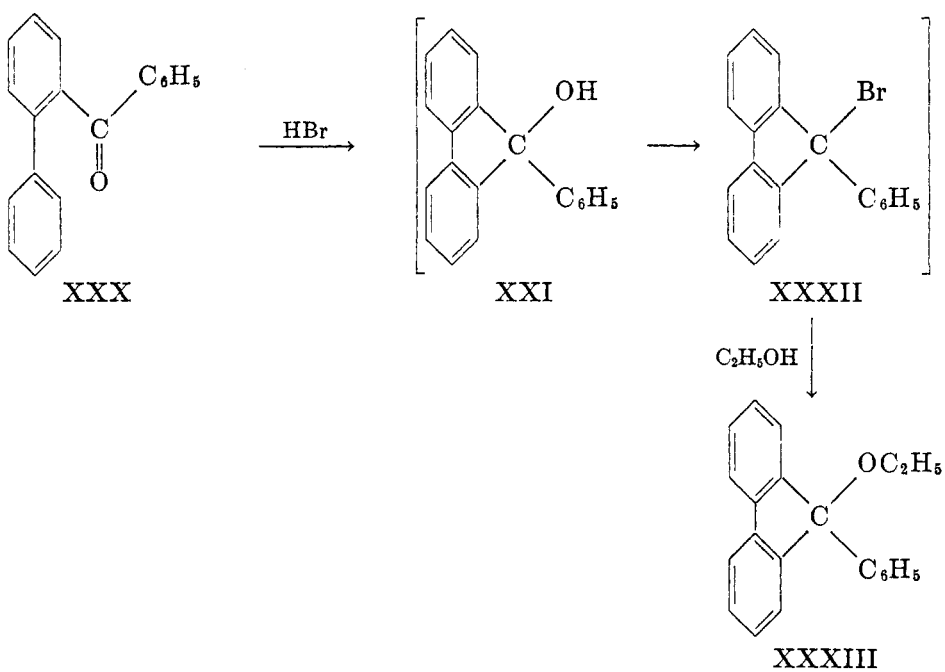


XXVIII XXIX

The Bergmann mechanism, later erroneously attributed (12) to Bradsher, involves enolization, cyclization with transannular migration of hydrogen, and finally dehydration. The author's opinion (27) that this acid-catalyzed cyclization cannot properly be considered an example of the Elbs pyrolysis has received the support of Fieser (65), although apparently not that of Cook (57).

The author suggested as a "satisfactory working hypothesis" that the intermediate in the cyclization was the enol (XXIX), which cyclized directly by loss of water in direct analogy to the mechanism proposed by Carter and Van Loon (55) for the dimolecular cyclization of β-phenylacetaldehyde (see Section II, A).

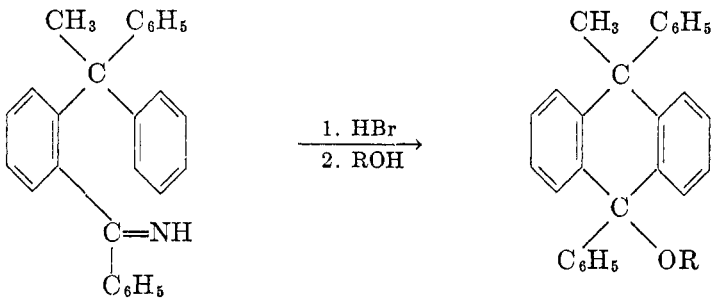
In conjunction with Smith (39, 41), an investigation was carried out which demonstrated by cyclization of *o*-phenylbenzophenone (XXX) to a fluorene derivative that enolization was not necessary for cyclization. In order to prevent the further condensation of the fluorenol believed to be first formed, the reaction was carried out in 48 per cent hydrobromic acid to effect conversion of the carbinol to the more stable bromide (XXXII). The latter was identified by



XXX XXI XXXII XXXIII

conversion to 9-ethoxy-9-phenylfluorene (XXXIII) by the action of ethyl alcohol.

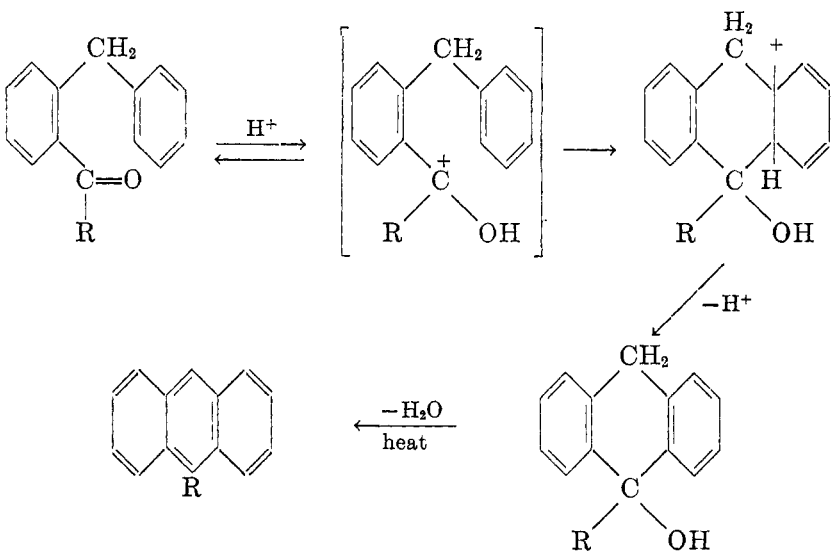
Since it might be objected that the formation of a five-membered ring is not exactly comparable to the formation of a six-membered ring, the imine (XXXIV) was prepared and subjected directly to the action of hydrobromic acid. The crude bromide obtained was refluxed with methyl and ethyl alcohols to yield compounds having the composition of the expected ethers (XXXV, R = CH_3 and C_2H_5).



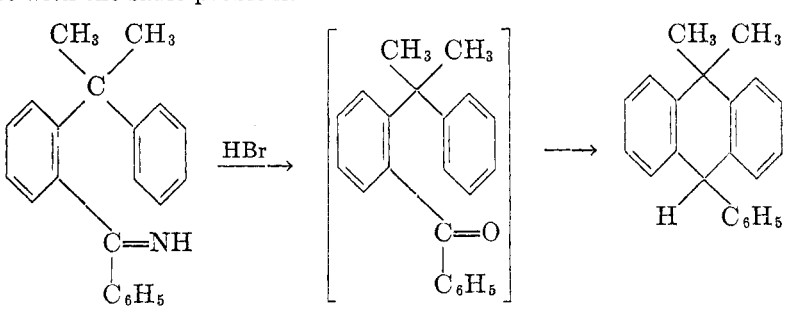
XXXIV XXXV

On the basis of their observation, the authors presented the following mechanism;

Mechanism of anthracene cyclization



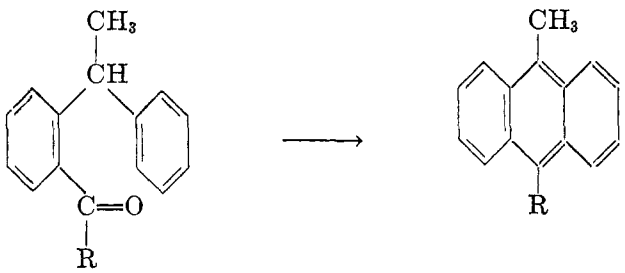
Essentially the same mechanism was offered by Berliner (12) in a paper dealing in part with the same problem.



XXXVI XXXVII XXXVIII

In an effort to effect a cyclization yielding a 9,10-dihydroanthracene derivative whose structure could be demonstrated by synthesis, Bradsher and Smith (42) refluxed the imine XXXVI with hydrobromic acid. Despite the obvious inability of the expected intermediate (XXXVII) to enolize, cyclization was effected, yielding by concomitant reduction a compound which was shown to be 9,9-dimethyl-10-phenyl-9,10-dihydroanthracene (XXXVIII).

Recently, Berliner (13) has found the rates of cyclization of some *o*-(α-phenylethyl)phenones to be first order with respect to the ketone. He has presumed



XXXIX XL

TABLE 12

KETONE R	*K*
	$min.^{-1} \times 10^{-2}$
Methyl	4.6
Ethyl	1.8
n-Propyl	0.99
n-Butyl	0.35
n-Pentyl	0.36
n-Hexyl	0.36

that the rate was determined by the attack of the carbonium ion on the benzene ring. The rate constants for the cyclization of the alkyl ketones are recorded in table 12. Berliner concluded that this decrease in rate with increasing size of the alkyl group up to the butyl ketone can best be attributed to the increase in electron-releasing character of the alkyl group concerned. This electron release results in an increase of electron density on the positive central carbon atom, resulting in a decrease in cyclization rate.

V. SUMMARY

An effort has been made to correlate those cyclodehydration reactions which yield a new, fully aromatic ring through the acid-catalyzed attack of a ketonic or aldehydic carbonyl group on an aromatic nucleus. In each system discussed, the apparent limitations of the cyclization are pointed out, together with the effect of substituents on the ease of cyclization. The mechanism has been briefly considered.

VI. REFERENCES

(1) AUTENRIETH, W.: Ber. **24,** 159 (1891).
(2) AUWERS, K. VON, AND KEIL, G.: Ber. **36,** 1861 (1903).
(3) AUWERS, K. VON, AND KEIL, G.: Ber. **36,** 3902 (1903).
(4) AUWERS, K. VON, AND KRAUL, R.: Ber. **58,** 543 (1925).
(5) AUWERS, K. VON, AND MÖLLER, K.: J. prakt. Chem. **109,** 124 (1925).
(6) AXE, W.: J. Am. Chem. Soc. **61,** 1017 (1939).
(7) AXE, W., AND BAILEY, J.: J. Am. Chem. Soc. **60,** 3028 (1938).
(8) AXE, W., AND BAILEY, J.: J. Am. Chem. Soc. **61,** 2609 (1939).
(9) BAYER, F., AND CO.: German patent 126,444; Chem. Zentr. **1902,** I, 78.
(10) BAYER, F., AND CO.: German patent 239,544; Chem. Zentr. **1911,** II, 1396.
(11) BERGMANN, E.: J. Org. Chem. **4,** 1 (1939).
(12) BERLINER, E.: J. Am. Chem. Soc. **64,** 2894 (1942).
(13) BERLINER, E.: J. Am. Chem. Soc. **66,** 533 (1944).
(14) BERNTHSEN, A.: Ann. **192,** 1 (1878).
(15) BERNTHSEN, A.: Ber. **15,** 3011 (1882).
(16) BERNTHSEN, A.: Ber. **16,** 767 (1883).
(17) BERNTHSEN, A., AND BENDER, F.: Ber. **16,** 1802 (1883).
(18) BESTHORN, E., BONZHAF, E., AND JAEGLE, G.: Ber. **27,** 3035 (1894).
(19) BESTHORN, E., AND FISCHER, O.: Ber. **16,** 68 (1883).
(20) BESTHORN, E., AND JAEGLE, G.: Ber. **27,** 907 (1894).
(20a) BETTZIECHE, F.: Z. physiol. Chem. **150,** 177 (1925).
(21) BEYER, C.: Ber. **20,** 1767 (1887).
(22) BISCHLER, A.: Ber. **25,** 2860 (1892).
(23) BISCHLER, A., AND FIREMAN, P.: Ber. **26,** 1336 (1893).
(24) BORSCHE, W.: Ann. **377,** 70 (1910).
(25) BOUGAULT, J.:Compt. rend. **159,** 745 (1915).
(26) BRADSHER, C.: J. Am. Chem. Soc. **61,** 3131 (1939).
(27) BRADSHER, C.: J. Am. Chem. Soc. **62,** 486 (1940).
(28) BRADSHER, C.: J. Am. Chem. Soc. **62,** 1007 (1940).
(29) BRADSHER, C.: J. Am. Chem. Soc. **64,** 1007 (1942).
(30) BRADSHER, C., AND AMORE, S.: J. Am. Chem. Soc. **63,** 493 (1941).
(31) BRADSHER, C., AND AMORE, S.: J. Am. Chem. Soc. **65,** 2016 (1943).
(32) BRADSHER, C., AND AMORE, S.: J. Am. Chem. Soc. **66,** 1280 (1944).
(33) BRADSHER, C., AND BURHANS, A.: J. Am. Chem. Soc. **62,** 3140 (1940).
(34) BRADSHER, C., AND RAPOPORT, L.: J. Am. Chem. Soc. **65,** 1646 (1943).
(35) BRADSHER, C., AND RAPOPORT, L.: J. Am. Chem. Soc. **66,** 1281 (1944).
(36) BRADSHER, C., AND RAPOPORT, L.: Unpublished work.
(37) BRADSHER, C., AND ROSHER, L.: J. Am. Chem. Soc. **61,** 1524 (1939).
(38) BRADSHER, C., AND SCHNEIDER, A.: J. Am. Chem. Soc. **60,** 2960 (1938).
(39) BRADSHER, C., AND SMITH, E.: Abstracts (page 20) of papers presented before the Division of Organic Chemistry at the 104th Meeting of the American Chemical Society, which was held in Memphis, Tennessee, April, 1942.
(40) BRADSHER, C., AND SMITH, E.: J. Am. Chem. Soc. **65,** 451 (1943).
(41) BRADSHER, C., AND SMITH, E.: J. Am. Chem. Soc. **65,** 854 (1943).
(42) BRADSHER, C., AND SMITH, E.: J. Am. Chem. Soc. **65,** 1643 (1943).
(43) BRADSHER, C., AND TESS, R.: J. Am. Chem. Soc. **61,** 2184 (1939).
(44) BRADSHER, C., AND WERT, R.: J. Am. Chem. Soc. **62,** 2806 (1940).
(45) BRADSHER, C., AND WISSOW, L.: J. Am. Chem. Soc. **65,** 2304 (1943).
(46) BRADSHER, C., AND WISSOW, L.: Unpublished work.
(47) BRAUN, J. VON, GMELIN, W., AND PETZGOLD, A.: Ber. **57,** 382 (1924).
(48) BROWN, W., AND BLUESTEIN, B.: J. Am. Chem. Soc. **62,** 3256 (1940).
(49) BÜLOW, C., AND ISSLER, G.: Ber. **36,** 2447 (1903).
(50) CLAISEN, L., AND FISCHER, L.: Ber. **20,** 2191 (1881).

(51) CLAISEN, L., AND FISCHER, L.: Ber. **21**, 1135 (1882).
(52) COLLET, A.: Bull. soc. chim. [3] **17**, 66 (1897).
(53) COMBES, A.: Bull. soc. chim. [2] **49**, 89 (1888).
(54) COMBES, A.: Compt. rend. **106**, 142 (1888).
(55) CARTER, H., AND VAN LOON, E.: J. Am. Chem. Soc. **60**, 1077 (1938).
(56) COOK, J.: J. Chem. Soc. **1931**, 487.
(57) COOK, J.: Annual Reports on the Progress of Chemistry **39**, 178 (1942), The Chemical Society, London.
(58) CULMANN, J.: Ber. **21**, 2595 (1888).
(59) DAMMAN, K., AND GATTERMANN, L.: Z. für farb. und text. Chem. **1**, 325 (1902); Chem. Zentr. **1902**, II, 368.
(60) DELISLE, A.: Ann. **260**, 250 (1890).
(61) DELISLE, A., AND SCHWALM, A.: Ber. **25**, 2980 (1892).
(62) ERLENMEYER, E., JR., AND KUNLIN, J.: Ber. **35**, 384 (1902).
(63) ERLENMEYER, E., JR., AND MATTER, O.: Ann. **337**, 271 (1904).
(64) FARBEN, I. G.: German patent 614,396; Chem. Zentr. **1935**, II, 2127.
(65) FIESER, L. F.: *Organic Reactions*, Vol. 1, p. 131. J. Wiley and Sons, Inc., New York (1944).
(66) FIESER, L. F., AND BRADSHER, C.: J. Am. Chem. Soc. **58**, 1738 (1936).
(67) FIESER, L. F., AND HOLMES, H.: J. Am. Chem. Soc. **58**, 2319 (1936).
(68) FIESER, L. F., AND HOLMES, H.: J. Am. Chem. Soc. **60**, 2548 (1938).
(69) FISCHER, E.: Ann. **236**, 126 (1886).
(70) FISCHER, E.: Ber. **26**, 764 (1893).
(71) FISCHER, E., AND SCHMITT, T.: Ber. **21**, 1071 (1888).
(72) FISCHER, E., AND SCHMITT, T.: Ber. **21**, 1811 (1888).
(73) FISCHER, O.: Ber. **16**, 1820 (1883).
(74) FISCHER, O., SCHIEBE, G., MERKEL, P., AND MÜLLER, R.: J. prakt. Chem. **100**, 91 (1920).
(75) FRIEDLÄNDER, P., AND KUNZ, K.: Ber. **55**, 1597 (1922).
(76) FRIEDLÄNDER, P., AND SCHICK, G.: Z. für farb. und text. Chem. **2**, 430 (1903); Chem. Zentr. **1904**, I, 101,
(77) FRIES, K., HERRING, H., HEMMICKEN, E., AND SICHERT, G.: Ann. **527**, 83 (1937).
(78) FRITSCH, P.: Ber. **26**, 419 (1893).
(79) FRITSCH, P.: Ann. **286**, 1 (1895).
(80) GEISSMAN, T., AND TESS, R.: J. Am. Chem. Soc. **62**, 514 (1940).
(81) GLENN, R., AND BAILEY, J.: J. Am. Chem. Soc. **61**, 2612 (1939).
(82) GLENN, R., AND BAILEY, J.: J. Am. Chem. Soc. **63**, 641 (1941).
(83) GRAVES, G., AND ADAMS, R.: J. Am. Chem. Soc. **45**, 2439 (1923).
(84) HANTZSCH, A.: Ber. **19**, 1290 (1886).
(85) HANTZSCH, A., AND PFEIFFER, G.: Ber. **19**, 1301 (1886).
(86) HAWORTH, R., RICHARDSON, T., AND SHELDRICH, G.: J. Chem. Soc. **1935**, 1576.
(87) HAWORTH, R., AND SHELDRICH, G.: J. Chem. Soc. **1935**, 636.
(88) HAWORTH, R., AND WOODCOCK, D.: J. Chem. Soc. **1938**, 809.
(89) HELL, C., AND BAUER, H.: Ber. **37**, 872 (1904).
(90) HELL, C., AND COBIN, H.: Ber. **37**, 866 (1904).
(91) HESSE, J.: Ber. **30**, 1438 (1897).
(92) HOWELL, W., AND ROBERTSON, A.: J. Chem. Soc. **1936**, 587.
(93) INCE, W.: Ann. **253**, 35 (1889).
(93a) INGOLD, C.: Annual Reports on the Progress of Chemistry **25**, 135 (1938), The Chemical Society, London.
(94) JACOBSEN, R., AND ADAMS, R.: J. Am. Chem. Soc. **45**, 2455 (1923).
(95) JAPP, F., AND MURRAY, T.: Ber. **26**, 2638 (1893).
(96) JENSEN, H., AND FRIEDRICH, M.: J. Am. Chem. Soc. **49**, 1049 (1927).
(97) JENSEN, H., AND RETHWISCH, F.: J. Am. Chem. Soc. **50**, 1144 (1928).

(98) JOHNSON, W.: *Organic Reactions*, Vol. 2, p. 120. J. Wiley and Sons, Inc., New York (1944).
(99) JOHNSON, W., AND MATTHEWS, F.: J. Am. Chem. Soc. **66**, 210 (1944).
(100) JULIAN, P., AND PIKL, J.: J. Am. Chem. Soc. **55**, 2105 (1933).
(101) KLIEGL, A.: Ber. **38**, 84 (1905).
(102) KOENIGS, W., AND JAEGLE, G.: Ber. **28**, 1046 (1895).
(103) KOENIGS, W., AND MENGEL, A.: Ber. **37**, 1322 (1904).
(104) LEMPERT, H., AND ROBINSON, R.: J. Chem. Soc. **1934**, 1419.
(105) LIONS, F.: J. Proc. Roy. Soc. N. S. Wales **63**, 159 (1930); Chem. Abstracts **24**, 5300 (1930).
(105a) LIONS, F., PERKIN, W., AND ROBINSON, R.: J. Chem. Soc. **127**, 1158 (1925).
(106) MARCKWALD, W., AND SCHMIDT, C.: Ann. **274**, 367 (1893).
(107) MAYER, F., AND FREUND, W.: Ber. **55**, 2049 (1922).
(108) MAYER, F., AND LEVIS, I.: Ber. **52**, 1641 (1919).
(109) MAYER, F., AND STEIN, B.: Ber. **50**, 1306 (1917).
(110) MEERWEIN, H.: Ann. **405**, 129, 173 (1914).
(111) MEISENHEIMER, J.: Ber. **57**, 1744 (1924).
(112) MITTER, P., AND DE, S.: J. Indian Chem. Soc. **16**, 35 (1939).
(113) MÖHLAU, R.: Ber. **14**, 171 (1881).
(114) MÖHLAU, R.: Ber. **15**, 2480 (1882).
(115) MÖHLAU, R.: Ber. **18**, 163 (1885).
(116) MÖHLAU, R.: Ber. **21**, 510 (1888).
(117) MURRAY, R., AND TURNER, E.: J. Chem. Soc. **1934**, 856.
(118) NENCKI, M., AND BERLINERBLAU, J.: Ber. **20**, 753 Ref. (1887).
(119) OHMAKI, T.: J. Pharm. Soc. Japan **58**, 4 (1938).
(120) VON PECHMANN, A.: Ber. **16**, 516 (1883).
(121) PERKIN, W., AND ROBINSON, R.: J. Chem. Soc. **105**, 2376 (1914).
(122) PICTET, A.: Ber. **19**, 1063 (1886).
(123) PICTET, A., AND DUPARC, L.: Ber. **20**, 3415 (1887).
(124) POMERANZ, P.: Monatsh. **14**, 116 (1893).
(125) POMERANZ, P.: Monatsh. **15**, 299 (1894).
(126) POMERANZ, P.: Monatsh. **15**, 739 (1894).
(127) POMERANZ, P.: Monatsh. **18**, 1 (1897).
(128) RINKES, I.: Rec. trav. chim. **39**, 200 (1920).
(129) ROBERTS, E., AND TURNER, E.: J. Chem. Soc. **1927**, 1832.
(130) ROBINSON, R., AND TOMLINSON, M.: J. Chem. Soc. **1934**, 1524.
(131) RUGHEIMER, L., AND SCHÖN, P.: Ber. **42**, 2374 (1909).
(132) SCHENK, L., AND BAILEY, J.: J. Am. Chem. Soc. **61**, 2613 (1939).
(133) SCHÖNBERG, A., AND WARREN, F.: J. Chem. Soc. **1939**, 1838.
(134) SPÄTH, E.: Monatsh. **33**, 1029 (1912).
(135) STAEDEL, W.: Ber. **21**, 2196 (1888).
(136) STAUB, P.: Helv. Chim. Acta **5**, 888 (1922).
(137) STOERMER, R.: Ber. **28**, 1253 (1895).
(138) STOERMER, R.: Ann. **312**, 237 (1900).
(139) STOERMER, R., AND ATENSTÄDT, P.: Ber. **35**, 3560 (1902).
(140) STOERMER, R., AND WEHLN, R.: Ber. **35**, 3549 (1902).
(141) STOLLÉ, R.: J. prakt. Chem. **105**, 137 (1922).
(142) THIELEPAPE, E.: Ber. **55**, 127 (1922).
(143) TYSON, F.: J. Am. Chem. Soc. **61**, 183 (1939).
(144) ULLMANN, F., AND BROIDO, J.: Ber. **39**, 356 (1906).
(145) ULLMANN, F., AND ERNST, H.: Ber. **39**, 298 (1906).
(146) VERKADE, P., AND JANETZKY, E.: Rec. trav. chim. **62**, 763 (1943).
(147) VERKADE, P., AND JANETSKY, E.: Rec. trav. chim. **62**, 775 (1943).
(148) VLADESCO, D.: Bull. soc. chim. [3] **6**, 807 (1891).

(149) WOLFF, L.: Ber. **21,** 123 (1888).
(150) WALSH, G., AND WEIZMANN, C.: J. Chem. Soc. **97,** 685 (1910).
(151) WEITZENBOCK, R.: Monatsh. **34,** 193 (1913).
(152) WERNER, A., AND GROB, A.: Ber. **37,** 2887 (1904).
(152a) WOODWARD, R., AND DOERING, W.: J. Am. Chem. Soc. **67,** 860 (1945).
(153) ZINCKE, T., AND BREUER, A.: Ann. **226,** 23 (1884).
(154) ZINCKE, T.: Ann. **240,** 137 (1887).