THE CHEMISTRY OF QUINOLINES

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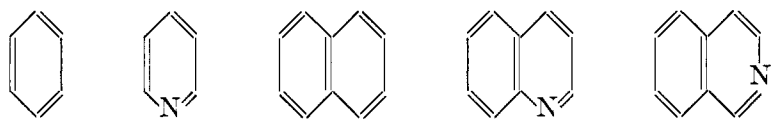
The review is an attempt to deal with the chemistry of quinolines under the following headings: (*a*) reactions which lead to the synthesis of quinolines; (*b*) the reactions of quinolines not dependent upon the presence of substituents; (*c*) the reactions of quinolines dependent upon substituents; and (*d*) the natural occurrence of quinolines.

The discovery of quinoline in 1842 by Gerhardt as the result of the drastic decomposition of quinine and of cinchonine antedates Anderson's discovery of pyridine by four years. It was not, however, until Weidel in 1879 and later Ladenburg studied the pyridine bases in detail that the foundations for the chemistry of quinoline and isoquinoline were well and truly laid. The latter was discovered in the quinoline fraction of coal tar by Hoogewerff and van Dorp in 1885. It was largely due to the efforts of these chemists that subsequent work on the isoquinoline alkaloids proved so fruitful in the next century.

The constitution of pyridine follows not only from the many syntheses but analytically from a number of important observations. Reduction adds six hydrogen atoms to pyridine, producing a secondary base,—namely, piperidine, $C_5H_{11}N$. Piperidine is a saturated compound and therefore monocyclic. A variety of methods are available for opening this ring, with the formation of an unbranched chain of five carbon atoms. It is thus possible to write pyridine (II) as a simple derivative of benzene (I) in which a methine group has been replaced by N≡.



I Benzene — II Pyridine — III Naphthalene — IV Quinoline — V Isoquinoline

Just as naphthalene (III) may be regarded as the condensation product of two benzene nuclei, it is possible to regard quinoline (IV) and isoquinoline (V) as benzpyridines, quinoline being benz-2,3-pyridine and isoquinoline being benz-3,4-pyridine.[1] Like the benzene nucleus, the pyridine nucleus possesses aromatic character. The double bonds do not add groups or radicals, and if reaction does occur (except with hydrogen), it is in general one of substitution.

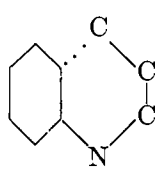
[1] The question of the nature of the unsaturation of the pyridine nucleus and the disposition of the double bonds is strictly analogous to the same problem of the benzene nucleus. No attempt will be made in this review to discuss such problems.

Whether or not the pyridine nucleus is more aromatic in character than the benzene nucleus depends upon the criteria chosen. Certainly it is extremely resistant to a variety of chemical changes, of which oxidation and decomposition by heat alone may be taken as examples. When benzpyridines are oxidized, the benzene nucleus is attacked first. The resultant products are generally pyridinedicarboxylic acids.

In the following pages an effort will be made to elucidate the salient points in the chemistry of quinolines. No attempt will be made to catalogue all of the compounds. This has been done by Hollins (109) up to the time of the publication of his very excellent book. Further, the naturally occurring alkaloids of the quinoline and isoquinoline group have been ably and exhaustively treated by Henry (105) in the third edition of his book and only casual reference to this subject is deemed desirable. There remains the subject of syntheses and of reactions.

I. SYNTHESES OF QUINOLINE AND OF QUINOLINE DERIVATIVES

Subsequent to the elucidation of its structure, the synthesis of quinoline by Skraup was probably the greatest single impetus to its further study. Not only was quinoline readily available from easily accessible materials, but a legion of substitution products could be as readily obtained. This reaction, which is one of the great classics of organic chemistry, has been the subject of numerous researches into its possible mechanism as well as of many attempts to improve its utility as far as yields and safety are concerned. In general, it is carried out by heating a mixture of an aromatic amine (with one of the ortho positions unsubstituted), glycerol, sulfuric acid, and an oxidizing agent. The last may be the nitro compound corresponding to the amine used, but arsenic acid, ferric oxide, and even picric acid have been recommended. There have been described some thirty procedures by which quinoline or its derivatives may be obtained. Some of these are but slight variations of the others, and all but a few require aniline or a derivative as one of the starting materials. That is to say, the benzene nucleus and the nitrogen of the quinoline are already joined. In these syntheses, therefore, it becomes a problem of ring closure between the nitrogen and the ortho position of the benzene ring, with the addition of the required number of carbon atoms. There are, therefore, only four fundamental syntheses possible, all others being variations of these. The following four partial formulas indicate this graphically. The dotted line indicates the two atoms which



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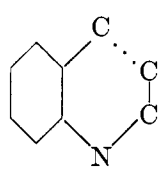

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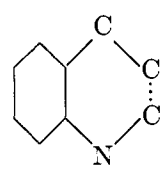

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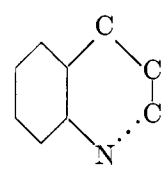


IV

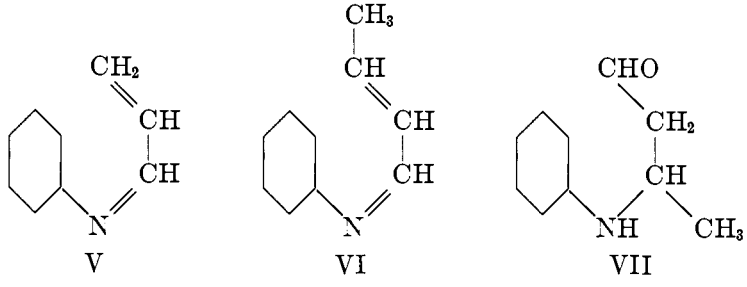
must be united to complete the hetero ring. In Type I the ring is to be completed by a union between the γ-carbon atom and the benzene nucleus; in Type II the

union is to be between the β- and γ-carbon atoms; in Type III the union is to be between the α- and β-carbon atoms; and in Type IV the union is to be effected between the nitrogen atom and the α-carbon atom. There are many syntheses which superficially do not fit into this simple classification. For example, the condensation of *o*-aminobenzaldehyde with ketones introduces carbon atoms α and β in the one procedure and in effect is a combination of Types II and IV. Nevertheless, it is virtually certain that this reaction goes in stages and that the last stage belongs to one of the simple types. The well-known Skraup synthesis is a combination of Types I and IV.

In the following résumé the four types will be discussed separately. In each synthesis where there are two or more stages, only the last will be considered as relegating the synthesis to a definite type. When the last stage is in doubt, a probable mechanism will be assumed. Lastly, a miscellaneous group of syntheses will be detailed.

Type I: The Skraup reaction

In Type I, ring closure is effected by the elimination of hydrogen from the benzene nucleus and of an atom or group from the γ-carbon atom. A prerequisite is an *N*-substituted aniline containing a chain of three carbon atoms. The latter may be prepared as a separate stage as in the first synthesis of quinoline by Koenigs (137), in which allylaniline was passed over heated litharge. Shortly thereafter, the same author (138) reported the second synthesis of quinoline by heating the condensation product of aniline and acrolein. In both cases the yields were mediocre but the basis for the classical Skraup synthesis (201) was established. In this synthesis aniline, glycerol, sulfuric acid, and an oxidizing agent are heated together. The action of the sulfuric acid on the glycerol yields acrolein, which condenses with the aniline. The nature of this first condensation product is in some doubt. Skraup's original suggestion that a Schiff base (V) is formed is not satisfactory. If it were so, crotonaldehyde, i.e., β-methyl-



V VI VII

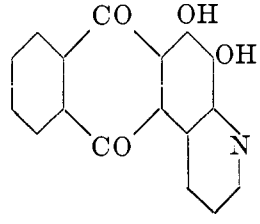
acrolein, should yield as an intermediate the Schiff base VI, which on ring closure would give lepidine. The product in the latter case, however, is quinaldine (10), and on this basis Simon (196) has suggested that the intermediate is either compound VII or the Schiff base of the latter. Loss of water or aniline then completes the hetero ring, which, as in Koenigs' synthesis, must still lose hydrogen to become aromatic. The formation of a compound analogous to VII by the

addition of an amine to a double bond is not without analogy. The addition of ammonia to α,β-unsaturated acids frequently gives rise to β-amino acids. Whereas Koenigs in his first synthesis used litharge as an oxidizing agent, Skraup employed nitrobenzene. Knueppel (136) suggested an improvement by employing arsenic pentoxide, particularly when nitroanilines are condensed. Other oxidizing agents such as picric acid (120) and ferric oxide (7) may be mentioned.

The reaction as carried out according to Skraup's procedure frequently proceeds with great violence. Several important modifications have been suggested (37, 41, 47). The one of Cohn (42) which employs, in addition to the Skraup reagents, ferrous sulfate and boric acid, in the writer's experience proceeds smoothly and safely and the yields are as claimed.

The utility of the Skraup reaction is very great. While it is not possible to prepare quinolines substituted in the hetero ring, the record of failures with aromatic amines is conspicuously small. With meta-substituted anilines both the 5- and the 7-substituted quinolines are generally produced if the meta substituent is ortho-para directing. When the substituent is meta directing, only the 5-substituted quinolines result. The same positions are assumed by the meta substituent in the Doebner–Miller synthesis (189).

The reaction takes place with di- and tri-amino-substituted benzenes (176, 203). Mono- and di-carboxylic derivatives of aniline react readily, although a carboxyl group may be eliminated. Thus the products from *m*-aminobenzoic acid (145, 203) and from 3-aminophthalic acid (221) are identical and consist mainly of 7-carboxyquinoline. The naphthylamines react readily. From β-naphthylamine only the angular isomer, namely, 5,6-benzquinoline, is obtained. An attempt to obtain the 6,7-benzquinoline from β-naphthylamine by blocking the α-position with a nitro group or a bromine atom results in the elimination of this substituent, with the formation of the angular isomer (23, 147). The linear isomer is indirectly available through the *ar*-tetrahydro-β-naphthylamine which yields both forms, the linear one predominating (147). An interesting case is that of β-nitroalizarin, from which Prud'homme (183) obtained a blue product by heating with glycerol and sulfuric acid. The product was shown by Graebe (94) to be an anthraquinoline of formula VIII; hence this constitutes the first synthesis of a quinoline derivative without the author being aware that he was to anticipate Skraup.



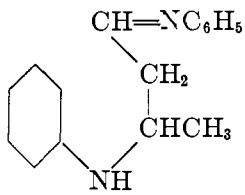
VIII

Among other substituted anilines which may be noted there are alkyl-, cyano-, sulfo-, hydroxy-, alkoxy-, halogen-, phenyl-, and other anilines which

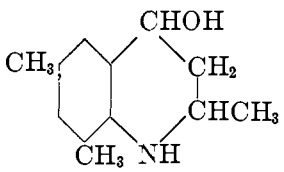
generally react with facility. Conspicuous by their absence are the reported failures. Among simple amines, *p*-aminoacetophenone (8) yielded no quinoline. Aminoquinolines themselves generally yield the expected condensation product, except for 7-amino-8-methylquinoline (153).

Type I: The Doebner and v. Miller Reaction

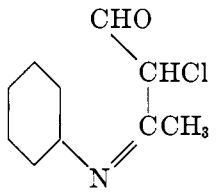
In this synthesis there is the closest analogy to the Skraup reaction. Whereas the latter depends upon the formation of acrolein, the method of Doebner and v. Miller (53) depends upon the intermediate formation of a substituted acrolein, thus yielding quinoline substituted in the hetero nucleus. Cinnamic (54), tiglic (190), and crotonic aldehydes (16) yield 2-phenyl-, 2,3-dimethyl-, and 2-methyl-quinoline, respectively. It is evident that the condensation of aniline with a substituted acrolein to yield quinoline involves the loss not only of water but of two hydrogen atoms as well. Obviously hydrogen is not liberated as gas. From a dimeric form of ethylideneaniline v. Miller obtained a 22 per cent yield of 1,2-dihydroquinaldine by the action of hydrogen chloride. Here a molecule of aniline is liberated and it is probable that the anil (IX) is an intermediate. Eibner (62) has shown that the liberated aniline may be condensed with benzal-



IX



X



XI

dehyde *in situ*. The products then are quinaldine or its benzal derivative and the reduction product of benzalaniline,—namely, benzylaniline. Jones and coworkers (61, 92, 116) have shown that the so-called "aldol bases" of v. Miller and Plöchl (162) obtained from 4-*m*-xylidine and acetaldehyde are *cis*- and *trans*-4-hydroxyquinolines of formula X. These compounds are converted by heat or by mineral acids into dihydroquinolines, which by dismutation yield the quinolines and tetrahydroquinolines. The more recent studies of Mills, Harris, and Lambourne (163) have shown that the hydrogen available in the reaction as usually carried out is utilized in the reduction of the anils of the aldehydes which may be present. In the case of acetaldehyde there is formed, in addition to quinaldine and a trace of 6-ethylquinaldine, ethylaniline and *n*-butylaniline, the latter arising from the reduction of the two double bonds in $C_6H_5N{=}CHCH{=}CHCH_3$. The 6-ethylquinaldine is regarded as being derived from *p*-ethylaniline formed as a result of the migration of the ethyl group from the nitrogen.

Substances which yield acetaldehyde on treatment with sulfuric acid, such as glycol (53) and lactic acid (178, 224), may be substituted for it without any advantage, however. An interesting variation is the synthesis of 3-chloroquinaldine by Busch and Koenigs (29) by heating aniline hydrochloride and

butylchloral hydrate with zinc chloride. Here the intermediate may be figured as having the structure shown in formula XI, and no hydrogen is available for reduction.

With meta-substituted anilines the ring closure takes place in the two possible ways (49), as in the Skraup synthesis, the 5-derivative predominating. In an earlier study Rist (188), however, claimed that the 7-derivative was always obtained.

The reaction is also capable of being extended to a mixture of aldehydes which condense in the course of the reaction to yield a substituted acrolein, and here the condensation of aniline, propionaldehyde, and methylal (161) to yield 3-methylquinoline deserves special mention. Most of the other recorded cases are ones in which benzaldehyde or a derivative is condensed in conjunction with an aliphatic aldehyde, and the products are 2-phenylquinolines (160).

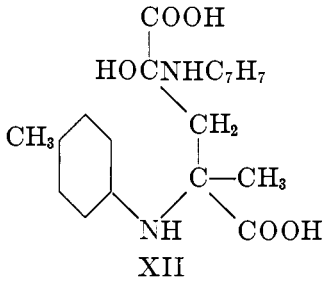
In general, the substituted anilines which yield quinolines in the Skraup synthesis also yield quinolines in the Doebner and v. Miller modification. Failures again are conspicuously absent, although *m*-phenetidine is an example (24). Whereas *p*-aminoacetophenone failed in the Skraup reaction, it does not do so here (8). While aniline reacts normally with acrolein, *p*-toluidine yields no quinoline (152).

Type I: Modifications of the Doebner and v. Miller reaction

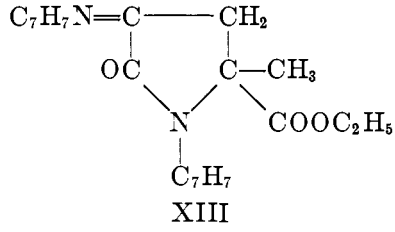
Under this heading may be classed a number of syntheses in which the precursors of the substituted acrolein are not necessarily aldehydes (although one of the reactants frequently is), but their derivatives such as pyruvic acids, ketones, β-ketonic esters, and β-diketones. Expressed in general terms, the reaction involves the condensation of two compounds, $RCOCH_2R'$ and $R''COR'''$ to yield $RCOCR'{=}CR''R'''$, which then reacts with an aromatic amine to yield $RCOCHR'CR''R'''NHAr$. Ultimate ring closure occurs under a variety of experimental conditions. Doebner (51) heated an alcoholic solution of aniline, pyruvic acid, and acetaldehyde and obtained quinaldine-4-carboxylic acid,—the aniluvitonic acid of Böttinger (22). Simon and Mauguin (200) obtained excellent yields by bringing together in cold benzene or chloroform a mixture of α-naphthylamine, benzaldehyde, and ethyl pyruvate. Hydrogen, of course, is not liberated. It is utilized in the reduction of some reactant or intermediate (35, 36).

Some attention has been paid to the mechanism of the condensations involving pyruvic acid. Borsche (25, 26) showed that benzalaniline in boiling alcohol first forms an addition compound with pyruvic acid, $C_6H_5NHCH(C_6H_5)CH_2COCOOH$, which easily yields 2-phenylquinoline-4-carboxylic acid.

Simon (197, 198) studied the reaction between *p*-toluidine and pyruvic acid and the ester. With pyruvic acid an intermediate is formed which is regarded as having the structure shown in formula XII. When heated with water it is converted into 6-methylquinaldine. When *p*-toluidine is condensed with ethyl pyruvate, the main product is not XII but XIII. The latter is obviously



XII



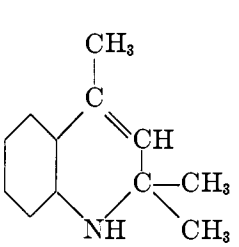
XIII

derived from the ester of XII by loss of ethyl alcohol and water and as a derivative of diketopyrrolidine will not yield a quinoline.

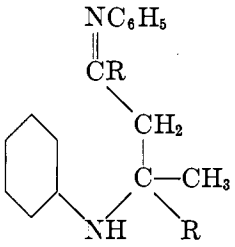
The work of Borsche (25, 26) has extended these observations to the condensation products of a number of arylamines, pyruvic acids, and aldehydes. In most cases involving substituted pyruvic acids, ring closure occurs between the nitrogen and the carboxyl, yielding a diketopyrrolidine which reacts with another molecule of amine forming an anil. The yields of quinoline were in general poor or nil. Only in the case of β-naphthylamine were the quinolines obtained in moderate amounts. The recorded failures with unsubstituted pyruvic acid are comparatively few. Arsanilic acid (115), *m*- and *p*-aminobenzoic acids (52), and the nitroanilines (3) failed to yield quinolines. Most of the other failures are recorded in attempts to use formaldehyde as the second ketonic component, although it has been utilized successfully in a number of cases (26). Aromatic aldehydes react most readily and the α-arylcinchoninic acids or atophans find some use in medicine. A large number of patents covering these substances have been granted

The reaction with an arylamine in which the second molecule of an aldehyde is substituted by that of a ketone was first described by Reed (185), who succeeded in condensing β-naphthylamine with acetaldehyde and acetone. Beyer (16) was the first to synthesize lepidine by this procedure from aniline, formaldehyde, and acetone. The reaction is of wide application and yields a quinoline derivative in which the γ-substituent is supplied by the alkyl of the ketone. Of special interest is the condensation of aniline with chloroacetone and methylal (180). It is remarkable that the chlorine is not eliminated and appears in the 3-chlorolepidine, in spite of the fact that two hydrogens must be removed to obtain the final product.

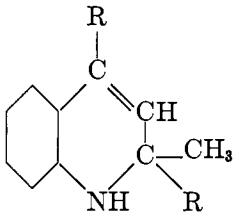
The fact that one of the molecules of the aldehydes can be replaced by a ketone leads logically to an attempt to realize the condensation in which both molecules of aldehyde are replaced by two molecules of a ketone. In other words, aniline, when condensed with two molecules of acetone, may be expected to yield a substance of formula XIV, that is, a dihydroquinoline from which hydrogen cannot be eliminated to yield a quinoline. Engler and Riehm (71) heated aniline hydrochloride with acetone in the presence or absence of condensing agents and obtained 2,4-dimethylquinoline, together with a gas which proved to consist of methane. So great is the tendency of the hetero ring to become aromatic that not only methane is evolved but other hydrocarbons as well.



XIV



XV



XVI

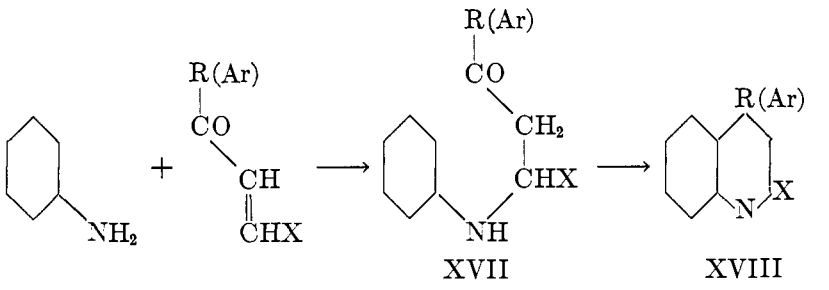
Knoevenagel and his coworkers (124, 126, 129), in their studies of ketone anils, have shed some light on the course of the condensation. The anils of acetone, of methyl ethyl ketone, and of acetophenone give excellent yields of 2,4-disubstituted quinolines when heated with hydrogen chloride at 180–200°C. It is assumed that an intermediate (XV) is formed from 2 moles of the anil which by loss of aniline yields XVI. When R in formula XVI is phenyl, benzene is ultimately eliminated in preference to methane and the main product is 2-methyl-4-phenylquinoline. Heat alone, or heating with phosphorus and hydrogen iodide, gives excellent yields. Mesityl oxide may replace the acetone and even *N*-methylaniline yields a quinoline in the usual manner, the *N*-methyl group being eliminated.

In a limited number of cases involving β-naphthylamine (but not aniline), an aromatic aldehyde, and ethyl oxaloacetate (i.e., carbethoxypyruvic ester), it has been possible to synthesize quinoline derivatives. Simon and Conduché (199) obtained a normal condensation product from benzal-β-naphthylamine and oxalacetic ester. This, on treatment with concentrated sulfuric acid, yielded a dihydroquinoline which readily lost hydrogen, yielding 2-phenyl-β-naphthoquinoline-3,4-dicarboxylic ester. The reaction is further limited, as is the Doebner pyruvic acid synthesis, by the tendency to form diketopyrrolidines or their anils.

Of interest is a synthesis by Halberkann (96), in which *p*-anisidine was condensed with oxalacetic ester alone, yielding 6-methoxycarbostyril-4-carboxylic acid. An analogous and very ingenious synthesis was achieved by Thielepape (219), in which *N*-methylacetanilide was first condensed with ethyl oxalate in the presence of sodium ethylate. The semi-amide of oxalacetic ester thus produced gave a quantitative yield of 1-methylcarbostyril-4-carboxylic ester on treatment with sulfuric acid.

Analogous to the reaction studied by Beyer (16) is one involving α,β-unsaturated ketones. Here the mechanism presumably involves the addition of the arylamine to the double bond, yielding a substance of formula XVII.

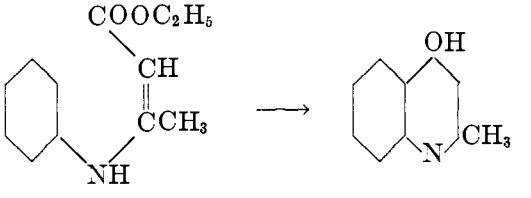
In the case where X and R(Ar) were carboxyl and phenyl respectively, i.e., benzoylacrylic acid, Koenigs and Meimberg (140) obtained 4-phenylquinoline-2-carboxylic acid (XVIII). Blaise and Maire (19), by condensing vinyl ethyl ketone or β-dichloroethyl ketone with aniline, obtained a substance of formula XVII (R = C_2H_5; X = H), which on heating with aniline hydrochloride yielded 4-ethylquinoline. Vinyl propyl ketone and aniline yield 4-propylquinoline and the reaction also goes with anthranilic acid.



XVII XVIII

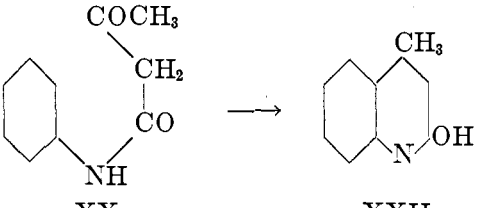
Type I: Condensations involving derivatives of β-diketones

Ethyl acetoacetate reacts with aniline, yielding either β-phenylaminocrotonic ester, $C_6H_5NHC(CH_3)=CHCOOC_2H_5$ (XIX) or acetoacetanilide, $CH_3COCH_2CONHC_6H_5$ (XX). In the cold a nearly quantitative yield of the former may be obtained, whereas at the boiling point the latter is obtained almost exclusively (73, 135), although in only moderate yields. The former on heating to about 240°C. and the anilide on treatment with sulfuric acid yield quinoline derivatives. The reaction was first observed by Conrad and Limpach (46), who prepared 4-hydroxyquinaldine (XXI) and a number of 4-hydroxyquinolines by



XIX XXI

4-Hydroxyquinaldine



XX XXII

4-Methylcarbostyril

this method. The reaction proceeds with formylacetic esters and with benzoylacetic ester (132), yielding 2-phenyl-4-hydroxyquinoline. Acetylacetone (44, 45) and aniline yield 2,4-dimethylquinoline, and aroylacetones yield 2-methyl-4-arylquinolines (12, 15). The reaction is of considerable applicability, a number of arylamines having been substituted for aniline. It fails, however, with *p*-phenylenediamine (154) and yields an aminoquinoline with *m*-phenylenediamine (154).

The preparation of 4-substituted carbostyrils was first investigated by Knorr (132, 133) and more recently by Ewins and King (73), who obtained excellent yields of 4-methylcarbostyril (XXII).

Oxalacetic ester (96), acetonedicarboxylic ester (14), and other β-ketonic compounds have been used with a variety of arylamines.

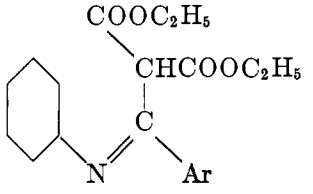
Malonic acid, being in effect a β-diketonic compound, has also been condensed with aniline to yield a quinoline derivative. The semi-anilide of malonic acid on treatment with phosphorus pentachloride yields 2,4-dichloroquinoline, presumably by way of 2,4-dihydroxyquinoline (191). The reaction has found only limited application.

The syntheses of the hydroxyquinolines here typified do not involve the elimination of hydrogen.

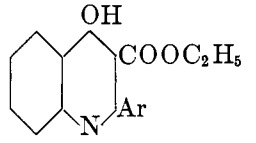
Type I: Miscellaneous syntheses

Under this heading may be grouped a number of quinoline syntheses which, though of limited application, are adaptable to the preparation of compounds difficultly accessible by other routes.

Aromatic imino-chlorides, ArN=CClAr, condense with sodiomalonic ester, yielding compounds of formula XXIII which on heating lose ethyl alcohol with



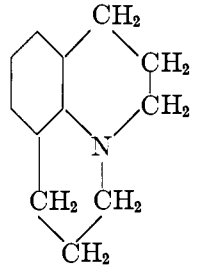
XXIII



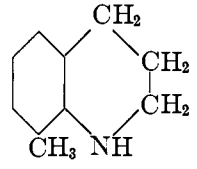
XXIV

the formation of 2-aryl-3-carbethoxy-4-hydroxyquinolines (XXIV) (117, 118, 119).

Julolidine (XXV) is a tertiary tetrahydroquinoline obtained by Pinkus (181)



XXV
Julolidine

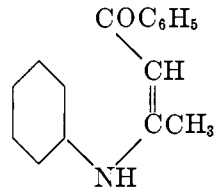


XXVI

by heating formanilide with trimethylene chlorobromide. The formyl derivative of *o*-toluidine yielded 8-methyltetrahydroquinoline (XXVI). Tetrahydroquinoline was obtained by Rindfusz and Harnack (187) by treating the con-

densation product of aniline and trimethylene chlorohydrin with phosphorus pentoxide. From dichlorohydrin and formanilide Bamberger and Kitschelt (5) obtained a complex mixture containing some quinoline as well as skatole.

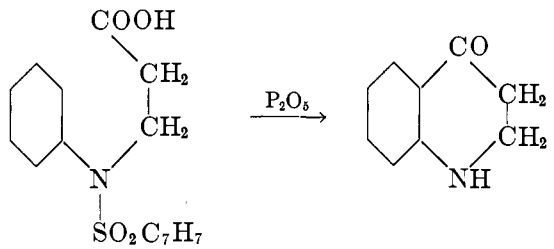
Reminiscent of the reaction of unsaturated ketones with aniline (*vide supra*) is one discovered by Spallino and Salimei (206). Acetanilide when heated with acetophenone and zinc chloride yielded 4-phenylquinaldine, presumably by way of XXVII.



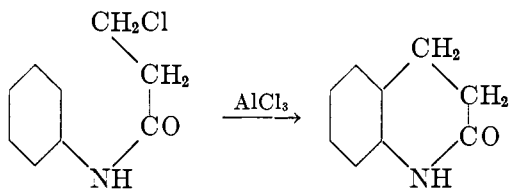
XXVII

Pictet and Barbier (175) had already condensed acetophenone with formanilide. Although an intermediate similar to XXVII is possible, the ultimate product was 2-phenylquinoline. In these reactions the elimination of hydrogen is not necessary.

There remain to be mentioned two syntheses of tetrahydroquinoline derivatives which are of interest in that they virtually amount to a modified Friedel–Crafts reaction. Clemo and Perkin (39, 40) prepared 4-ketotetrahydroquinolines by treating the toluenesulfonyl derivative of β-arylaminopropionic acids with dehydrating agents, the toluenesulfonyl group being eliminated during the reaction or later by acid hydrolysis.



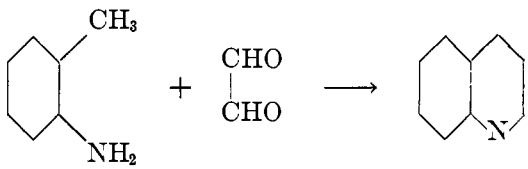
Mayer, van Zütphen, and Philipps (155) developed a general method for preparing dihydrocarbostyrils from the arylamides of β-chloropropionic acid. Aluminum chloride was used to close the ring, and in the twenty-one cases cited the yields were mostly good.



Type II syntheses

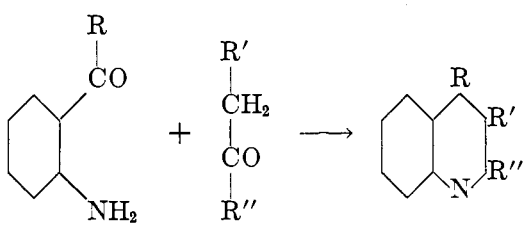
The reactions described under this heading lead to the synthesis of the hetero ring by a union of carbon atoms 3 and 4. There is frequently a certain element of ambiguity as to the mechanism of these processes. In many cases a reaction involving ring closure by union between the nitrogen atom and the 2-carbon atom is also a feasible one. Nevertheless, the latter type is well recognized as a special one where no other mechanism is possible, and those will be considered under Type IV.

Generally speaking, the reactions of Type II necessitate the condensation of an ortho-substituted arylamine with a compound containing two or more carbon atoms. The amino group first condenses with some reactive substance, yielding a product which simultaneously or by a separate condensation eliminates water to form the hetero ring. The simplest example is the synthesis of quinoline from *o*-toluidine and glyoxal in some 35 per cent yield by heating with sodium hydroxide to 150°C. (141).



The reaction is not general and fails with benzil (142), although with ethyl pyruvate in the presence of alcoholic zinc chloride Kulisch (142) obtained a compound which was almost certainly 3-hydroxyquinaldine. The Madelung synthesis of indoxylic acid (149), i.e., by heating oxalyl-*o*-toluidine with sodium ethylate, yields a small amount of 2,3-dihydroxyquinoline.

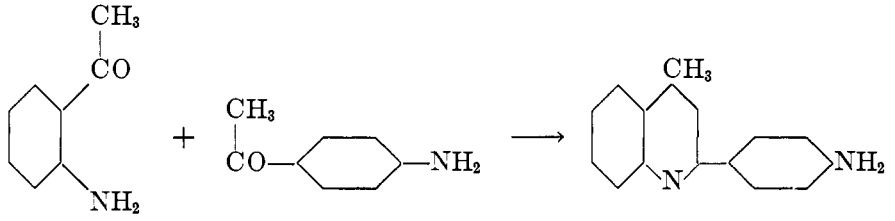
Perhaps the most important type of reaction in this section is the one involving an ortho-amino aroyl compound (I) condensed with a carboxyl compound containing an α-methylene group (II), thus yielding a fully aromatic hetero



I II III

ring (III). The earliest example of this type of condensation is the synthesis of flavaniline by heating acetanilide with zinc chloride. The constitution of this substance and the mechanism of its synthesis were, however, elucidated by Besthorn and Fischer (13) only after Friedlaender (84) in 1882 obtained quinoline by condensing *o*-aminobenzaldehyde with acetaldehyde in the presence of sodium hydroxide. (R, R′, and R″ = H in formulas I, II, and III.) Propionaldehyde condenses with *o*-aminobenzaldehyde to yield a compound which on distillation

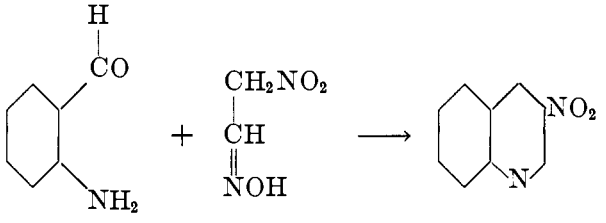
loses water and forms 3-methylquinoline (228). When acetanilide is heated with zinc chloride, the acetyl group migrates to the ortho and para positions and the aminoacetophenone thus formed yields flavaniline (IV) (13).



IV
Flavaniline

Two molecules of *o*-aminoacetophenone can be condensed by heating with formic acid, yielding an *o*-aminophenylquinoline (18).

The Friedlaender synthesis is of special importance because of the wide choice of the groups R, R′, and R″, in addition to the fact that the benzene ring may carry a diverse number of substituents. R may be H (*o*-aminoaldehydes), CH_3 and C_6H_5 (*o*-aminoketones), COOH (isatic acids), or OH (anthranilic acids). R′ may be H, alkyl, aryl, NO_2, SO_3H, SO_2Ar, $COOH(C_2H_5)$, CN, $COCH_3$, COC_6H_5, OH, and other groups. R″ may be H, alkyl, aryl, OH, CH=NOH, COOH, etc. It is evident, therefore, that aldehydes, ketones, ketonic esters, acids, nitriles, and other compounds containing at least one carboxyl group may be condensed with aminoaryl compounds containing an ortho-carbonyl group. Failures to effect a quinoline synthesis are exceptional. In the case of *o*-aminobenzaldehyde, the reaction fails with desoxybenzoin (223). Of special interest is the synthesis of β-nitroquinolines by condensations involving methazonic acid, HON=CHCH=NOOH, which reacts as the oxime of nitroacetaldehyde (222, 223). A large number of β-nitroquinolines have been recorded in the patent literature.

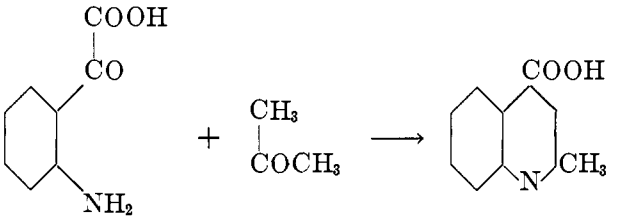


β-Nitroquinoline

Diacetyl condenses with two molecules of *o*-aminobenzaldehyde, yielding α,α′-diquinolyl (205). The methyl group of methyl alkyl ketones, CH_3COCH_2R, takes the α-position in the resulting quinoline (67). The condensations with *o*-aminobenzaldehyde are generally brought about by dilute alkali, by heat alone (228), or by means of piperidine (211).

The extension of the Friedlaender synthesis to isatic acid (V) is due to Pfitzin-

ger (172) who substituted this substance for the *o*-aminobenzaldehyde. Thus the condensation with acetone yields aniluvitonic acid (VI). The isatic acid is

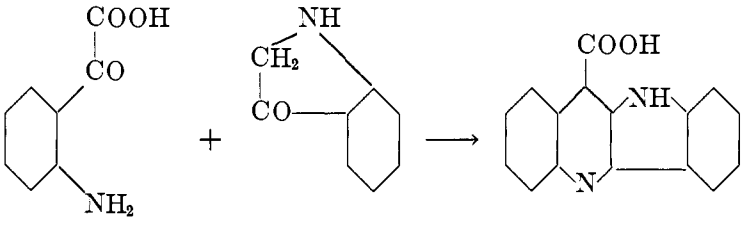


V
Isatic acid

VI
Aniluvitonic acid

obtained by heating isatin with aqueous sodium hydroxide and is used directly. With aldehydes the condensation proceeds normally, except that resinification of the aldehyde by the strong alkali may occur. The oximes of the aldehydes react as readily and do not resinify in the presence of alkali (173). The β-oxime of isatin is then obtained as a by-product.

The earliest example of the Pfitzinger reaction is the formation of "flavindin," a substance obtained by the over-reduction of indigo (195). Its constitution (quindoline-5-carboxylic acid) (VIII) and its mode of formation were elucidated



VII
Indoxyl

VIII
"Flavindin"

as follows (75, 167): The reduction of the indigo yielded a mixture of isatin, which hydrolyzed to isatic acid, and indoxyl (VII) and these in the presence of the alkali condensed to yield the flavindin.

Although acetaldehyde failed to yield cinchoninic acid, the oxime did so (173). Recorded failures in other cases are rare. Levulinic acid, which does not yield a quinoline derivative with *o*-aminobenzaldehyde, reacts normally with isatic acid (70). Acids yield carbostyrils (96).

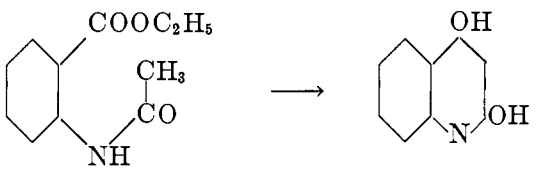
v. Walther (225) in 1903 introduced an important modification of the Friedlaender–Pfitzinger synthesis. The imino-nitriles of the type $NH{=}CRCH_2CN$ (i.e., dinitriles) react like the corresponding ketones and with isatic acid yield 2-alkyl-3-cyanocinchoninic acid. The reaction has been extended to a number of amino-nitriles in conjunction with *o*-aminobenzaldehyde and with *o*-aminoacetophenone (158). The reaction fails with isatin, yielding instead a complex dihydropyridine (225). This would indicate that the first phase of the condensation is one involving the amino and the imino groups, yielding an arylimino

compound through loss of ammonia; this compound subsequently loses water with the formation of the heterocyclic ring. The mechanism of Borsche and Jacobs (27) to account for the condensation of isatin with malonic acid to yield 2-hydroxycinchoninic acid involves the primary condensation between the carboxyl of the isatin and the methylene of the malonic acid. Equally reasonable is the primary formation of a malonylisatin, followed by hydrolysis to malonylisatic acid and ultimate loss of water (and carbon dioxide under the conditions used by them).

In many cases anthranilic acid, when condensed with aldehydes, yields the 8-carboxyquinolines,—the normal product of the Doebner–Miller reaction. Niementowski (166), however, discovered that in some cases the Schiff base of anthranilic acid and an aldehyde (heptaldehyde) (165) yield a small amount of 3-alkyl-4-hydroxyquinoline when heated to 200°C. Acetophenone and anthranilic acid yield 2-phenyl-4-hydroxyquinoline (166). Acetoacetic ester with anthranilic acid yields the 8-carboxycarbostyril by the usual Knorr reaction, but when the position ortho to the amino group is occupied by a methoxyl group, the reaction yields 2-methyl-3-carbethoxy-4-hydroxy-8-methoxyquinoline (86).

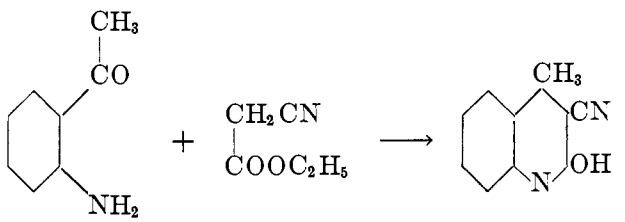
Methazonic acid first forms an anil, which on heating with acetic anhydride yields 3-nitro-4-hydroxyquinoline (59). Benzoylacetic ester yields a complex mixture (166).

An application of the Dieckmann reaction to the synthesis of a quinoline derivative is the conversion of ethyl acetylanthranilate into 2,4-dihydroxyquinoline by treatment with sodium, although the yield in the writer's experience is low (57).

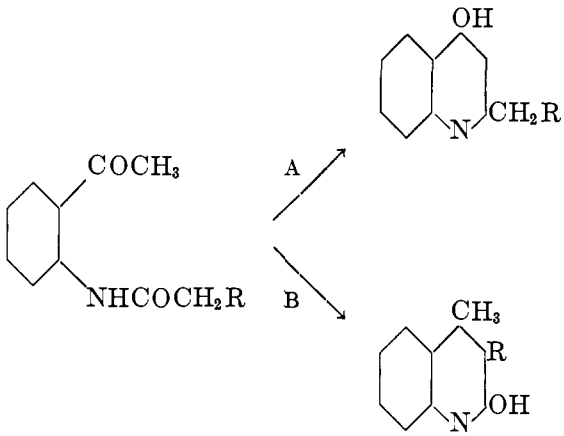


Ethyl acetylanthranilate — 2,4-Dihydroxyquinoline

The important reaction by which 4-alkyl (and aryl) derivatives of quinoline may be readily obtained from *o*-acylanilines was extensively studied by Camps (30, 31, 32, 33), who recorded his well-planned experiments in a series of papers. The reaction was discovered by Guareschi, who obtained 2-hydroxy-3-cyano-4-methylquinoline by condensing *o*-aminoacetophenone with ethyl cyanoacetate.



The reaction is strictly analogous to the syntheses involving *o*-aminobenzaldehyde. It offers the advantage that a wide choice of substituents can be introduced into positions 3 and 4, although the 2-position in these cases carries a hydroxyl group. The reaction has been carried out with *o*-amino derivatives of benzophenone, acetophenone, propiophenone (230), benzoylacetic ester (31), and benzoylcarbinol (31). With esters of aliphatic acids two reactions occur simultaneously, the intermediate acylamino compounds forming the ring in two ways. Since the carbostyrils are non-basic, they may be easily separated

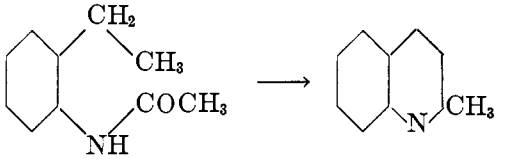


from the 4-hydroxy compounds which are soluble in acids. When R is C_6H_5, CN, $COCH_3$, COC_6H_5, or $COOC_2H_5$, the reactivity of the hydrogen atoms in the methylene group is greater than that of those in the methyl group and only carbostyrils are obtained. The condensation is brought about by heating the ester with the amino compound, and the yields are good. It is to be observed that reaction A above is an example of ring closure between atoms α and β, that is, Type III.

Type III syntheses

The number of syntheses which may be classed as being of Type III is small and of little general utility. The most important examples are, in fact, those described in the last section, which arise from the fact that the Camps synthesis can take either of two courses.

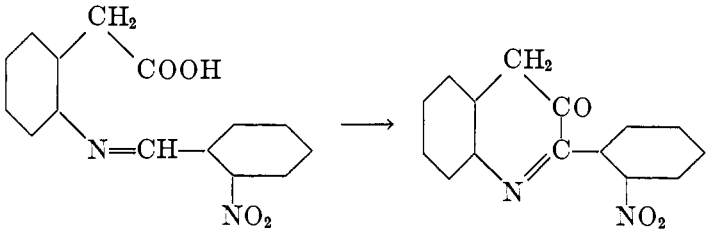
When acetylethylaniline is heated with zinc chloride, a mixture of *o*- and *p*-ethylacetanilides is formed. The former is regarded as giving rise to the small amount of quinaldine that is obtained (177).



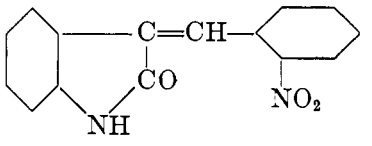
Quinaldine

Acetylmethylaniline, however, yields quinoline under the same conditions (179) and obviously the reaction cannot be formulated in the same way. A more authentic example of ring closure of Type III is one recorded by Gabriel and Löwenberg (89), which by an involved series of reactions led to a complex 4-ketotetrahydroquinoline. Equally involved is the formation of a quinoline derivative from *N*-benzoyltetrahydrocarbazole (170), and the original papers should be consulted. Only slightly less complex is the synthesis of 2,3-dimethyl-6,7-methylenedioxyquinoline from *o*-nitrosafrole (81).

Neber (164) claimed the ring closure of I to yield II, but Kliegl and Schmalen-



I II



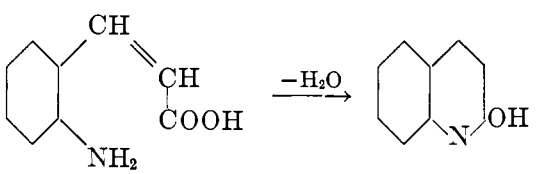
III

bach (123) showed that the compound formulated as II was *o*-nitrobenzaloxindole (III).

Type IV syntheses

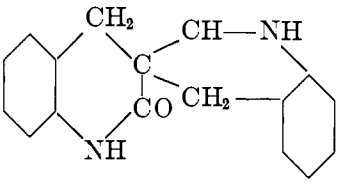
The reactions classed under Type IV involve ring closure between the nitrogen atom and the β-carbon atom by the loss of water or its equivalent. The ortho-substituting group must therefore consist of a chain of at least three carbon atoms, the end one carrying a reactive group.

In this section belongs what is probably the first synthesis of a quinoline derivative, namely, carbostyril. It was obtained by Chiozza (34), by reducing *o*-nitrocinnamic acid with ammonium sulfide, the aminocinnamic acid being the intermediate.

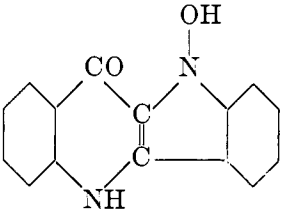


The reaction has been the subject of numerous later investigations. A variety of reducing agents has been used (93, 220). The *o*-aminocinnamic acid may be obtained from the *o*-chloro acid by the action of ammonia (159). There seem

to be no particular limitations which restrict the utility of the reaction except the accessibility of suitable *o*-nitro- or *o*-amino-cinnamic acids. The reduction with specific reagents frequently yields a 1-hydroxycarbostyril, but further reduction eliminates the hydroxyl group (85, 104, 216). The dihydrocarbostyrils result from the reduction of *o*-nitrodihydrocinnamic acids (65). The preparation of 1-aminodihydrocarbostyril from *o*-hydrazino-β-phenylpropionic acid has been described by Fischer and Kuzel (78). The reduction of di-(*o*-nitrobenzyl)-malonic ester yields a spiro-carbostyril (I) (146), whereas heating with caustic



I

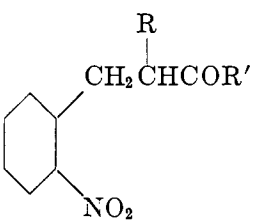


II

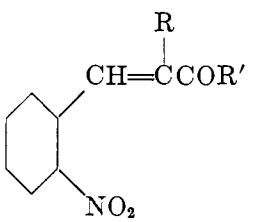
soda results in the loss of the carbethoxyl groups and an intermolecular oxidation–reduction, with the ultimate formation of a substance which has been given formula II and is therefore a quindoline derivative (74).

o-Aminophenylpropiolic acid does not spontaneously yield a quinoline derivative, but in the presence of sulfuric acid it yields 2,4-dihydroxyquinoline (3). In this reaction *o*-aminobenzoylacetic acid is a probable intermediate. When dilute hydrochloric acid is used, the condensation product is 4-chlorocarbostyril (3, 4). The synthesis of 5-methylquinoline is of interest, in that it cannot be conveniently obtained by any of the methods thus far described. It was obtained by Gabriel and Thieme (90) from 2-nitro-6-methylbenzoylmalonic ester by reduction with phosphorus and hydrogen iodide to 2,4-dihydroxy-5-methylquinoline, which was ultimately reduced to 5-methylquinoline *via* the 2,4-dichloro compound.

An important extension of the carbostyril synthesis is one involving, not the cinnamic acids or their dihydro derivatives, but the β-(*o*-nitroaryl) ketones (III) and their unsaturated derivatives, the *o*-nitrobenzal ketones (IV).



III

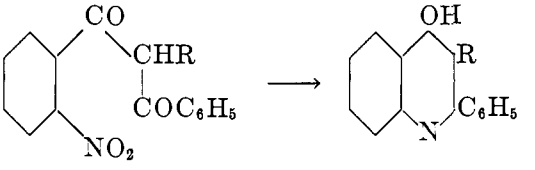


IV

Jackson (111) obtained tetrahydroquinaldine by reducing *o*-nitrobenzyl-acetone, whereas the reduction of *o*-nitrobenzalacetone yielded quinaldine (56). The reduction of *o*-nitrobenzalpyruvic acid (formula IV, R = H and R′ = COOH) yields, not the expected quinaldinic acid, but its 4-hydroxy deriva-

tive (99). Reduction of *o*-nitrobenzylacetoacetic esters yields quinolines, not the dihydro compounds (112).

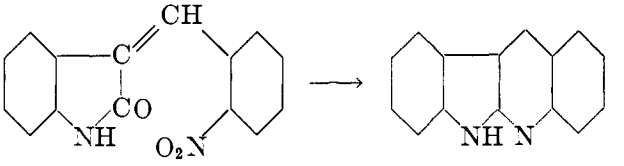
The *o*-nitrobenzoylketones of the type V on reduction yield substituted



V VI

2-phenyl-4-hydroxyquinolines (VI) (R = H, CN, or $COOC_2H_5$) (88).

The reduction of *o*-nitrobenzalisatin (VII) is of interest in that it leads to



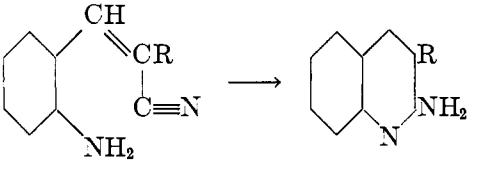
VII VIII

o-Nitrobenzalisatin peri-Quindoline

peri-quindoline (VIII), an example of a condensed compound containing both the indole and the quinoline nuclei.

The lone example of the addition of an *o*-amino group to a carbon–carbon double bond to yield a quinoline is recorded by Fischer and Kuzel (79). Reduction of *o*-nitrocinnamylideneacetone yielded 2-acetonylquinoline.

Strictly analogous is the addition of the *o*-amino group to the carbon–nitrogen triple bond in compounds of the formula IX, to yield 3-substituted 2-aminoquinolines of formula X.



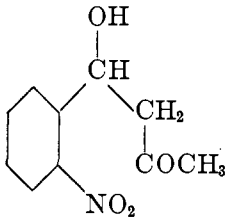
IX X

Compounds of formula IX are obtained by condensing *o*-acetylaminobenzaldehyde with arylacetonitriles and may yield the aminoacetylquinoline directly or on treatment with alkali (184). Acetonitrile does not condense with *o*-acetylaminobenzaldehyde, but its condensation product with *o*-nitrobenzaldehyde may be reduced to *o*-aminocinnamic nitrile, which on treatment with alkali yields 2-aminoquinoline.

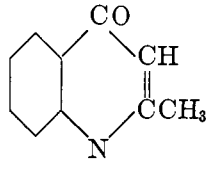
Reduction of *o*-nitrobenzoylcyanoacetic ester with hydriodic acid and phosphorus yields 2-amino-4-hydroxyquinoline. The carbethoxyl group is eliminated under these conditions and 2,4-dihydroxy-3-cyanoquinoline is obtained (87).

The condensation of *o*-nitrobenzaldehyde with acetone yields a representative

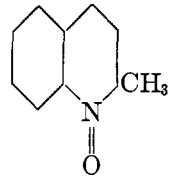
of the so-called lactic methyl ketones (XI). This substance on gentle reduction gave a compound which Heller and Sourlis (102) regarded as being 4-keto-dihydroquinaldine (XII). It was shown, however, by Meisenheimer and



XI



XII



XIII

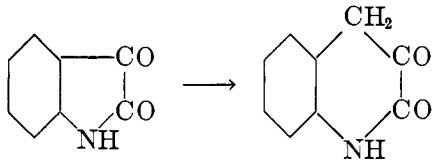
Stotz (157) to be identical with quinaldine *N*-oxide (XIII). The latter, of course, is readily obtainable by the oxidation of quinaldine with perbenzoic acid.

Miscellaneous syntheses

Under this heading it is proposed to group a number of syntheses which have resulted in compounds known to be, or regarded as being, quinolines. In a number of cases the mechanisms are obscure and frequently the reactions lack generality. In many cases the starting materials are difficultly accessible or the yields are poor.

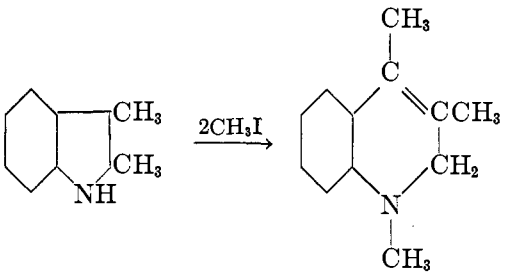
Dziewonski and Mayer (60) obtained 2-phenyl-3-methyl-4-aminoquinoline by heating a mixture of *sym*-diphenylthiourea and propiophenone to 250–260°C. Although a mechanism is postulated, it lacks conviction.

Heller (101) obtained 2,3-dihydroxyquinoline by the reaction of isatin in ether with diazomethane. This reaction finds an analogy in the ring enlargement of cyclic ketones by the same reagent.



An interesting example of a Beckmann rearrangement leading to a quinoline derivative is the preparation of hydrocarbostyril from the oxime of α-hydrindone (122). As is to be anticipated, no isoquinoline derivative is formed.

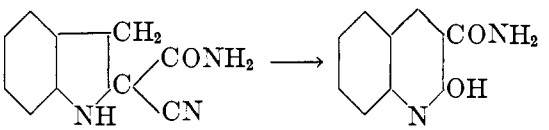
Fischer and Steche (80) have shown that the treatment of indoles with alkyl iodides at 100°C. yields dihydroquinolines carrying an alkyl group on the nitrogen atom. The ring is enlarged between the nitrogen atom and what is to become the β-carbon atom. With ethyl iodide, therefore, the resulting quinoline is a derivative of 1-ethyl-2-methyldihydroquinoline. The yields are good but the mechanism is obscure.



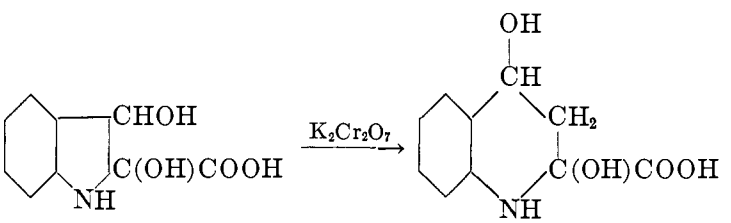
A similar transformation of an indole into a quinoline derivative was observed by Magnanini (150, 151). When 2-methylindole is heated with chloroform and sodium ethylate, it is converted into 2-methyl-3-chloroquinoline. Under the same conditions 3-methylindole yields 3-chloro-4-methylquinoline (69). The entering carbon atom takes up the β-position in the resulting quinoline, and the reaction appears to be quite general (121). Ellinger (68) has suggested a mechanism which, however, is not convincing.

Quinoline is obtained in small yield from either 1- or 2-methylindole when each is passed through a tube heated to dull redness (174).

Finally, mention may be made of two transformations of dihydroindoles into quinoline derivatives which were discovered by Heller and Wunderlich (103) and by Heller (100). In the first example nitrous fumes effected the change,



and the second example was written thus:



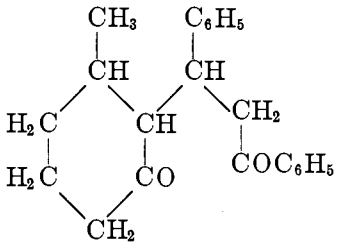
The source of the added carbon atom was not adequately explained, although the dihydroxy acid on treatment with acetic anhydride yielded quinaldinic acid.

Other syntheses

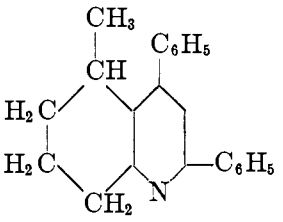
There remain to be described a number of reactions which yield hydroquinolines from compounds in which the nitrogen is not already joined to the benzene nucleus. The resulting products are usually hydrogenated in the benzene nucleus.

Stobbe condensed β-methylcyclohexanone with benzalacetophenone, thus obtaining a 1,5-diketone (214, 215), which on treatment with hydroxylamine

yielded II. The reaction is obviously a simple variation of the pyridine synthesis of Knoevenagel (125, 130). The position of the methyl group is in doubt.

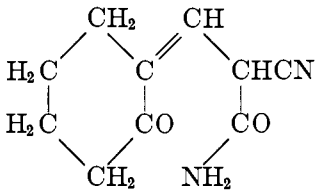


I

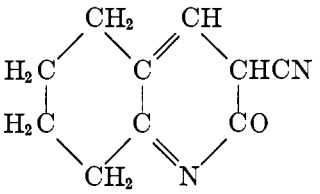


II

The condensation of hydroxymethylenecyclohexanone, i.e., formylcyclohexanone, with cyanoacetamide yields a substance formulated as III, which by further loss of water leads to the quinoline (IV) (204).

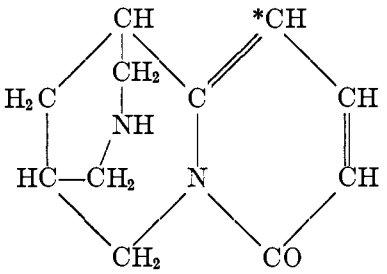


III

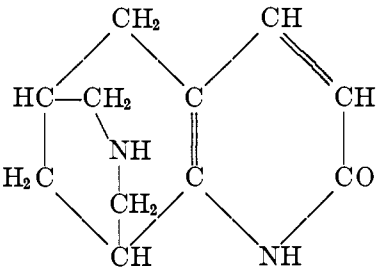


IV

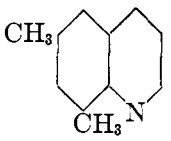
Knoevenagel and Fries (127, 128) condensed ethyl malonate with ethyl β-aminocrotonate and obtained a compound which was regarded as being 2-methyl-3-carbethoxy-4,5,7-trihydroxyquinoline.



V
Cytisine



VI



VII

Quinoline may be obtained from acridines under certain conditions. Acridine with hydrogen when passed over reduced nickel at 250–270°C. yielded a small

amount of 2,3-dimethylquinoline (169). Oxidation of certain acridine derivatives leads to quinolinecarboxylic acids (107, 127).

The formation of 6,8-dimethylquinoline (VII) from cytisine (V) by heating with zinc dust (72) or with phosphorus and hydrogen iodide (83) is a rather remarkable example of a rearrangement which obscured the true constitution of the alkaloid for many years. Owing to the researches of Ing (110) and of Späth and coworkers (207, 208, 209), the true formula is now known. If it be assumed that the transformation to a quinoline derivative first involves the severance of the bond from tertiary nitrogen to CH_2 and a new ring is formed at the position marked with an asterisk, a substance of formula VI would result. It is obvious that the latter could readily lose the necessary elements to yield 6,8-dimethylquinoline. Further support to such a mechanism is given by the fact that cytisoline, the main product of the hydrogen iodide–phosphorus reaction, is the 2-hydroxy derivative of VII.

II. REACTIONS OF QUINOLINE

In the course of the very extensive work on quinoline and its derivatives, a large number of reactions of these compounds has been observed. In many cases, of course, the reactions are those met with in general organic chemistry and call for no special mention. Such reactions, as the esterification of acids or the hydrolysis of esters, in general follow the anticipated courses and will not be discussed further.

There are, however, a great many observations which could not have been predicted with certainty. They are in some measure peculiar to the chemistry of quinoline and call for some discussion. In the space available it is not possible to give a detailed account of even all salient observations. An attempt will be made to select typical reactions which admit of certain generalizations and to draw attention to some cases which seem more or less unique. The references quoted are not claimed to be complete. It is hoped, however, that the citations given will be adequate to trace any particular subject. For this reason it has been deemed desirable in many cases to give only the more recent references.

In the following pages there will be discussed first those reactions of quinoline and derivatives which do not specifically involve substituents. The next section will be devoted to reactions which involve the substituents.

A. Reactions not involving substituents

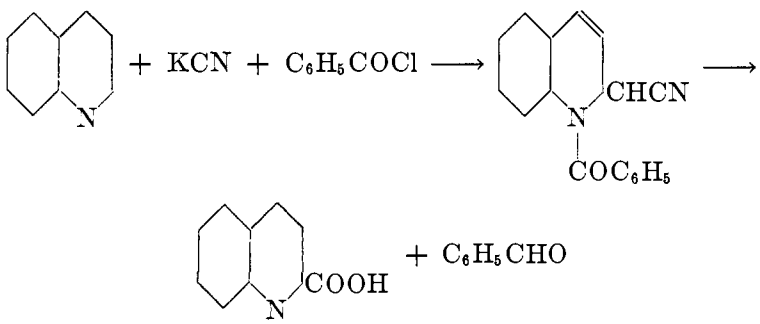
One of the earliest known reactions of quinoline is its reduction to tetrahydroquinoline by means of zinc and hydrochloric acid, and this reduction can be carried out with most alkyl and aryl derivatives. A variety of reducing agents may be used,—tin and hydrochloric acid, sodium amalgam (139), sodium and alcohol (226),—and in these cases only the pyridine nucleus is reduced.

Catalytic reduction of quinoline hydrochloride in ethanol in the presence of platinum oxide yields a mixture of *cis*- and *trans*-decahydroquinolines, whereas reduction of the base in glacial acetic acid yielded only the *trans*-modification (168). Reduction in the vapor state over nickel yields a mixture of products.

Good yields of tetrahydroquinoline were obtained by catalytic reduction in the presence of osmium and cerium dioxide (192). The tetrahydroquinolines are also obtainable by reducing the carbostyrils with sodium in absolute alcohol (73, 134). The nitroso derivative of tetrahydroquinoline on reduction yields 1-aminotetrahydroquinoline (108).

Oxidation of quinoline yields pyridine-2,3-dicarboxylic acid, and the preparation of this acid in good yield has been studied by Stix and Bulgatsch (213). Hydrogen peroxide is the reagent recommended. The oxidation is carried out in the presence of copper sulfate and the sparingly soluble copper salt separates as oxidation proceeds. The absence of iron is important.

Reissert (186) treated quinoline with benzoyl chloride in the presence of aqueous potassium cyanide. He obtained 1-benzoyl-2-cyano-1,2-dihydroquinoline, which on hydrolysis with hydrochloric acid yielded benzaldehyde and quinaldinic acid. The reaction has been extended by Sugasawa and Tsuda (217) to a number of substituted benzoyl chlorides with the object of preparing the correspond-



ing aldehydes. In a number of cases the yields were good, but the reaction failed with phenylacetyl chloride and with heptoyl chloride.

Perbenzoic acid in benzene solution reacts readily with quinoline and its alkyl derivatives to yield the *N*-oxides (156). Mild reducing agents reconvert the latter to the original quinolines. Quinoline *N*-oxide reacts with sulfuryl chloride to give 4-chloroquinoline and a small amount of 2-chloroquinoline (21). With benzoyl chloride the *N*-oxide yields carbostyril, while the added presence of aqueous potassium cyanide results in the formation of 2-cyanoquinoline (106).

The nitration of quinoline has led to contradictory results, presumably because the conditions of the nitration have a decided influence on the course of the reaction: Schorigin and Toptschiew (194) obtained the 7-nitro- or the 5,7-dinitroquinoline, depending upon the temperature, when nitrogen peroxide was the nitrating agent. Bacharach, Haut, and Caroline (2) showed that nitration with fuming or with concentrated nitric acid and sulfuric acid yielded only the 5- and 8-nitroquinolines. However, a mixture of acetic anhydride, lithium nitrate, and copper nitrate yields exclusively the 7-nitro compound.

Doebner and v. Miller (55) reported that quinaldine on nitration in sulfuric acid yielded the 7- and the 8-nitro derivatives. Decker and Remfry (49) and Hammick (98) showed, however, that only the 5- and the 8-nitroquinaldines

are obtained. The nitration of lepidine yields only the 8-nitro derivative (189), presumably because of the steric effect of the 4-methyl group on the 5-position.

The action of halogens leads to mixtures. Bromination has been studied under a variety of experimental conditions. In carbon disulfide a tetrabromoquinoline is formed, whereas bromine reacts with quinoline in the absence of solvent to yield a tetrabromide. An aqueous solution of a quinoline salt reacts with bromine at an elevated temperature to yield a mixture from which 3-bromoquinoline can be isolated in reasonable yield (38). The vapor-phase bromination has been investigated by Jansen and Wibaut (113). When the vapors were separately preheated and passed over pumice at 300°C., a 25 per cent yield of 3-bromoquinoline was obtained. At 450°C. a 24 per cent yield of 2-bromoquinoline was obtained, together with only a trace of the 3-bromo compound.

Quinoline and its derivatives readily react with alkyl halides, yielding *N*-alkylquinolinium halides (202). The latter are readily reduced (for example, by means of zinc and hydrochloric acid) to *N*-alkyltetrahydroquinolines (82), and this is certainly one of the best methods for obtaining such substances.

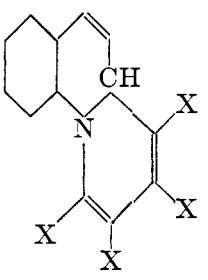
The alkylquinolinium hydroxides are strong water-soluble bases which on oxidation with potassium ferricyanide yield the *N*-alkyl-α-quinolones (48, 76). The *N*-alkylquinolinium iodides (or nitrates) in combination with the corresponding quinaldinium and lepidinium compounds and their derivatives yield, on treatment with sodium methylate, the so-called cyanine dyes, which have found extensive use in photography as photosensitizing agents. The study of these complex compounds and their application is a very specialized one and can be treated adequately only in a separate review.

Barium amide in liquid ammonia reacts with quinoline to yield 2-aminoquinoline with the elimination of hydrogen. Other amides give smaller yields and alkali amides give only resinous products (9).

Aryl and alkyl lithium compounds react with quinolines to yield largely 2-alkyl or 2-aryl-quinolines, the 1,2-dihydro compounds being obtainable as intermediates. Quinaldine yields a lithium derivative, which on treatment with alkyl halides is converted to alkylquinaldines, the alkyl group entering the side chains (231).

Aryl and alkyl Grignard reagents react with quinoline to yield insoluble addition compounds, which on heating to 150–160°C. rearrange to 2-aryl- and 2-alkyl-quinolines, respectively (10).

The Diels–Alder reaction with quinoline and quinaldine has been studied in detail (50). Two molecules of dimethyl acetylenedicarboxylate form a labile addition compound with quinoline, which on heating rearranges to the stable ester (I; X = $COOCH_3$).

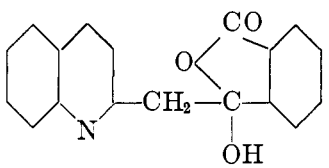


I

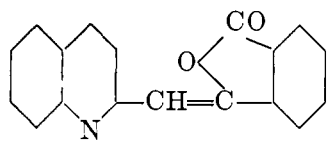
B. Reactions involving substituents

The simple alkyl derivatives of quinoline on oxidation frequently give rise to the acids carrying a carboxyl in place of the alkyl group. The methyl group in quinaldine or in lepidine but not that in 3-methylquinoline displays a special reactivity. The condensation of quinaldine (224) and of lepidine (224) with benzaldehyde and other aldehydes in the presence of zinc chloride leads to the formation of 2- and 4-styrylquinolines, respectively. Substituents frequently interfere with such reactions. Stark (212) failed to obtain condensation products with 3-aminoquinaldine or its acetyl derivative. Wislicenus and Kleisinger (229) condensed quinaldine and lepidine with ethyl oxalate by means of potassium ethylate. The compounds, $C_9H_6NCH_2COCOOC_2H_5$, were obtained in good yield. With chloral the products have the formula, $C_9H_6NCH_2CH(OH)CCl_3$, and these compounds can be hydrolyzed to β-quinolylacrylic acids with potassium carbonate (66).

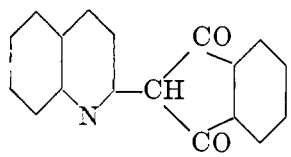
Eibner and Lange (64) and Eibner and Hofmann (63) made an extensive investigation of the reaction of quinaldine with phthalic anhydride. On gently heating a mixture of these substances, there is first formed a compound (II) which when further heated loses water and yields quinoisophthalone (III). This compound is moderately stable but on heating to a still higher temperature



II



III
Quinoisophthalone



IV
Quinophthalone

suffers a rearrangement to yield quinophthalone (IV). This reaction is of diagnostic value in identifying quinaldine and its derivatives and has been so used by Bailey and his coworkers in their study of the quinoline bases from petroleum distillates (143). The quinophthalones are sparingly soluble crystalline compounds of high melting point.

Quinaldine on bromination yields only the ω-tribromoquinaldine and this on

hydrolysis with dilute sulfuric acid yields quinaldinic acid (97). Selective bromination to a mono- or a di-bromo derivative could not be effected. However, reduction of the trichloroquinaldine with stannous chloride could be controlled to yield the dichloro or the monochloro derivatives. Treatment of these compounds with silver nitrate in ethanol or acetone gave quantitative yields of quinaldinic aldehyde and 2-quinolylcarbinol, respectively (98).

Hydroxyquinolines carrying the hydroxyl in the benzene ring behave like ordinary phenols. When the hydroxyl is in the pyridine nucleus it undergoes a number of reactions not common to a phenolic hydroxyl, although these compounds are soluble in strong alkalis. Heating with zinc dust in an atmosphere of hydrogen yields the corresponding quinoline (73, 131). The hydroxyl in position 2 or 4 is readily replaceable by chlorine when the compounds are treated with a mixture of phosphorus pentachloride and phosphorus oxychloride. These chloro compounds can be reduced to quinolines by heating with red phosphorus and hydrogen iodide (131). When 2-chloroquinoline is treated with potassium methylate, 2-methoxyquinoline is obtained and this when heated to a high temperature rearranges to yield *N*-methyl-2-keto-1,2-dihydroquinoline, which is also obtained by treating carbostyril with methyl iodide and alkali. The latter with phosphorus pentachloride in dichlorobenzene is easily reconverted to 2-chloroquinoline (77). The 2-hydroxyquinolines (i.e., the carbostyrils) are very weak bases, and the salts are almost completely hydrolyzed even in moderately strong acid solutions. The other hydroxyquinolines are in general as strong bases as the corresponding quinolines, so that in reactions where a mixture of the 2- and 4-hydroxyquinolines may be formed they are easily separable because of the difference in their solubilities in acid (33).

When 3-hydroxyquinoline is heated under pressure with ammonia, it yields 3-aminoquinoline (58). The Reimer–Tiemann reaction, that is, treatment with chloroform and alkali, with 4-hydroxyquinoline yields 4-hydroxy-3-aldehydoquinoline (20).

The aminoquinolines carrying the substituent in the hetero ring do not yield diazo compounds. When 4-aminoquinoline is treated with sodium nitrite in hydrochloric acid solution, it yields 4-chloroquinoline (227). 2-Phenyl-3-hydroxyquinoline can be prepared from the corresponding amino compound by treatment with nitrous acid (6).

In addition to the methods already described, the py-amino derivatives may be obtained by reducing the nitro compounds with tin and hydrochloric acid (43).

The 2- and 3-bromo derivatives of quinoline, when heated with cuprous cyanide, yield the corresponding nitriles and when heated with ammonia in the presence of copper powder yield the corresponding amines (114).

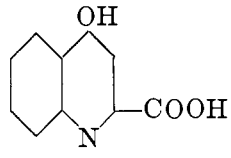
III. NATURAL OCCURRENCE OF QUINOLINES

The most important occurrence of quinoline derivatives in plants is that of the cinchona and angostura alkaloids. The alkaloid echinopsine (95), present

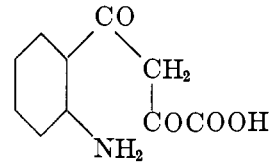
in *Echinops ritro*, was shown by Späth and Kolbe (210) to be identical with synthetic 1-methyl-4-quinolone. It was readily prepared by heating 4-hydroxyquinoline with methyl iodide in the presence of sodium methylate.

Suzuki and coworkers (218) isolated from rice bran several acids, one of which is regarded as a dihydroxyquinoline-5-carboxylic acid (193).

In animals the only quinoline derivative of importance is kynurenic acid (I). It occurs normally in the urine of dogs but not in that of cats. It is a product of the catabolism of tryptophan, the ultimate intermediate being *o*-aminobenzoylpyruvic acid



I
Kynurenic acid



II
o-Aminobenzoylpyruvic acid

The presence of quinoline or isoquinoline bases in petroleum distillates was demonstrated by Maberry and Wesson (148). Later, Bailey and coworkers in a series of researches isolated and identified a number of quinolines, among which may be mentioned the following: 2,3,8-trimethylquinoline (182); quinoline and quinaldine (28); 2,3,4,8-tetramethylquinoline and 2,3-dimethyl-8-propylquinoline (1); 2,4,8-trimethylquinoline and 2,4-, 2,3-, and 2,8-dimethylquinolines (17).

Ganguli and Guha (91) record the isolation of 5,8-dimethylquinoline. It was isolated as the picrate (m.p. 198°C.). The writer has prepared the same picrate and has found that it melts at 186°C.

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