THE CHEMISTRY OF 4-HYDROXYQUINOLINES

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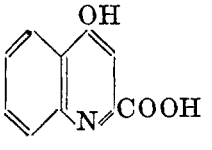
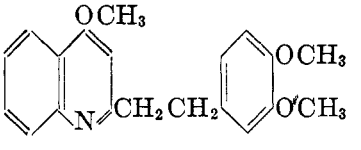
CONTENTS

I. Introduction

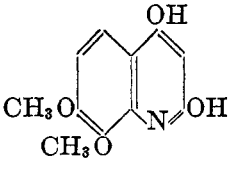
The search for new drugs useful in the treatment of malaria has resulted in the recognition of the value of 4-alkylaminoquinoline derivatives. The most general synthesis of these drugs has been through the 4-hydroxyquinolines. Consequently many chemists, especially those working for the Committee on Medical Research in the United States, recently have investigated the chemistry of 4-hydroxyquinolines. Another reason for the interest in 4-hydroxyquinolines is the occurrence of their derivatives in nature. These include kynurenic acid (I); angostura alkaloids such as cusparine, galipine (II), and 2-*n*-amyl-4-methoxyquinoline (72); and derivatives of *Rutaceae* such as 2,4-dihydroxy-7,8-dimethoxyquinoline (III) (55, 129).



I
Kynurenic acid



II
Galipine



III

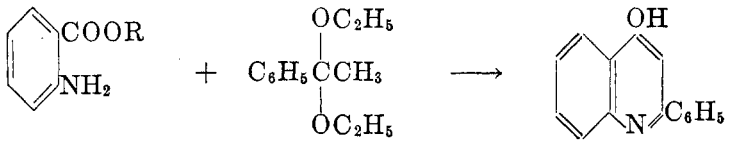
The preparation of 4-hydroxyquinolines has been divided into three classes. Syntheses in the first class are based upon quinoline formation from ortho-disubstituted aromatic compounds, those in the second class upon ring closure of arylamine derivatives, and those in the third class upon conversion of 4-chloro- and 4-amino-quinolines to 4-hydroxyquinolines.

Since 4-hydroxyquinolines possess interesting peculiarities in their reactions, a short discussion of their physical and chemical properties has been included.

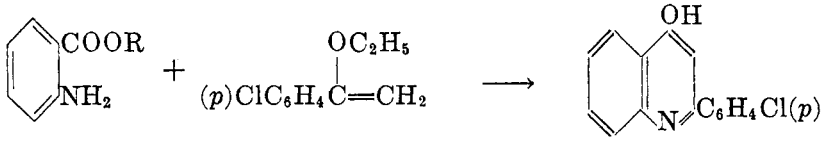
II. Syntheses of 4-Hydroxyquinolines

A. From disubstituted aryl rings

Anthranilic acid derivatives can be converted to 4-hydroxyquinolines by treatment with ketones. This method is particularly useful for preparing 2-aryl-4-hydroxyquinolines (84). Although an early report indicated that only a 3–5 per cent yield of 4-hydroxy-2-phenylquinoline was obtained from anthranilic acid and acetophenone (138), Fuson and Burness (64) reported that the anthranilic acid ester and the ketal of acetophenone gave an 84 per cent yield.

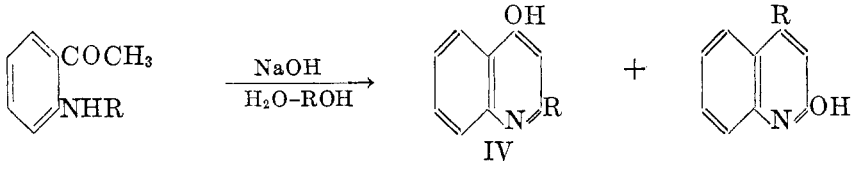


Owing to decarboxylation under the conditions of the reaction the free acid gave only a 50 per cent yield. The preference for the ester is not general however, since in the preparation of 4-hydroxy-3-methyl-2-phenylquinoline from the ketal of propiophenone, the free acid gave a 70 per cent yield while the ester gave only a 52 per cent yield. Further investigation of the reaction showed that *p*-chlorophenyl-α-ethoxystyrene was at least as useful as the ketal for the preparation of 2-(*p*-chlorophenyl)-4-hydroxyquinoline.



This reaction suggested that the ethoxystyrene may have been the intermediate in the reaction of the ketal.

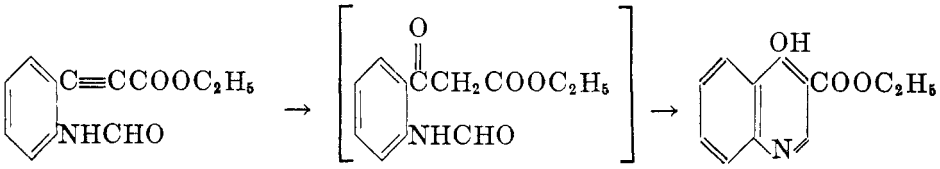
o-Aminoacetophenones have been used instead of the anthranilates. The formyl derivative of *o*-aminoacetophenone yielded 4-hydroxyquinoline (IV, R = H) in very moderate yields (24, 36, 37). Acetylaminoacetophenone yielded 16–20 per cent of 2-methyl-4-hydroxyquinoline (IV, R = CH_3) in addition to a large amount of 2-hydroxy-4-methylquinoline (35).



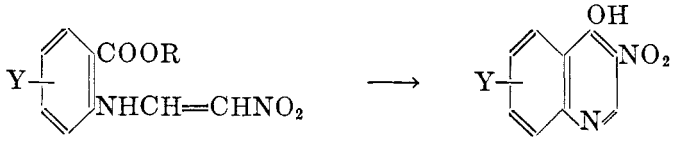
In a similar way IV has been prepared, where R was ethyl (190) or isopropyl (34). By similar methods other types of groups can be introduced in the 2-position. The oxamide derivative gave 2-carboxy-4-hydroxyquinoline (IV, R = COOH) (37), while the ethyl carbamate derivative gave 2,4-dihydroxyquinoline (IV, R = OH) (34). Extension to propiophenones gave 3-methyl-4-hydroxyquinolines (190).

Glyoxalation of *o*-nitroacetophenone and cyclization during reduction yielded 2-carboxy-4-hydroxyquinoline in 40–50 per cent yield (110). The 6-methoxy derivative also has been prepared by this method (5).

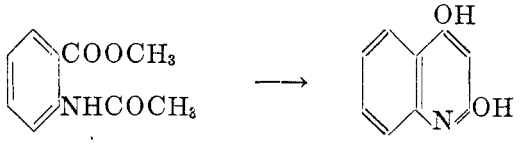
Some syntheses from less readily obtainable starting materials also have been reported. Ethyl *o*-formylaminophenylpropiolate produced 3-carbethoxy-4-hydroxyquinoline in 90 per cent yield (36, 37). This reaction has been postulated as occurring through the ketone.



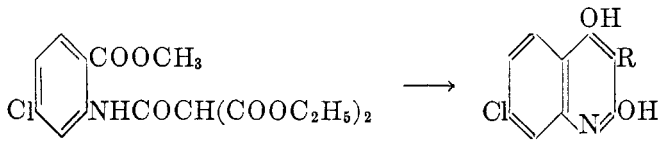
Closely related to this is the synthesis of dihydro-4-hydroxy-2-phenylquinoline from benzal-*o*-nitroacetophenone (119). From anthranilic acid derivatives and potassium methazoate were obtained 4-hydroxy-3-nitroquinolines (11, 45, 46, 133).



2,4-Dihydroxyquinolines constitute an important group often prepared by variations of the above methods. Treatment of methyl *N*-acetylanthranilate with sodium in xylene was reported to give a 60 per cent yield of 2,4-dihydroxyquinoline (33).



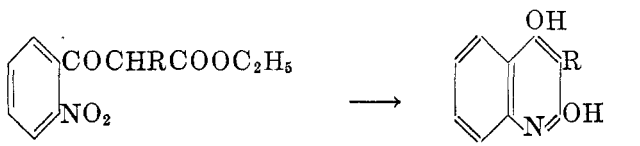
Later workers have been unable to obtain more than 28–40 per cent yields by this method (5, 30, 32). A still less satisfactory method employed methyl anthranilate and ethyl acetate with metallic sodium (61). One of the best methods of this type which had been reported by Koller (108) has been developed by Lutz and coworkers (117). The amide obtained from methyl 4-chloroanthranilate and malonic ester was cyclized, saponified, and decarboxylated to yield 7-chloro-2,4-dihydroxyquinoline in 72 per cent over-all yield.



R = $COOC_2H_5$, COOH, H.

Tetrahydroanthranilic ester gave a 71.5 per cent yield of the corresponding 5,6,7,8-tetrahydroquinoline (141). Sodium ethoxide has been used as the condensing agent in the reaction of methoxyanthranilyl chlorides with malonic ester to give undisclosed yields of 2,4-dihydroxy-5-, 6-, 7-, and 8-methoxyquinolines (21).

Bischoff has described the reduction of *o*-nitrobenzoylmalonates to 3-carbethoxy-2,4-dihydroxyquinoline (V) with tin and hydrochloric acid (4,22,66). In a similar reaction ethyl *o*-nitrobenzoylpropionate was reduced with phosphorus and hydriodic acid to 2,4-dihydroxy-3-methylquinoline (VI). Quinolines with methoxy groups in the benzenoid ring have also been reported (4, 140).

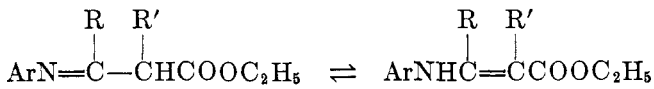


V: R = $COOC_2H_5$
VI: R = CH_3

The great advantage which the syntheses of this first class have in common is that no ring isomers are possible. The procedures are useful therefore to locate substituents exclusively in the 5- or 7-position of the quinoline ring. The main disadvantage aside from generally moderate yields is that the preparation of quinolines with substituents on the benzene ring often requires starting materials which are not readily available. The alternate syntheses from arylamines are preferable then, since only one substituent is needed for ring formation.

B. FROM RING CLOSURE OF ARYLAMINE DERIVATIVES

A large number of methods have been developed for the preparation of 4-hydroxyquinolines from arylamines possessing an unsubstituted ortho position. The intermediates in all cases can be considered as Schiff bases or as derivatives of acrylic acid.

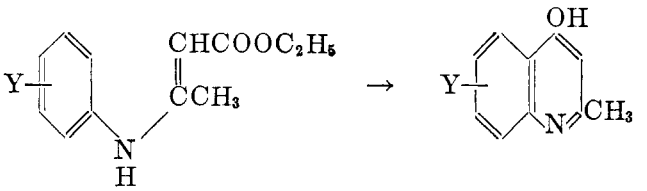


In this discussion this tautomerism will be ignored, and for clarity of nomenclature all intermediates will be regarded as β-arylaminoacrylates.

1. β-Anilinoacrylates

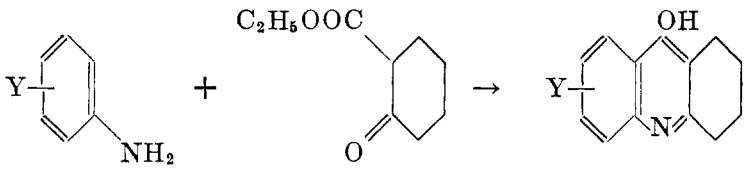
The Conrad–Limpach method is the most general reaction for the preparation of 2-alkyl-4-hydroxyquinolines. From arylamines and β-keto esters are obtained β-anilinoacrylates. When these are heated to around 250°C. ring closure occurs (48, 49, 50, 51).

$ArNH_2 + CH_3COCH_2COOC_2H_5 \rightarrow$



In the early work the cyclization was accomplished by heating the ester without a solvent and yields were very moderate. Limpach reported many years later that the yields in the cyclization were raised from below 30 per cent up to 95 per cent in many cases when an inert solvent such as mineral oil was used for the reaction (112, 113). Four to ten parts of solvent were used for each part of crotonate. Generally the cyclization was rapid. Heating for 20 min. at 240–250°C. was adequate to give 90–95 per cent yields of 4-hydroxy-2-methylquinoline.

Application of the Conrad–Limpach reaction to almost every type of arylamine has been made. The substituents in the benzene ring have included alkyl, nitro, halogen, and alkoxy groups. In table 1 will be found examples of 4-hydroxyquinolines prepared by this method. Some of the older work is included, despite lower yields to demonstrate the scope of the reaction. Often the yields of certain compounds are low even with a solvent, because of decomposition, as in the preparation of the 8-acetylaminoquinoline. A number of polycyclic derivatives also have been made. Aminocarbostyril (76), aminoacenaphthene (137), and 3-aminopyrene (187) have given polycyclic substituted 4-hydroxyquinaldines. Another interesting series was reported by Hughes and Lyons (85, 114) from 2-carbethoxycyclohexanone and arylamines.



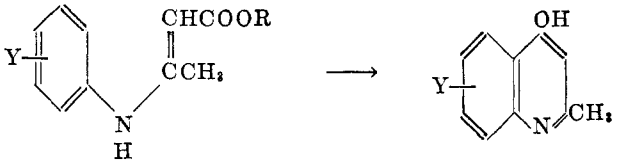
The arylamines used included 3,4-dimethoxyquinoline, 3- and 4-bromoanilines, and 2-phenylaniline. The arylamine and keto ester were warmed at 100°C. and then added to mineral oil and heated at 250°C. for a few minutes.

The preparation of the anilinocrotonate has caused a good deal of confusion in the early literature. As Limpach has pointed out, the mixture of acetoacetic ester and arylamines gave crotonates at room temperature, while at 140–160°C. the anilide was formed (112).

It is apparent now that reports such as that of Knoor (101, 102) in which the free acid VII was postulated were in error. The amide was obtained, as Knoor

TABLE 1

4-Hydroxyquinolines prepared by the Conrad–Limpach reaction

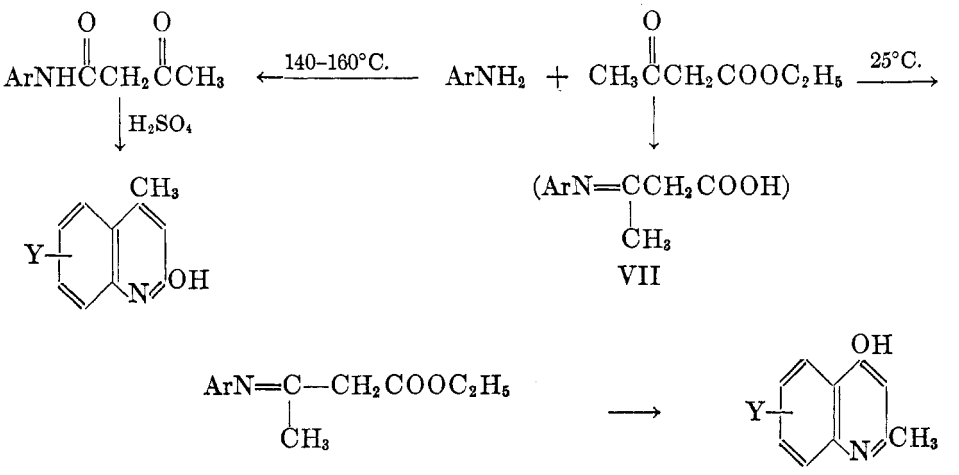


Y	YIELD FROM $ArNH_2$	SOLVENT	REFERENCE
	per cent		
H	—	None	(48, 175)
H	90–5	Mineral oil	(112)
6-CH_3	—	None	(51)
8-CH_3	27	None	(51)
5,7-$(CH_3)_2$	—	None	(51)
6,8-$(CH_3)_2$	—	None	(51, 84)
5,6,8-$(CH_3)_3$	50	None	(51)
5,6-Benzo	67	None	(51)
7,8-Benzo	90	Mineral oil	(70, 112, 113)
6-CH_3O	90	Mineral oil	(113)
6-CH_3O	61	None	(171)
6-C_2H_5O	90	Mineral oil	(112)
7(5)-OH	29*	Petrolatum	(134)
8-OH	50*	Paraffin oil	(136)
6,7-$(CH_3O)_2$	—	None	(114)
6,7-$(C_2H_5O)_2$	70	None	(114)
7,8-$(CH_3O)_2$	30	None	(78)
6-OH-8-$(CH_3)_2CH$	—	Vaseline oil	(85)
5-OH-8-Cl	—	Petrolatum	(134)
6-Cl	75	Paraffin oil	(98)
6-Br	56	Paraffin oil	(98)
7-Cl	72	Dowtherm	(146)
7-COOH-5,6-benzo	Quantitative	Mineral oil	(76)
5-CH_3CONH	30	Paraffin oil	(100)
6-CH_3CONH	79 (70*)	Paraffin oil	(87, 98, 161)
8-CH_3CONH	25*	Mineral oil	(124)
7,8-(3,4-Pyridyl)	60*	Mineral oil	(124)
7,8-(3,2-Pyridyl)	30*	Mineral oil	(124)

* Yield based on acrylate.

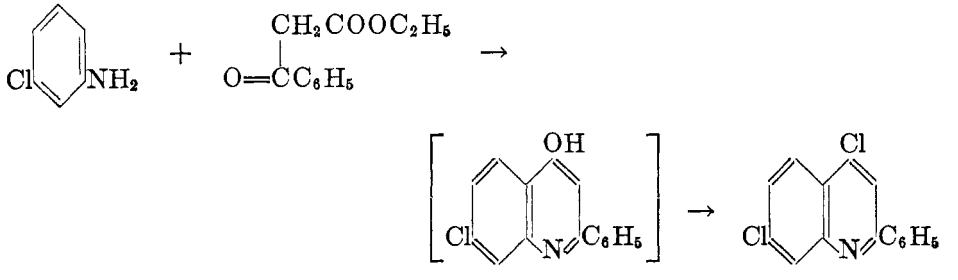
himself indicated later (104). Hauser (79a) has discussed some factors governing the direction of this reaction.

An investigation of various reaction conditions for the preparation of the crotonate has been reported by Coffey, Thompson, and Wilson (44). With very pure aniline 20 days were required for complete reaction, while commercial ani-



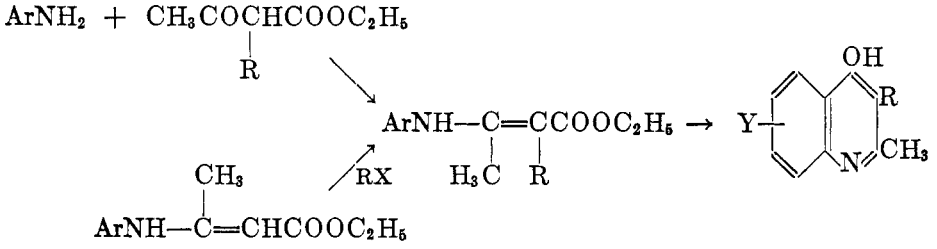
line required but a few days. One drop of strong acid caused the reaction to occur within 5 min. The rate of reaction was found to be in direct proportion to the acid strength. Although the reaction was very sensitive to acids, no effect was noticed with alkaline catalysts, contrary to some earlier reports. Some limitations to the preparation of crotonates have been noted, especially with *o*-, *m*-, and *p*-nitroanilines and derivatives such as *m*-nitro-*p*-toluidine, *p*-chloro-*o*-nitroaniline, 2,4-dinitroaniline, and *p*-methoxy-*o*-nitroaniline (44, 124).

The preparation of 2-aryl-4-hydroxyquinolines by the method of Conrad and Limpach, despite their report of the synthesis of 2-phenyl-4-hydroxyquinoline (50), has not proved as successful. Reaction of ethyl benzoylacetate with *m*-chloroaniline and treatment of the product with phosphorus oxychloride gave 3–5 per cent of 4,7-dichloro-2-phenylquinoline (58).

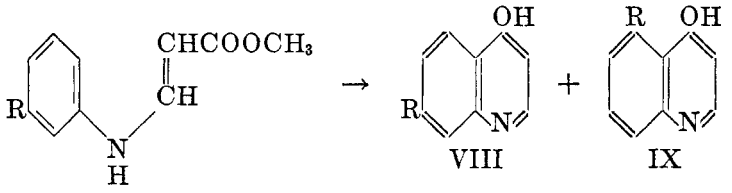


Ethyl *β*-methoxycinnamate in place of the ethyl benzoylacetate did not improve the yield. In this case at least, the use of anthranilic acid derivatives is superior.

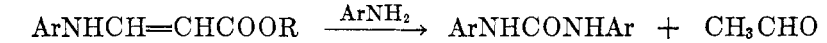
Another class of compounds prepared by the Conrad–Limpach method is the 2,3-disubstituted 4-hydroxyquinolines. They have been prepared either from the substituted acetoacetic ester (98, 143, 180), or better by alkylation of the intermediate crotonate (111).



The Conrad–Limpach method has had only limited application to the synthesis of quinolines with an unsubstituted 2-position. The preparation of 4-hydroxyquinoline itself has been accomplished in 44 per cent yield from methyl β-anilinoacrylate (146).

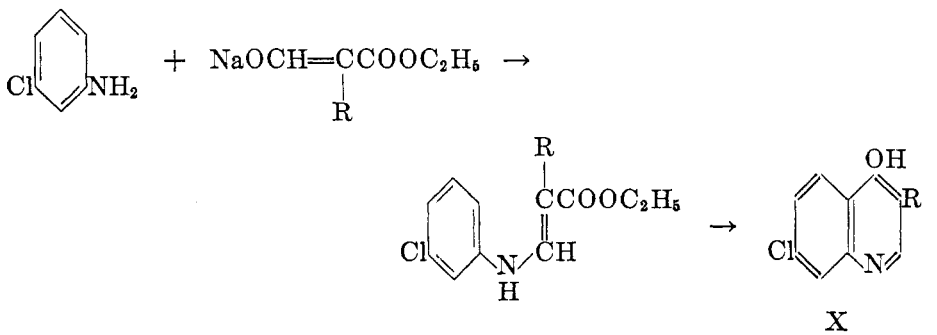


With *m*-chloroanilinoacrylate (R = Cl) 40 per cent of VIII and 10 per cent of IX were obtained. A large volume of solvent is necessary for the cyclization to avoid decomposition and production of diarylureas.



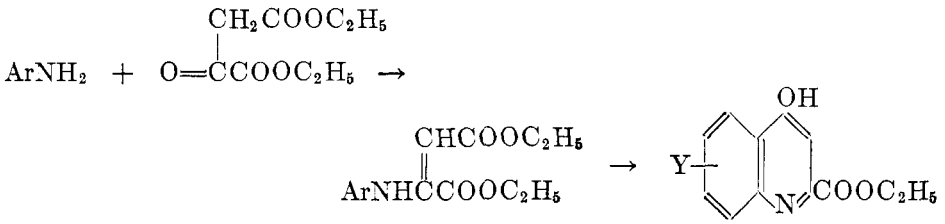
This side reaction parallels a similar decomposition of acetoacetic ester with arylamines (88, 103). Apparently this reaction confused Reissert (152, 153), and the physical properties he reported for the product he thought to be 4-hydroxyquinoline agree well with those for diphenylurea.

The formyl derivatives of esters other than ethyl acetate give 3-substituted quinolines. Thus, ethyl formylpropionate gave 7-chloro-3-methylquinoline (X, R = CH_3) in 60–65 per cent yield (146). The 3-phenyl derivative (X, R = C_6H_5) was prepared from ethyl α-formylphenylacetate in 36.5 per cent yield from *m*-chloroaniline (60) by an improvement on the original procedure of Wislicenus (189).



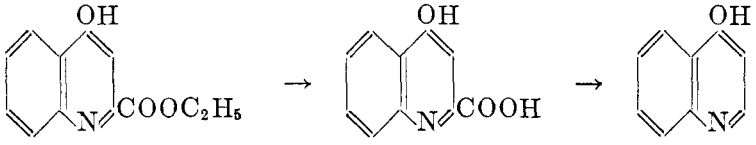
2. β-Carbethoxy-β-anilinoacrylates

The second general cyclization procedure for the synthesis of 4-hydroxyquinolines uses the intermediate acrylates formed from arylamines and oxalacetic esters. This method is identical with the normal Conrad–Limpach reaction except for the replacement of the methyl or other substituent in the 2-position with a carbethoxy group. As with the original Conrad–Limpach reaction, the cyclization was accomplished by heating the acrylate or mixture of arylamine and oxalacetic ester in an inert solvent at about 250°C.



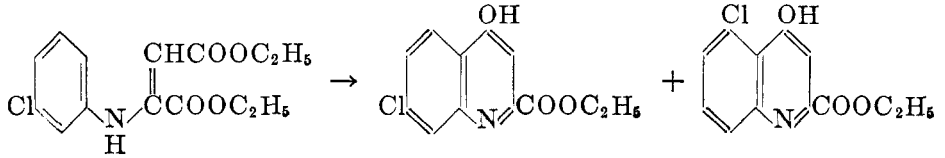
The acrylates were prepared in 78–95 per cent yields in methylene chloride or glacial acetic acid solution (177). For the cyclization solvent Dowtherm A was superior to mineral oil, since less decomposition occurred in that medium (179).

The usual investigation also required removal of the carbethoxy group by saponification and decarboxylation. Decarboxylation was carried out conveniently by heating the acid in Dowtherm.



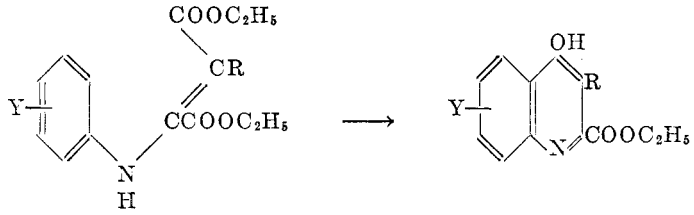
As indicated in table 2 the yields of the 2-carbethoxy-4-hydroxyquinolines are good. Some of the variations in yields result from basing the yield on either the intermediate acrylate or on the arylamine. The removal of the carbethoxy group is accomplished regularly in high yields. One disadvantage of the method is that widely varying conditions for cyclization and decarboxylation are necessary, depending upon the groups in the ring (159).

Table 2 also shows that 3-alkyl- or 3-aryl-quinolines are available. The majority of cases have a methyl group in the 3-position, although longer alkyl groups have been used. The substituents in the benzene ring are dependent upon the arylamine used. The demand for 7-chloro-4-hydroxyquinoline has led to an extensive investigation of the compounds produced by the cyclization of the *m*-chloroaniline derivative. In addition to the 7-chloroquinoline the 5-chloroquinoline was obtained.



The combined yield of the isomers based upon the arylamine was 56 per cent (182). This mixture was composed of nearly equal amounts of the 5- and 7-

TABLE 2



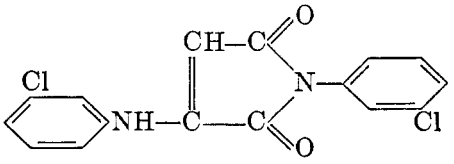
R	Y	YIELD FROM $ArNH_2$	YIELD FROM ACRYLATE	REFERENCE
		per cent	*per cent*	
H	H	61		(13, 38, 83, 133)
H	CH_3		87	(177)
H	5,6-Benzo		65	(131)
H	7,8-Benzo		89	(63)
H	6-CH_3O		85	(158, 162, 163)
H	8-CH_3O		85	(177)
H	8-C_2H_5		72	(177)
H	5-OH-8-Cl	—		(135)
H	5- and 7-Cl		32	(115, 182)
H	8-Cl		62	(177)
H	8-Br		59	(177)
H	5,7-Cl_2		55	(183)
H	5,7-Br_2		20	(183)
H	5,8-Cl_2		50	(183)
H	6,8-Cl_2		42	(183)
H	5-CH_3CONH	11		(97)
H	6-CH_3CONH	—		(99)
CH_3	6-CH_3		92	(176)
CH_3	6-CH_3O		97	(176)
CH_3	6-C_2H_5O		95	(176)
CH_3	7,(5)-CH_3O	62		(29)
CH_3	6-Cl		95	(176)
CH_3	6-Br	73	97	(29, 176)
CH_3	6-I		82	(179)
CH_3	5- and 7-Cl		97*	(178)
CH_3	5- and 7-Br		98*	(178)
CH_3	5- and 7-I		92*	(179)
CH_3	8-Cl	68		(29)
CH_3	8-I		89	(179)
CH_3	6-CH_3-7-Cl	60		(29)
CH_3	5-CH_3-8-Cl	62		(29)
$C_6H_{11}(CH_2)_3$	H	45–50		(13)

* Yield of combined isomers.

chloro isomers. *m*-Iodoaniline, however, gave nearly twice as much 7-iodo as 5-iodo derivative, indicating that the bulkiness of the group may be one factor

in determining the relative amounts of each isomer (179). Lisk and Stacey (115) found that in concentrated solution virtually none of the 5-chloro isomer was found, but the yield was prohibitively low. In dilute solutions about 40 per cent of the product was the 5-chloroquinoline, but at the same time the yield of the combined isomers was at a maximum.

In addition to the two ring isomers a by-product was isolated which proved to be a molecular compound of 7-chloro-4-hydroxyquinoline and *N*-(*m*-chlorophenyl)-α-(*m*-chloroanilino)maleimide (XI) (181).

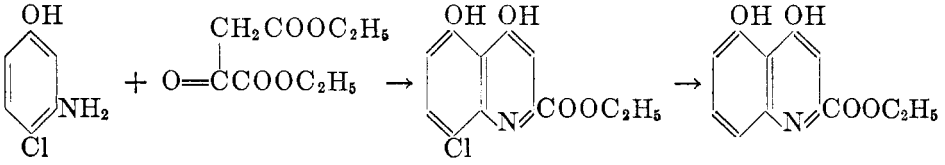


XI

The formation of XI indicates some decomposition of the acrylate, followed by reaction of the liberated *m*-chloroaniline with the β-carbethoxy ester to form the imide. It is apparent that the presence of excess arylamine will lower the yield of the quinoline appreciably, as has been shown also in the original Conrad–Limpach reaction (146).

The cyclization of the derivative of *m*-acetylaminoaniline is a rather surprising case. Only the 5-isomer was reported (97). Since the yield was very low, it is possible that the 7-isomer was formed but not isolated. This result is similar to the cyclization of the anil from *m*-acetylaminoaniline and acetoacetic ester related by one of the same authors (table 1) (100).

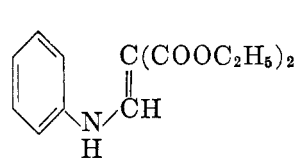
Musajo and Minchilli (135) obtained the pure 5-substituted derivative by by using the familiar device of blocking the most favored ortho position with a chlorine atom which was removed subsequently.

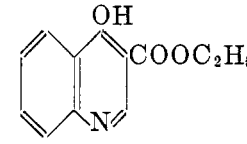


The 6-, 7-, and 8-substituted compounds are usually obtained in satisfactory yields from the *p*-, *m*-, and *o*-substituted anilines, although preparation of the 7-substituted quinolines by this method again involves a tedious separation from the 5-isomer.

3. α-Carbethoxy-β-anilinoacrylates

A very useful synthesis of 4-hydroxyquinoline and one which promises to be the most general was devised by Gould and Jacobs (76). The α-carbethoxy-β-anilinoacrylate esters were cyclized in mineral oil to 3-carbethoxy-4-hydroxyquinolines.





The cyclization is clean and results are generally uniform. This method was developed by Price and Roberts (148) for the synthesis of 7-chloro-4-hydroxyquinolines and has been applied by numerous groups to various arylamines.

(a) Syntheses from ethoxymethylenemalonic ester

Ethoxymethylenemalonic ester ("EMME") is prepared from diethyl malonate and ethyl orthoformate (39). This is the intermediate used by Gould and Jacobs and by most of the subsequent investigators for the preparation of the desired acrylates.

$$CH_2(COOC_2H_5)_2 + HC(OC_2H_5)_3 \rightarrow$$

$$C_2H_5OCH{=}C(COOC_2H_5)_2 \xrightarrow{ArNH_2} ArNHCH{=}C(COOC_2H_5)_2$$

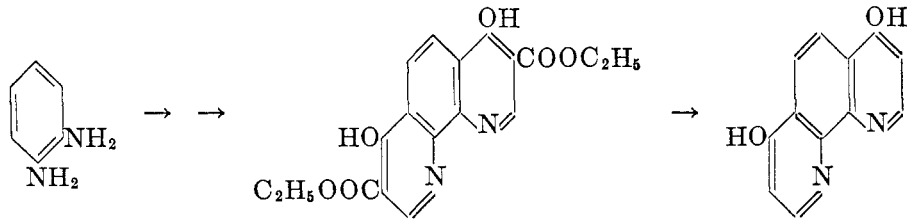
Fuson, Parham, and Reed (65) have prepared ethoxymethylenemalonic ester by condensing methyl diethoxyacetate and malonic ester and eliminating a molecule of ethanol.

$$(C_2H_5O)_2CHCOOCH_3 + CH_2(COOC_2H_5)_2 \rightarrow$$

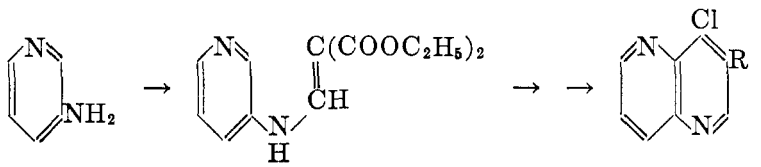
$$(C_2H_5O)_2CHCH(COOC_2H_5)_2 \rightarrow C_2H_5OCH{=}C(COOC_2H_5)_2$$

As in other reactions of the Conrad–Limpach type, the cyclization is carried out in refluxing diphenyl ether or Dowtherm. Mineral oil is a less desirable reaction medium. The saponification is generally accomplished in quantitative yield, and the acid is then decarboxylated by heating either dry or in the cyclization solvent. It has been noted that decarboxylation of certain nitroquinolines by the usual procedure never gave above 50 per cent yields and only small batches could be run. The preparation of the silver salt eliminated this difficulty (15). In another case impurities of the sodium salt caused completely altered behavior of the acid upon decarboxylation. Preliminary digestion with an excess of acid was found to be a remedy (109).

The generality of the method is shown by the fact that besides 4-hydroxyquinoline itself (77), 4-hydroxyquinolines have been prepared with substituents in the benzenoid ring such as the following: chloro (29, 148, 159, 184); fluoro and trifluoromethyl (173); methoxy and phenoxy (109, 159, 173); sulfide and disulfide (147); benzylmercapto, amino, and acetyl (149); and nitro (15, 77, 150, 159). The use of *o*-phenylenediamine yielded 4,7-dihydroxy-1,10-phenanthroline in an over-all yield of 58 per cent (172).



Other phenanthrolines have been obtained from the aminoquinolines (172). 4-Chloro-1,5-naphthryridine was obtained from 3-aminopyridine (1).



4-Hydroxy-6-sulfonamidoquinoline could not be prepared by this method, and although 6,6′-bis(4-hydroxyquinolyl) disulfide was obtained it could not be decarboxylated (14, 147).

Generally the synthesis gives mainly the 7-isomer from *m*-substituted anilines. *m*-Chloroaniline gave 15 per cent of the 5-isomer. However, *m*-fluoroaniline gave a large amount of the 5-isomer, and *m*-cyanoaniline gave only the 5-isomer (150).

A variation of the "EMME" synthesis was developed which used ethoxymethylenecyanoacetic ester rather than the malonate (144, 174). The product of the cyclization was a 3-cyano-4-hydroxyquinoline. The variation offered no advantage over the use of the malonate. Actually, the cyclization was slower, required a larger proportion of solvent, and yields from the cyclization were lower. Furthermore, the cyanoquinolines were much less tractable compounds than the esters.

b. Syntheses from amidines

Since ethyl orthoformate and consequently ethoxymethylenemalonic ester are relatively expensive, attempts have been made to find cheaper substitutes in the synthesis of α-carboxyanilinoacrylates. One of the more encouraging prospects is the decomposition of arylamidines with malonic ester itself (53, 144, 149, 174). Arylamidines (XII) have been prepared from formic acid and the arylamine in excellent yields.

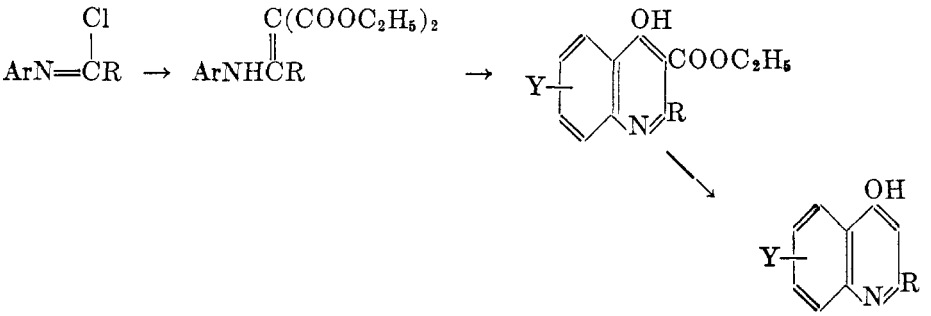
$$ArNH_2 + HCOOH \rightarrow \underset{\text{XII}}{ArNHCH{=}NAr} \xrightarrow{CH_2(COOC_2H_5)_2} ArNHCH{=}C(COOC_2H_5)_2 + ArNHCH{=}C(COOC_2H_5)CONHAr$$

XIII XIV

The formation of the anilide (XIV) occurred in 70 per cent yield when the reaction was carried out at 150–165°C. (144). By operating at 120°C. the yield of XIV was 10 per cent, while the desired acrylate XIII was formed in 38 per cent yield. Unreacted amidine could be recovered. This raised the yield of the acrylate to around 90 per cent (149). It was possible to cyclize XIV but, as with the nitrile, a much higher dilution was required.

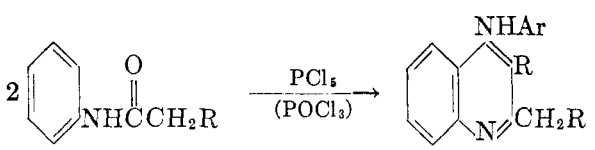
c. Syntheses from imido chlorides

A synthesis of 2-aryl-4-hydroxyquinolines which depended upon the cyclization of α-carboxy-β-aryl-β-arylaminoacrylates was described by Just (94, 95, 96). These acrylates were obtained from malonic ester and imido chlorides.



Seha and Fuchs (178) used this same procedure to prepare a series of 2-aryl-4-hydroxyquinolines with various substituents in the benzenoid ring. An improved yield followed from the use of toluene as the solvent and from the addition of one equivalent of malonic ester to reduce the amount of dicondensation product (169). In this manner an over-all yield of 30–40 per cent of various 2-aryl-4-hydroxyquinoline esters was obtained. The method has been used by Elderfield and coworkers for the synthesis of the 4-hydroxy-6- and 7-methoxy-2-phenylquinolines and 7-chloro-4-hydroxy-2-phenylquinolines (58). In the latter series the intermediate acrylate was not isolated but was cyclized directly to the quinoline in yields of 35–38 per cent.

A closely related reaction of acylanilines has been reported in a number of papers (26, 27, 28, 79, 82, 169).

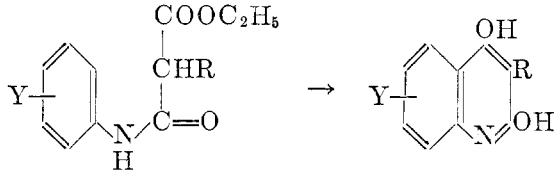


R = Cl, CH_3, C_2H_5, C_6H_5.

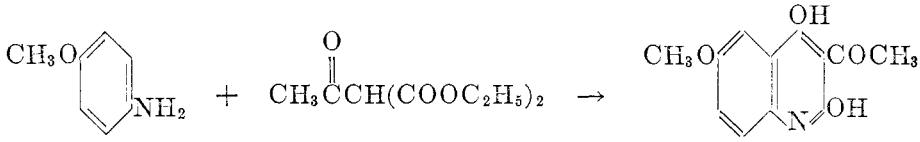
4. Malonic acid anilides

The most direct synthesis of 2,4-dihydroxyquinolines is by the cyclization of the half-anilides of malonic ester. The method for the same compounds described previously, using anthranilic acid derivatives, is usually preferable only

for derivatives of *m*-substituted arylamines. The present method gives both the 5- and the 7-isomer although the 7-isomer predominates. Rugheimer used phosphorus pentachloride as a condensing agent and obtained chlorinated quinolines (164, 165, 166, 167). By heating the malonanilides at 250°C. the 2,4-dihydroxyquinolines have been obtained in over 80 per cent yields (17, 122).



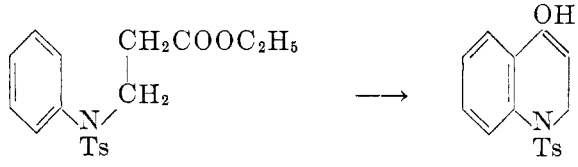
Nitrobenzene has been used as a solvent for the cyclization, and in this way a 63 per cent yield of 3-acetyl-2,4-dihydroxy-6-methoxyquinoline has been obtained (68, 185).



Baker, Lappin, and Riegel (16) found that earlier cyclization methods were not successful when applied to a mixture of cyclohexylpropylmalonic ester and aniline. The use of diphenyl ether as a reaction medium gave nearly quantitative yields of the desired 3-alkyl-2,4-dihydroxyquinoline from *p*-dimethylaminoaniline and cyclohexylmalonic ester or cyclohexylpropylmalonic ester. This modification was not suitable for *o*-nitroaniline or for cyclizations with allylmalonic ester or 3-diethylaminopropylmalonic ester.

5. β-Anilinopropionates

Some mention should be made of the attempts to prepare 4-hydroxyquinolines from β-anilinopropionates by cyclization and subsequent dehydrogenation. Clemo and Perkin (42, 43) found that the reaction of aniline and ethyl β-chloropropionate looked unpromising. However, they were able to cyclize the toluenesulfonyl derivative of the anilinopropionate. With phosphorus pentoxide a compound corresponding to 4-hydroxy-1-tosyl-1,2-dihydroquinoline was obtained. The work has been repeated by Backberg (6).



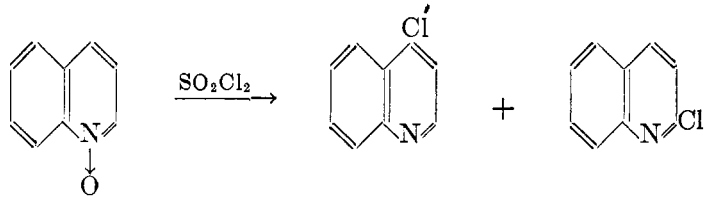
The product obtained by cyclization in phosphorus oxychloride contained chlorine, and Clemo and Perkin considered it to be 3-chloro-4-hydroxyquinoline. This gave 4-methoxyquinoline with sodium methoxide, and Diesbach and Kra-

mer (54) interpreted this to indicate that actually the 4-chloro derivative was obtained. Since the anilinopropionates are readily available from arylamines and acrylic esters, Elderfield and coworkers have reinvestigated the reaction (57). These authors came to the conclusion that the reactions are obscure and information is still needed to interpret the reported reactions.

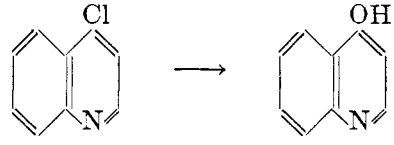
C. FROM 4-SUBSTITUTED QUINOLINES

1. From 4-chloroquinolines

The best synthesis of 4-chloroquinolines by far is the treatment of 4-hydroxyquinolines with phosphorus halides. Therefore the chloroquinolines would be of very little importance in the synthesis of 4-hydroxyquinolines if it were not for the reaction of quinoline *N*-oxides with sulfuryl chloride or phosphorus oxychloride reported by Meisenheimer (120).



Occasionally the conversion of 4-aminoquinolines to 4-haloquinolines by diazotization has gone very well, as in the preparation of 4-bromo-2-phenylquinoline (90). The halogen atom can then be replaced with the hydroxyl group. Bobranski (24) prepared 4-hydroxyquinoline in 69 per cent yield by treatment of the chloroquinoline with hydrochloric acid at elevated temperatures.



Similar acid hydrolyses have been reported by Skraup (170) and by Bachman and Cooper (10).

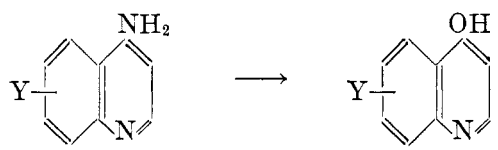
Further investigation of the reaction of quinoline *N*-oxide demonstrated that the reaction product obtained in 73 per cent yield consisted of about 62 per cent 4-chloroquinoline and 38 per cent 2-chloroquinoline (24, 25). The ratio of the isomers depended mainly upon substituents in the benzene ring (10). For instance, 6-methoxyquinoline gave 55 per cent of the 2-chloro- and 35 per cent of the 4-chloroquinoline, whereas 6-nitroquinoline gave 16 per cent of the 2-chloroquinoline and 56.5 per cent of the 4-chloroquinoline. Reaction conditions had little effect upon the ratio of isomers. Possible catalysts such as sulfuric, phosphoric, or acetic acid caused undesirable side reactions (10). Sulfuryl chloride was often superior to phosphorus oxychloride, but it failed to give a monochloro derivative of *m*-phenanthroline, while phosphorus oxychloride gave the 2-chloro derivative (97). By eliminating the possibility of isomers by blocking the 2-

position, very satisfactory yields of 2-aryl-4-chloroquinolines have been obtained by Gilman and coworkers (73, 74, 75). A methyl group also has been used to block the 2-position (47, 81). The Meisenheimer reaction could not be used to prepare the 4-chloro derivatives, for example, from 7-chloroquinoline (159), 8-nitroquinoline (77), 6-methoxy-8-nitroquinoline (77), 8-quinolinesulfonic acid (159), 8-methylquinoline (73), or 3-chloroquinoline (160). This lack of generality, the preparation of the oxides, and the separation of isomers decrease the usefulness of this reaction.

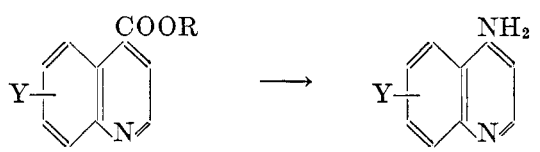
2. From 4-aminoquinolines

At present the most general synthesis of 4-aminoquinolines is from 4-chloroquinolines, which are best prepared from 4-hydroxyquinolines. Consequently the conversion of 4-aminoquinolines to the 4-hydroxyquinolines is of much less importance than formerly. In special cases, however, either primary or secondary 4-aminoquinolines are available and a brief survey of this source of 4-hydroxyquinolines would be of interest.

One of the earliest methods for the synthesis of 4-hydroxyquinolines was the treatment of 4-aminoquinolines with nitrous acid (18, 40, 41, 184, 188).



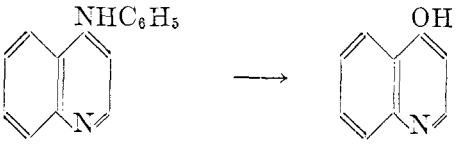
These 4-aminoquinolines were generally obtained from the corresponding carboxylic acid derivatives by a Hofmann rearrangement.



Recently, workers have developed the reaction and given more specific details than are available in the early literature. Renshaw and Friedman (156), for example, have obtained 4-aminoquinoline in 68 per cent yield from cinchoninic acid. 7-Methyl-4-aminoquinoline was prepared in 70 per cent yield (151). With dioxane as the solvent a 68 per cent yield of 4-amino-6-methoxyquinoline was obtained from the amide (59). The Curtius method has been used a great many times for the preparation of 4-aminoquinolines such as 4-aminoquinoline itself (31), 4-amino-2-phenylquinoline (89), and 4-amino-7-chloro-2-phenylquinoline (58).

Isolated methods of preparing the primary aminoquinolines are known. Coupling of benzenediazonium chloride to 3-aminoquinoline and subsequent hydrogenolysis gave 3,4-diaminoquinoline (157). Bergstrom has developed the amination with potassium amide to give good yields of certain 2-substituted 4-aminoquinolines (18, 19).

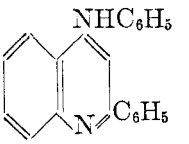
4-Arylaminoquinolines are converted to 4-hydroxyquinolines much less readily than are the primary aminoquinolines. Alkali fusion has been used with undisclosed yields (56). Treatment with concentrated hydrochloric acid at 165°C. gave a 77 per cent yield of 4-hydroxyquinoline (27).



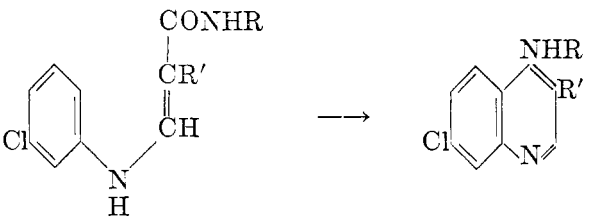
These arylaminoquinolines themselves are relatively inaccessible. One scheme, reported in a very long series of Russian papers by Dziewonski, Moszew, and others, made use of diarylthioureas and arylketones (56).

$$(C_6H_5NH)_2C{=}S \longrightarrow C_6H_5NH_2 + C_6H_5NCS$$

$$C_6H_5NH_2 + C_6H_5COCH_3 \longrightarrow C_6H_5N{=}C(C_6H_5)(CH_3) \xrightarrow{C_6H_5NCS}$$



A more general synthesis with fair yields by the cyclization of amides has been reported recently by Price and Boekelheide (142). This type of reaction is common in the acridine series.

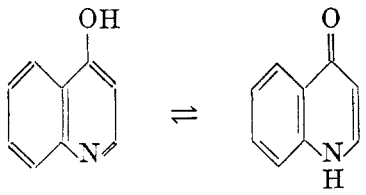


The method was useful where R′ was a nitrile or ester group and R was phenyl, chlorophenyl, butyl, hexyl, or cyanopentyl. If R contained a cyanoethyl group or any alkylaminoalkyl group, no quinoline was obtained.

III. Properties of 4-Hydroxyquinolines

A. Structure

In addition to ordinary α-naphthol resonance forms, two tautomeric forms can be written for 4-hydroxyquinoline, representing the compound as a phenol or as a ketone which would also be a vinylog of an amide.



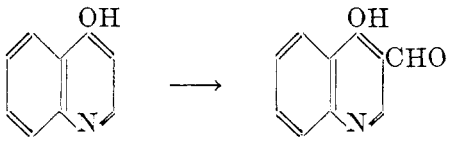
As expected, neither structure completely explains all the properties of the compound. The absorption spectra of 4-hydroxyquinoline would indicate that the ketonic form is predominant, as a result of the failure to obtain the shift in maxima in basic solution which would be expected were a phenolic group present (62). At the same time it was pointed out that definite assignment of the ketonic form could not be made if chemical reactions were considered. The compound behaves like a typical phenol in chemical reactions such as the Reimer–Tiemann reaction, and in formation of the 4-methoxyquinoline and 4-mercaptoquinoline. Bromination and other reactions at the 3-position also indicate the phenolic nature. The enolic structure is most useful in explaining the preparation of the 4-chloro derivative with phosphorus oxychloride and the generally enhanced acidic nature (3, 185). 4-Hydroxyquinolines, including 4-hydroxyquinoline itself, generally give colors with ferric chloride solutions.

The ketonic nature is shown in the formation of *N*-alkyl derivatives by reaction with alkyl halides. 4-Hydroxyquinoline cannot be reduced to the tetrahydro stage, although this is accomplished easily with the 5-, 6-, 7-, or 8-hydroxyquinoline (38). This again indicates a similarity to amides. Reduction of the benzoate of 4-hydroxyquinoline gave hydrogenolysis and subsequent formation of toluene and 4-hydroxyquinoline. Tin and hydrochloric acid were useful in the reduction of 3-carbethoxy-4-hydroxy-2-phenylquinoline to the tetrahydro stage (80). This carbethoxyquinoline is also peculiar in that alkylation at the 3-position is possible, indicating a greater contribution of the ketonic structure.

The problem of structure is the same as with 2-hydroxyquinolines and with 2- and 4-hydroxypyridines. The conclusion is that the ketonic character is predominant especially in physical tests, but that the phenolic character is present as indicated by certain chemical reactions.

B. REACTIONS AT THE 3-POSITION

In a great many reactions with nitrogen heterocycles the position beta to the nitrogen is attacked. It is not surprising that if this is also ortho to a phenolic group some reactions occur quite readily. One example of this is the preparation of 4-hydroxy-3-quinolylaldehyde by the Reimer–Tiemann reaction (24, 52).

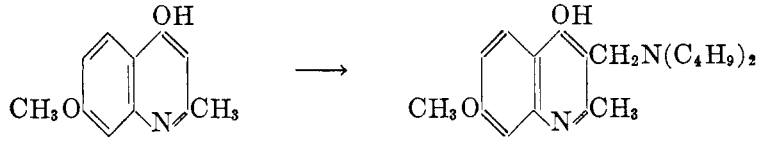


In a similar manner 4-hydroxy-2-methyl-3-quinolylaldehyde is prepared (52).

Bromination of 4-hydroxyquinolines gives 3-bromo-4-hydroxyquinolines in good yields (12, 160).

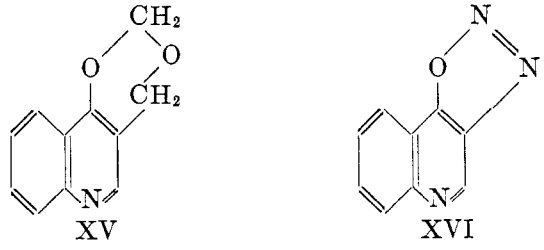
Chlorination produces a trichloro derivative. A di- and a tri-bromoquinaldine also have been described (49). Nitration of 4-hydroxy-2-methylquinoline has been reported to give the 6-nitro derivative (98). Other reports indicate that the 3-position also is attacked, as a result of the isolation of anthranilic acid from the oxidation of the nitrated quinoline (52, 98, 175).

The Mannich reaction again gives support to the aromatic structure. 4-Hydroxyquinolines give the 3-aminomethyl-4-hydroxyquinoline, as expected of phenols (73). It is well known that 2-methylquinolines will undergo a Mannich reaction to produce the 2-β-aminoethylquinolines. It is interesting therefore to note that 2-methyl-4-hydroxyquinoline gives the 3-aminomethyl derivative and the 2-methyl group is not affected (143).



The proof of structure given for this compound makes it probable that the structure of a similar Mannich reaction product (69) is the 3-substituted quinoline rather than the indicated β-aminoethylquinoline. Methylolchloroacetamide also attacks 2,8-dimethyl-4-hydroxyquinoline in the 3-position (125). Further evidence that the 2-methyl group is not attacked is found in the failure of 2-methyl-4-hydroxyquinolines to condense with benzaldehyde as do 2-methylquinolines (123).

Closely related to the Mannich reaction and even stronger evidence for the existence of the enol form of 4-hydroxyquinolines is the formation of cyclic ethers (XV) by treatment with formaldehyde (XVI) (127). Similar to this are the cyclic azo derivatives of 3-amino-4-hydroxyquinolines (XVI) (52).

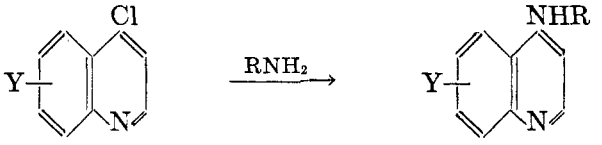


Coupling of groups such as diazo (52) and xyanthyl (128) also is known to occur at the 3-position. 4-Allyloxyquinolines behave as typical phenols and 3-allyl-4-hydroxyquinolines are produced by rearrangement (118).

C. CHLORINATION AND SUBSEQUENT REACTIONS

Phosphorus oxychloride, phosphorus pentachloride, or a mixture of the two are the reagents most useful for the conversion of the 4-hydroxyquinoline to the 4-chloroquinoline. Phosphorus oxychloride in excess also can act as a solvent, or an inert solvent such as diphenyl ether may be used.

The chloroquinolines have a characteristic mouse-like odor. They are much lower melting than the hydroxyquinolines. The technique especially useful for the preparation of unsubstituted aminoquinolines is the treatment of the chloroquinoline in hot phenol with ammonia (29, 59, 145). The phenoxy compound, prepared easily by refluxing the chloroquinoline in phenol (9), may be the intermediate in this reaction, for the ethers can be converted to the aminoquinoline (86). Furthermore, no 4-aminoquinoline is produced if an inert solvent is used in place of phenol. The same method has been used to prepare some 4-alkylaminoquinolines, but a better method is to heat the 4-chloroquinoline with an excess of alkylamine. The latter method has been used most often for the large number of 4-alkylaminoquinolines reported recently. From 1929 to 1943, 172 derivatives of 4-aminoquinoline were prepared in the I. G. Farbenindustrie laboratories alone (23).



The 4-aminoquinolines present the same structure problems that the hydroxyquinolines do, and information about the aminoquinolines is useful for confirmation of conclusions about the hydroxyquinolines. Two extreme forms can be represented.

XVII XVIII

pK_a studies (3) give evidence for the quinoid form, since they show that 4-aminoquinolines are more basic than other aminoquinolines. The chemical evidence is more direct. Alkylation with alkyl halides leads to derivatives of XVIII (20), and the imino form can be isolated and hydrolyzed to the quinolone (145). On the other hand, formation of the sodium salt before treatment with the halide enables one to prepare derivatives of XVII. The dual possibilities of alkylation are additional reason for preparing alkylaminoquinolines from the 4-chloroquinoline rather than from the primary amine.

The reaction of 4-chloroquinolines with hydrazine is interesting, since in addition to the normal hydrazide at elevated temperature an isomer distinct from

3,4-diaminoquinoline is obtained (8, 107). Reduction of the azide derived from the hydrazide (7) or the phenylhydrazide (106) yields 4-aminoquinolines.

Other derivatives have been prepared from the 4-chloroquinolines. 4-Alkoxyquinolines are obtained by reaction with sodium methoxide (12, 105) or with sodium ethoxide (32). Many other ethers have been prepared from the chloroquinoline and sodium alkoxide or from the 4-hydroxyquinoline and the alkyl halide (92, 93, 116, 121, 132). With sodium bisulfite (161) or sodium sulfite (93, 139) the 4-sulfonic acids are produced in 84 per cent and 86 per cent yields. Sulfides are prepared from mercaptans (12, 52, 93) and substituted sulfonamides are prepared from primary sulfonamides (161).

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