A SYNTHESIS OF

4,7-DICHLOROQUINOLINE

By

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degree of Doctor of Philosophy

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INTRODUCTION

A considerable number of synthetic compounds showing antimalarial activity contain a substituted amine group at the 4-position of 7-chloroquinoline. Wiselogle, for example, lists some thirty pages of this type of compound.[1] The key intermediate for a great many of these compounds is 4,7-dichloroquinoline (commonly called DCQ), which is condensed with an amine at the 4-position by the splitting out of hydrogen chloride. An important case in point is SN 7618, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline.[2,3] Drake, et al., give detailed directions for this type of synthesis (Scheme A).[4]

Since 4-hydroxy-7-chloroquinoline is rather easily converted to 4,7-dichloroquinoline, the synthesis of DCQ is very often closely tied to that of the hydroxy compound. Invariably, moreover, one finds the historical basis for the preparation of the 4-hydroxy-7-chloro compound lies in the preparation of 4-hydroxyquinoline itself. While there have been a rather large number of methods offered

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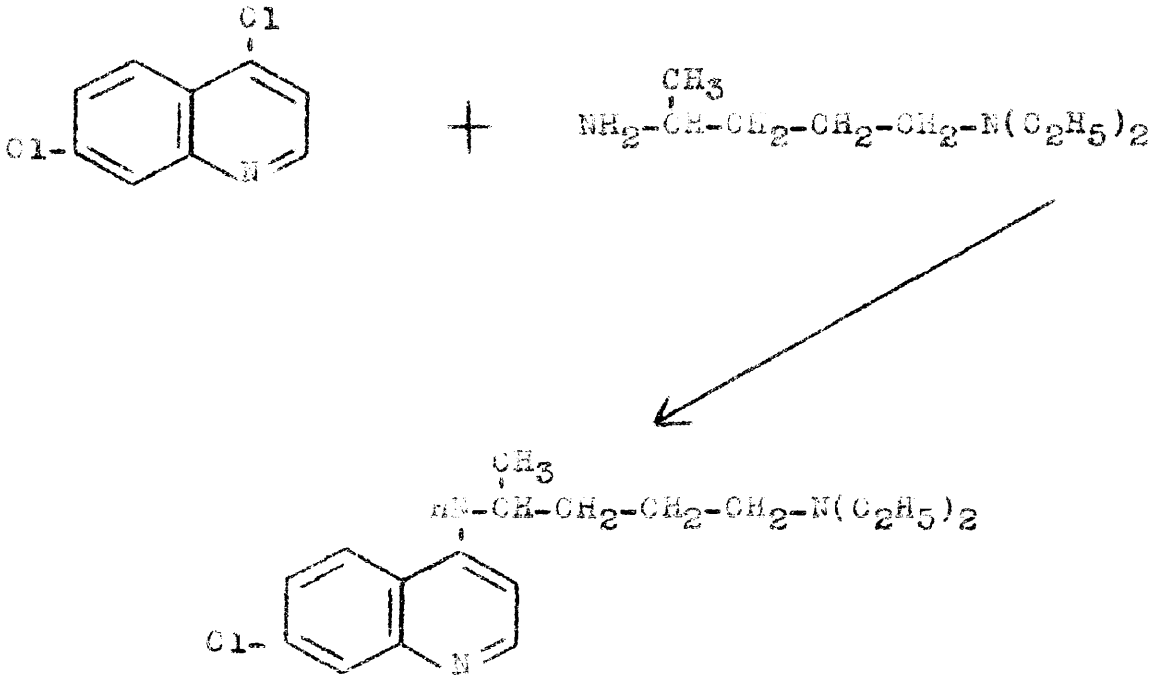
[1]Wiselogle, "Survey of Antimalarial Drugs 1941-1945," Vol. II, Pt. 2, J. W. Edwards, Ann Arbor, Mich., 1946, pp. 1140-1170.

[2]Andersag, Breitner, and Jung, U.S. Patent 2,233,970 March 4, 1941.

[3]Surrey and Hammer, J. Am. Chem. Soc., 68, 113 (1946).

[4]Drake, et al., ibid., 68, 1214 (1946).



Scheme A

for the preparation of various 4-hydroxyquinolines,[5,6] only some of them are readily applicable to the synthesis of the 4-hydroxy-7-chloro derivative. In the resume' that follows, an attempt will be made to summarize those methods of synthesizing 4-hydroxyquinoline which are directly useful in the synthesis of the 4-hydroxy-7-chloro compound and to show, wherever possible, how these methods were actually employed.

Although several investigators have attempted to synthesize DCQ without recourse to the hydroxy compound, their experiments did not prove very successful. The work is of historic interest, however, and is also briefly outlined.

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[5]Reitsema, Chem. Rev., 43, 43-68 (1948).

[6]Manske, ibid., 30, 113-144 (1942).

HISTORICAL

4-Hydroxy- and 4-Hydroxy-7-chloroquinoline by Methods Obviating a Final Decarboxylation

(a) Methods producing the 4-hydroxy group during cyclization. The first series of syntheses of 4-hydroxyquinolines to be considered here are those that do not involve a final decarboxylation. Camps treated o-aminoacetophenone with formic acid and cyclized the resulting o-formaminoacetophenone in dilute alkali to obtain 4-hydroxyquinoline (Scheme B, X=H).[7] This work was repeated by Brobranski but he could not obtain as high a yield.[8] A similar cyclization using o-formamino-p-chloroacetophenone to obtain the 4-hydroxy-7-chloroquinoline is described in the experimental section of this thesis (Scheme B, X=Cl).

The method of Conrad and Limpach has found very great application in the field of quinoline synthesis. In the original synthesis, aniline and the β-ketoester, acetoacetic ester, were condensed to ethyl β-anilinocrotonate, and the condensation product was heated at 250° to produce the 2-methyl-4-hydroxyquinoline (Scheme C).[9]

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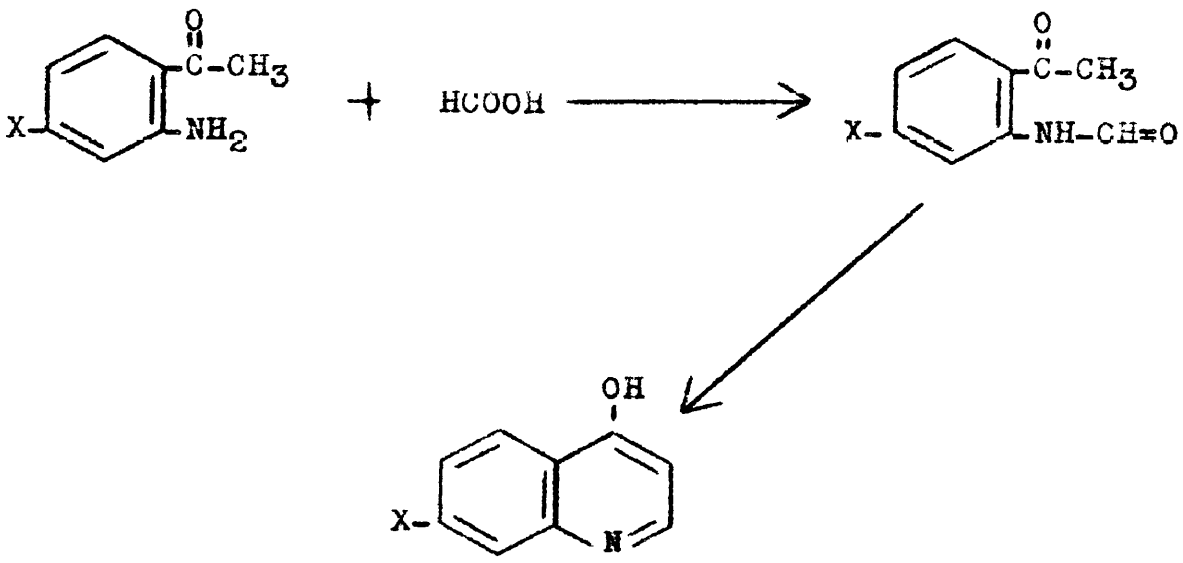
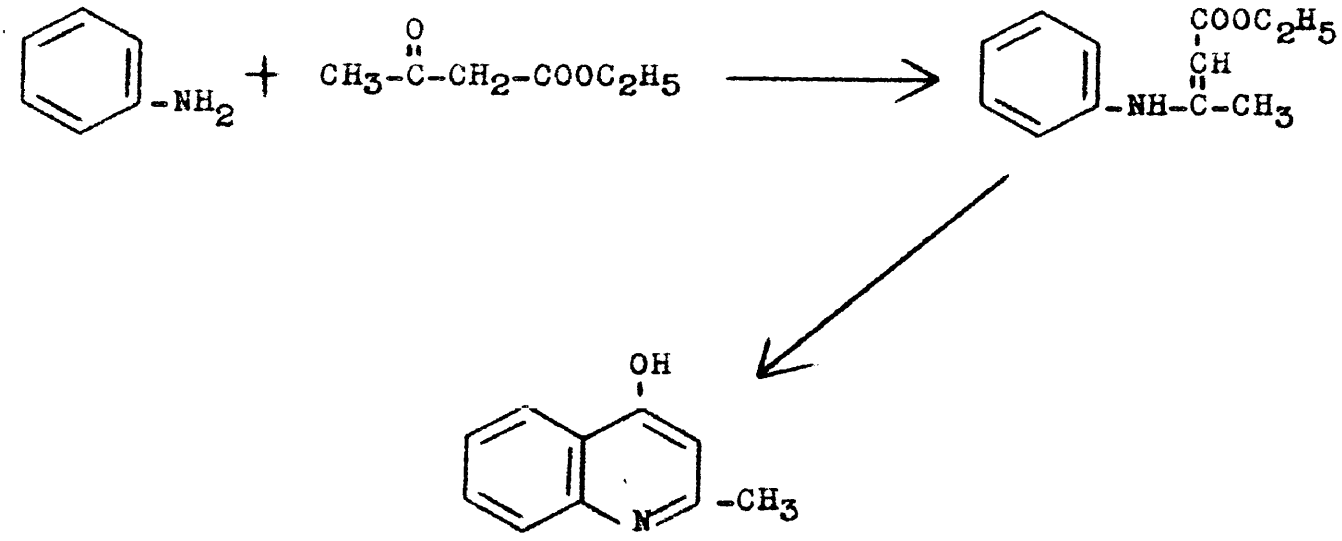
[7]Camps, Ber., 32, 3288 (1899); ibid., 34, 2703 (1901); Z. Physiol. Chem., 33, 390 (1900).

[8]Brobranski, Ber., 69B, 1113 (1936).

[9]Conrad and Limpach, ibid., 20, 944 (1887).



Scheme B



Scheme C

In order to apply this synthesis to 4-hydroxyquinoline, it was necessary to cyclize the aniline derivative of acrylic ester itself. Von Pechman had already condensed sodium ethyl formylacetate and aniline to obtain ethyl β-anilinoacrylate.[10] In a very similar manner, Price, Leonard, and Reitsema condensed aniline with sodium methyl formylacetate to obtain methyl β-anilinoacrylate. They cyclized the acrylate in Dowtherm and secured 4-hydroxyquinoline in 44% yield (Scheme D, X=H).[11]

Applying this method to the synthesis of the desired 4-hydroxy-7-chloroquinoline, the same authors condensed sodium methyl formylacetate with m-chloroaniline and cyclized the resulting methyl β-(m-chloroanilino)acrylate (Scheme D, X=Cl).[11] Two isomers are possible, however, and they obtained 40% of the 7-chloro isomer and 10% of the 5-chloro isomer.

A somewhat similar line of attach has been reported by Clemo and Perkin.[12] They cyclized the p-toluensulfonyl derivative of ethyl anilinopropionate with phosphorus pentoxide and apparently obtained the 4-hydroxy-1-tosyl-1,2-dihydroquinoline (Scheme E). This part of the work was

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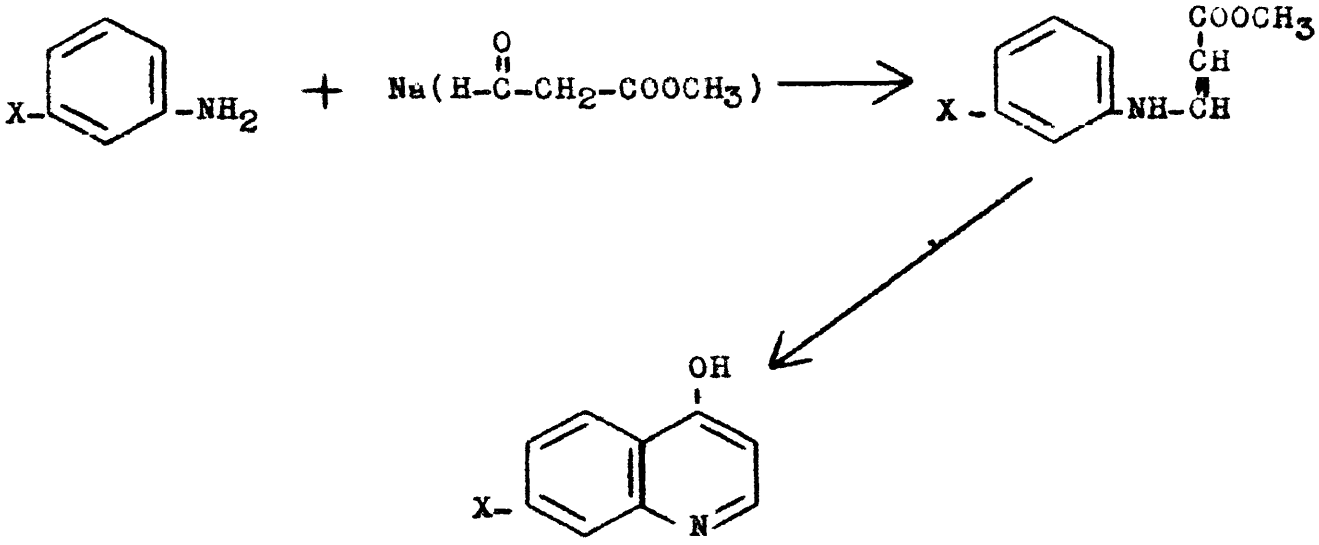
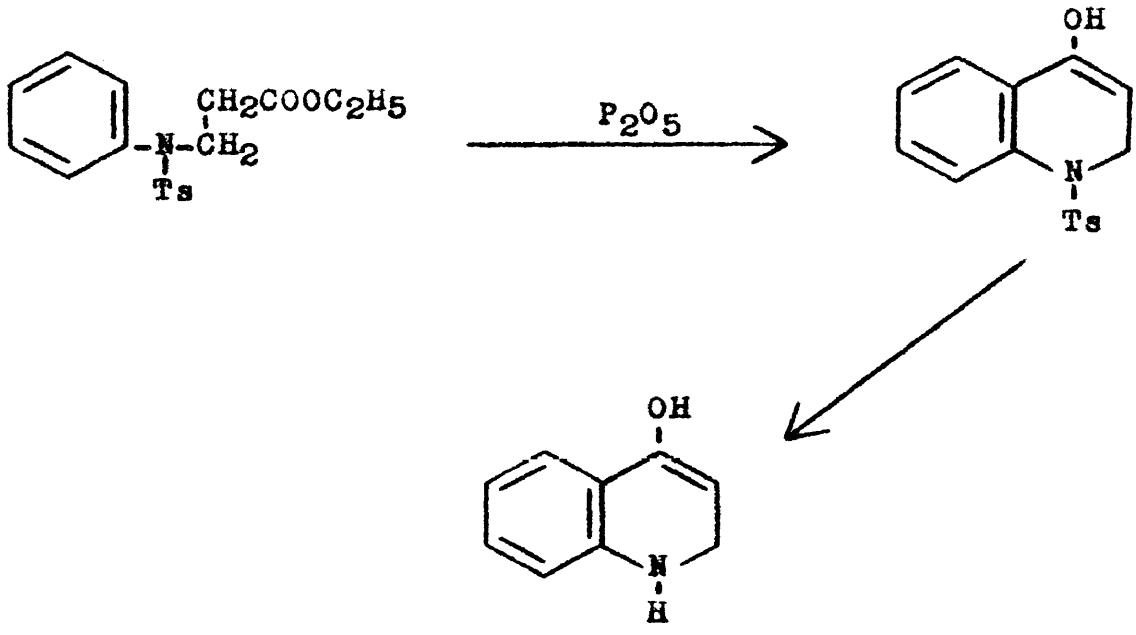
[10]Von Pechman, Ber., 25, 1051 (1892).

[11]Price, Leonard, and Reitsema, J. Am. Chem. Soc., 68, 1256 (1946).

[12]Clemo and Perkin, J. Chem. Soc., 125, 1608 (1924); ibid., 127, 2297 (1925).



Scheme D



Ts= p-toluenesulfonyl group

Scheme E

confirmed by Backberg.[13] Elderfield, however, attempted to dehydrogenate the dihydro compound but a long series of reagents proved unfruitful, and he even cast doubt on the nature of the hydroxy compound.[14]

(b) Methods producing the 4-hydroxy group by replacement. Another possible avenue for the synthesis of 4-hydroxyquinolines is through the quinoline-4-carboxylic acid (cinchonic acid). Renshaw and Friedman[15] have given directions for the conversion of this acid to the 4-aminoquinoline via the amide and the Hoffman rearrangement, while Brydowna[16] has used the Curtius reaction to obtain the same compound. 4-Aminoquinoline has been converted to 4-hydroxyquinoline by Claus and Howitz who diazotized it in sulfuric acid and poured the reaction mixture into water (Scheme F).[17]

It is also possible to hydrolyze 4-arylaminoquinolines to 4-hydroxyquinolines. Dziewonski and Moszew[18] have reported the use of alkali for this purpose, while

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[13]Backberg, J. Chem. Soc., 1933, 618.

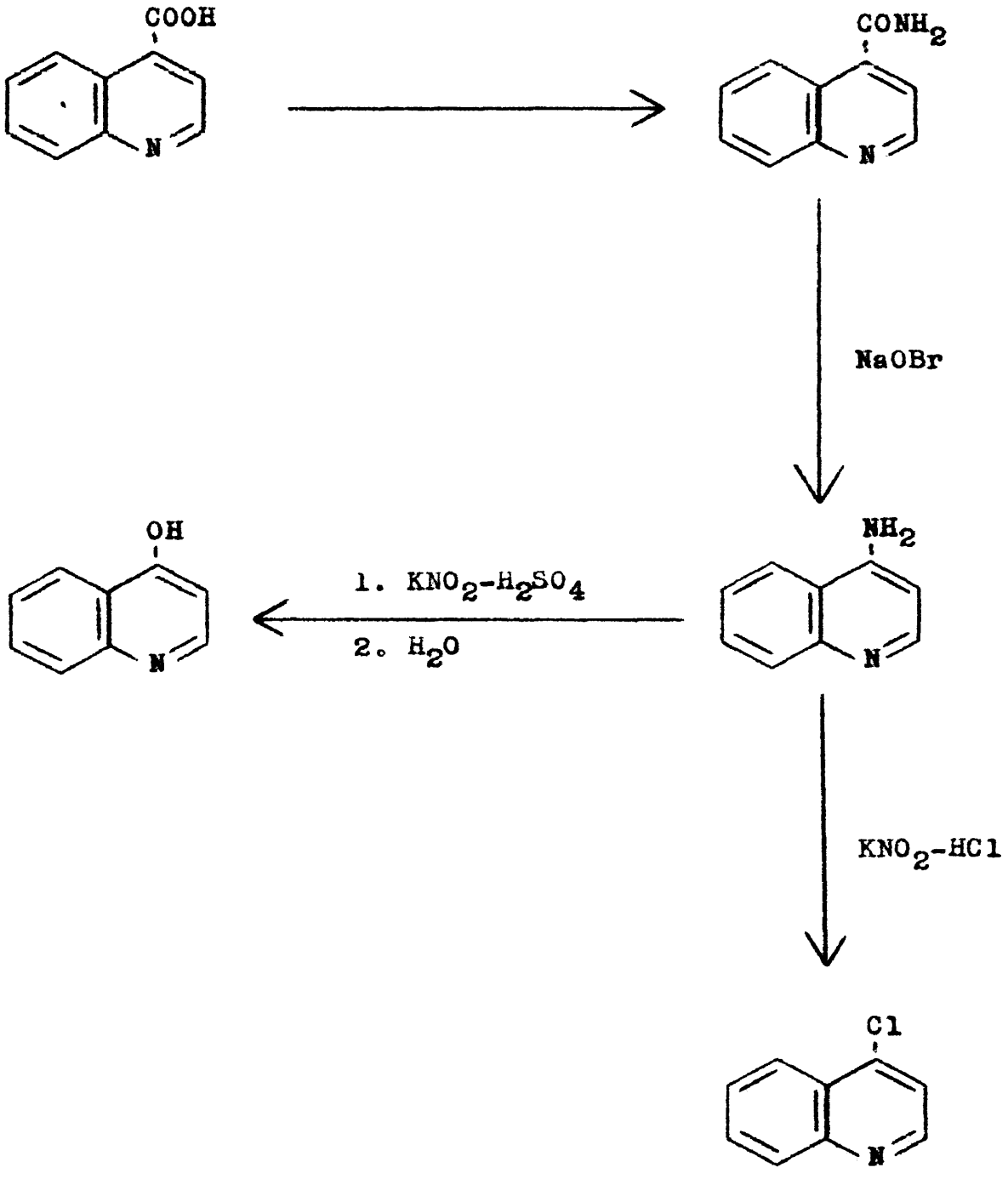
[14]Elderfield, et al., J. Am. Chem. Soc., 68, 1272 (1946).

[15]Renshaw and Friedman, ibid., 61, 3320 (1939).

[16]Brydowna, Rocznicki Chem., 12, 89 (1932); Chem. Abstracts, 27, 2986 (1933).

[17]Claus and Howitz, J. Pr. Chem., (2) 50, 232 (1894).

[18]Dziewonski and Moszew, Rocznicki Chem., 13, 530 (1934); Chem. Abstracts, 28, 1697 (1934).



Scheme F

Von Braun and Heymons reported a 77% yield of 4-hydroxyquinoline by the use of hydrochloric acid at 165°.[19]

4-Hydroxy- and 4-Hydroxy-7-chloroquinoline by Methods Necessitating a Final Decarboxylation

(a) Methods involving decarboxylation of the 2-position. Most of the important methods of synthesizing 4-hydroxyquinolines involve a decarboxylation of either the 2- or 3-carboxylic acid derivative. Camps[7] reacted o-aminoacetophenone with ethyl oxalate and the resulting ethoxalyl o-aminoacetophenone was cyclized with base to give 4-hydroxyquinoline-2-carboxylic acid. This acid (kynurenic acid) had already been decarboxylated to 4-hydroxyquinoline (kynurin) by Schmeidberg and Schultzen (Scheme G).[20]

It is also possible to effect reduction of a nitro group and cyclization simultaneously. Baeyer and Drewson had prepared o-nitrobenzalpyruvic acid by condensing o-nitrobenzaldehyde with pyruvic acid.[21] Heller reduced the unsaturated keto acid with ferrous sulfate to obtain 4-hydroxyquinoline-2-carboxylic acid. He postulated a hydroxylamine as an intermediate (Scheme H).[22]

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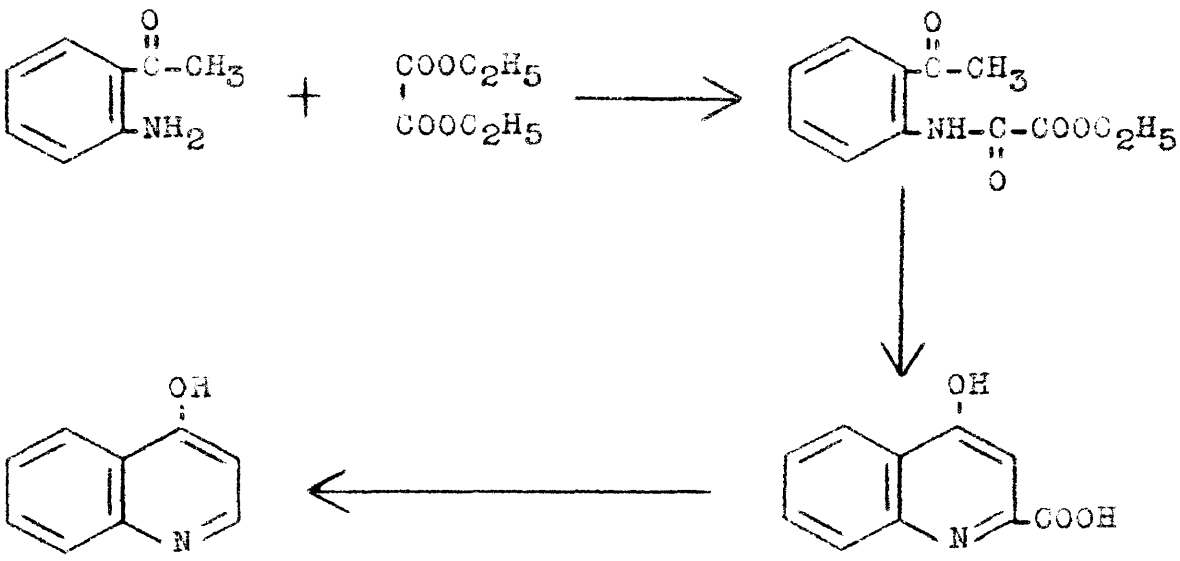
[19]Von Braun and Heymons, Ber., 63B, 3191 (1930).

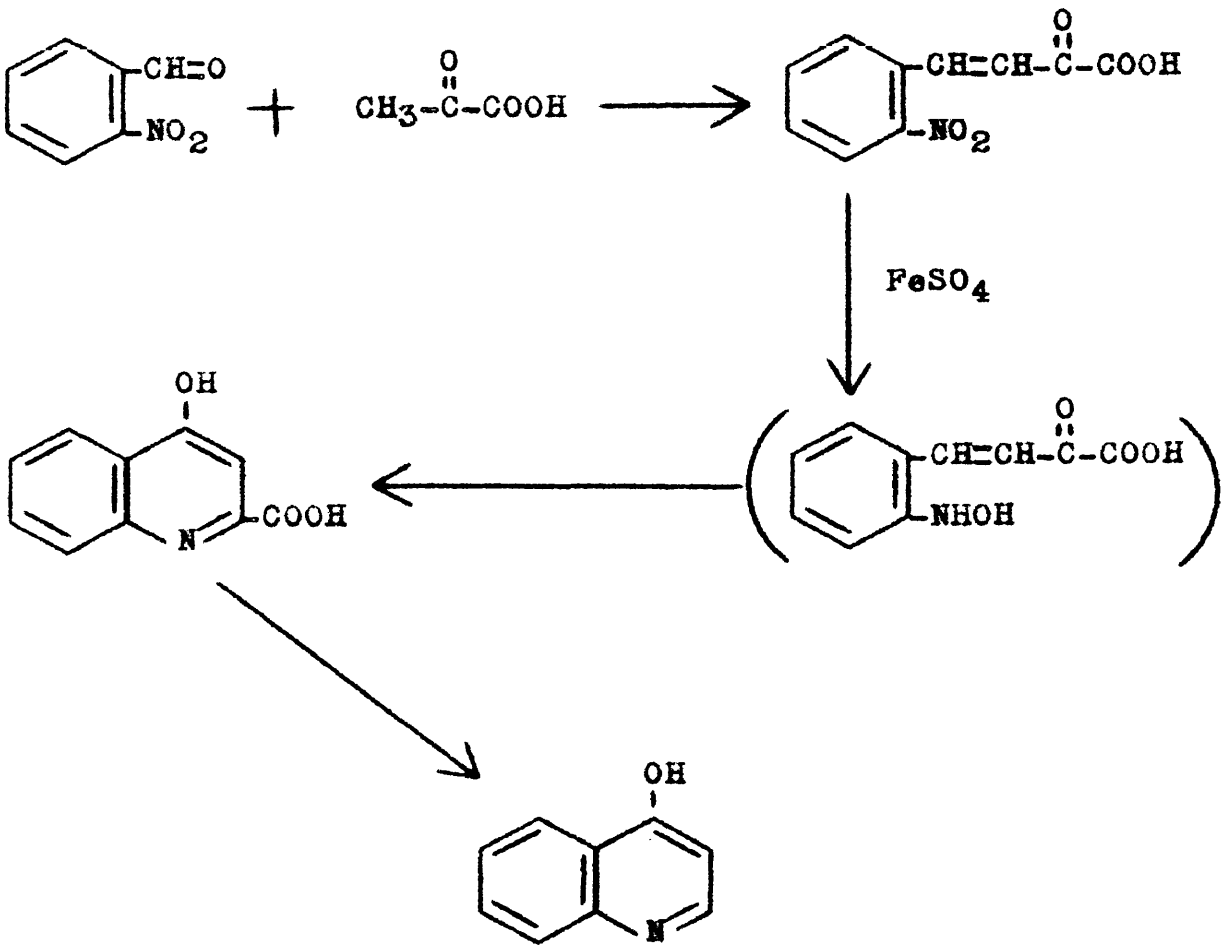
[20]Schmeidberg and Schultzen, Ann., 164, 58 (1872).

[21]Baeyer and Drewson, Ber., 15, 2862 (1882).

[22]Heller, ibid., 43, 1923 (1910).



Scheme G


CH=O
NO2
CH3-C-COOH
O
CH=CH-C-COOH
NO2
FeSO4
OH
COOH
N
CH=CH-C-COOH
NHOH
OH
N

Scheme H

Perkin and Robinson also employed ethyl oxalate by condensing it with 6-nitroacetoveratrone to give 6-nitroveratroylpyruvic acid.[23] The acid was simultaneously reduced and cyclized to 4-hydroxy-6,7-dimethoxyquinoline-2-carboxylic acid. On heating the quinolinic acid in glycerol they obtained 6,7-dimethoxy-4-hydroxyquinoline (Scheme I).

An important variation of the Conrad-Limpach method cited previously is the treatment of an amine with an oxalacetic ester to obtain a β-carbethoxy-β-anilinoacrylate; the acrylate is heated to about 250° in an inert solvent to give the 2-carbethoxy-4-hydroxyquinoline. After the ester is hydrolyzed, a decarboxylation affords the 4-hydroxyquinoline (Scheme J, X=H).[24,25,26] Patents developed by Andersag, Breitner, and Jung indicate application of this method to the chloro-hydroxyquinoline.[2] Surrey and Hammer, however, have given a much more detailed description.[3] They condensed m-chloroaniline and oxalacetic ester in glacial acetic acid and heated the resulting β-carbethoxy-β-(m-chloroanilino)acrylate in mineral oil to give a mixture of equal

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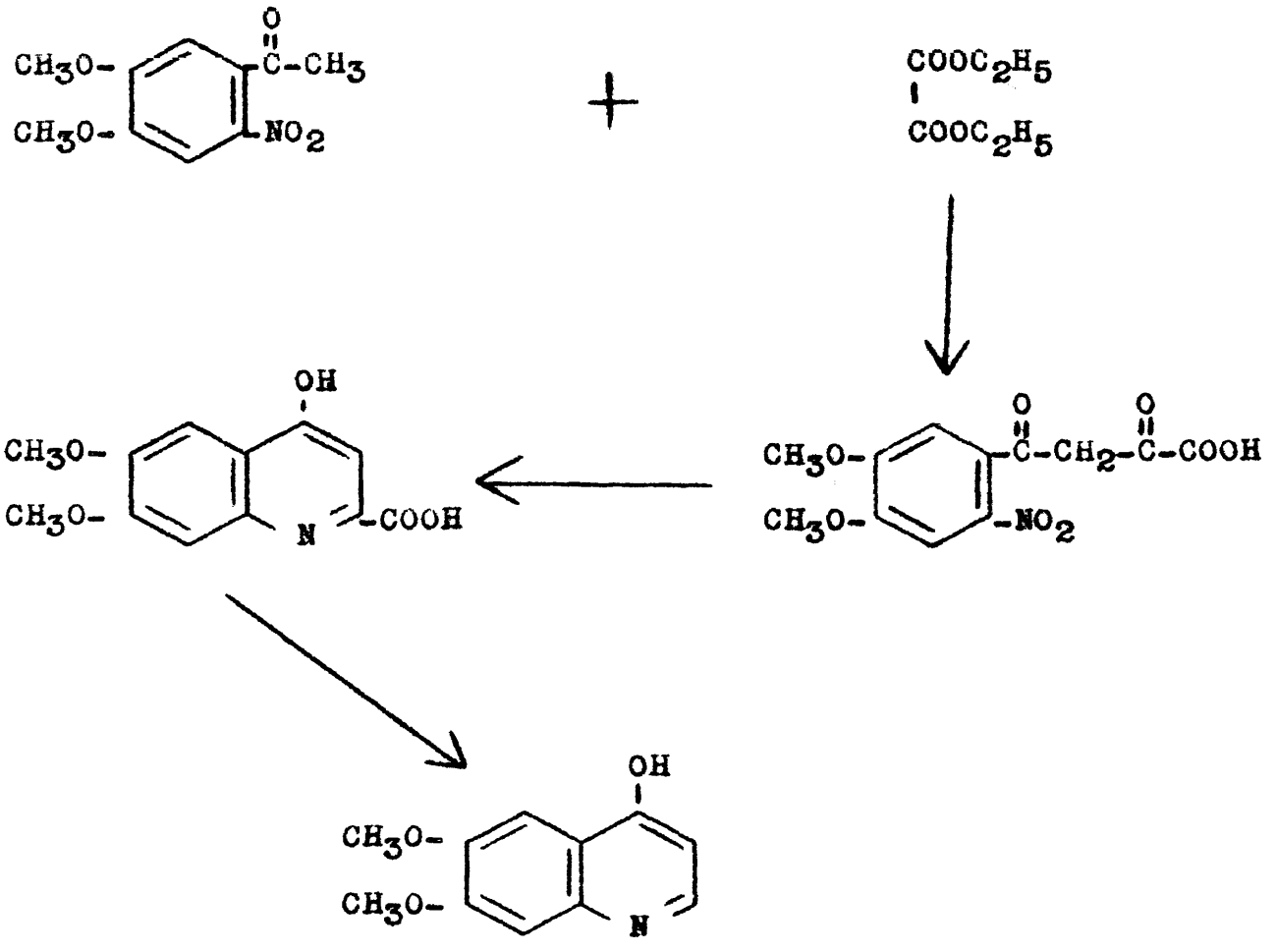
[23]Perkin and Robinson, J. Chem. Soc., 125, 626 (1924).

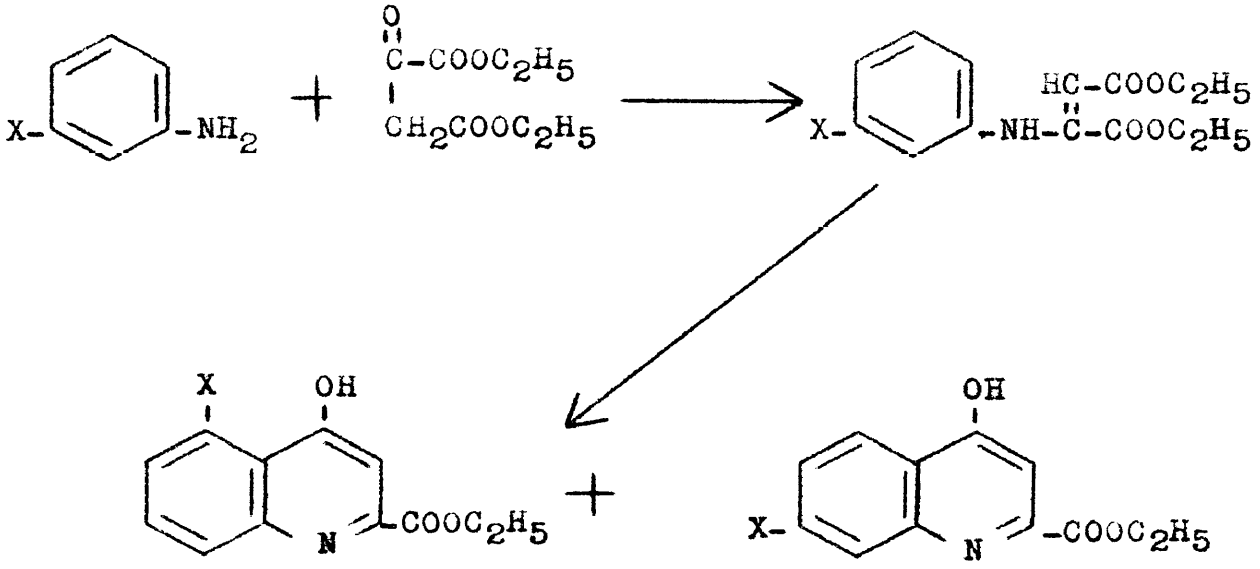
[24]Hoffman La Roche, Inc., Germ. Pat. 575,534, April 28, 1933.

[25]Gavallito and Haskell, J. Am. Chem. Soc., 66, 1166 (1945).

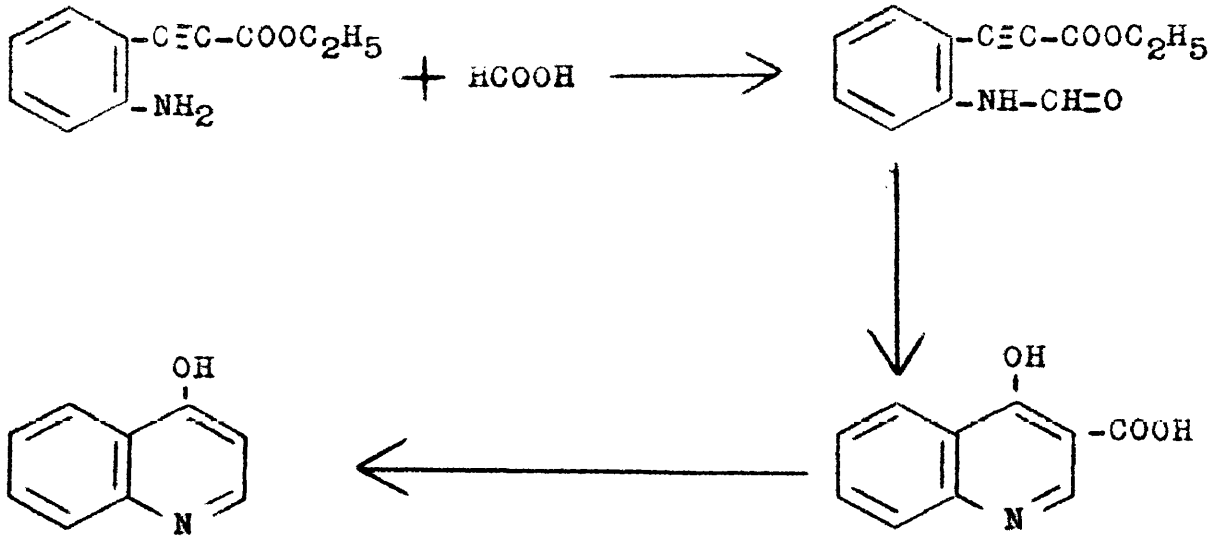
[26]Baker and Dodson, ibid., 68, 1283 (1946).



Scheme I



Scheme J



Scheme K

amounts of 5-chloro and 7-chloro-4-hydroxy-2-carbethoxy-quinoline (Scheme J, X=Cl). These esters were separated by fractional crystallization from glacial acetic acid, the higher melting 7-chloro compound being less soluble. Lisk and Stacy made detailed studies of the reaction conditions in order to increase the percentage of one of the isomers over the other, but they were not particularly successful.[27]

(b) Methods involving decarboxylation at the 3-position. It is similarly possible to close the heterocyclic ring in such a way as to leave an ester group at the 3-position for subsequent hydrolysis and decarboxylation. By treating ethyl o-aminophenylpropiolate with formic acid, Camps prepared ethyl formyl-o-aminopropiolate which he cyclized to 4-hydroxyquinoline-3-carboxylic acid. The acid was then decarboxylated to 4-hydroxyquinoline (Scheme K).[7]

A very substantial improvement with respect to freedom from isomers in the Conrad-Limpach type of cyclization was due to the work of Price and Roberts. The basic starting compound was described by Claisen who had treated aniline with ethoxymethylenemalonic ester (EMME) and obtained

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[27]Lisk and Stacy, J. Am. Chem. Soc., 68, 2686 (1946).

ethyl α-carbethoxy-β-anilinoacrylate.[28] The cyclization had been accomplished by Gould and Jacobs who had heated the acrylate in mineral oil to secure 4-hydroxyquinoline-3-carboxethylate.[29] They easily hydrolyzed this ester to 4-hydroxyquinoline-3-carboxylic acid which, as shown above, had already been decarboxlated to 4-hydroxyquinoline. The sequence is shown in Scheme L (X=H).

Price and Roberts[30] now applied this method to m-chloroaniline to obtain ethyl α-carbethoxy-β-(m-chloroanilino)acrylate. The acrylate was cyclized in Dowtherm to 3-carbethoxy-4-hydroxy-7-chloroquinoline which was easily hydrolyzed and decarboxylated to 4-hydroxy-7-chloroquinoline (Scheme L, X=Cl). Unlike the cyclization of the β-carbethoxy-β-(m-chloroanilino)acrylate (Scheme J, X=Cl), however, the ring closure in the case of the α-carbethoxy compound produced very little, if any, of the 3-carbethoxy-4-hydroxy-5-chloroquinoline.

One important drawback to Scheme L, on the other hand, was the fact that the ethoxymethylenemalonic ester was rather expensive. Consequently, the next attempts were centered around syntheses which would eliminate the use of the malonic ester but which would retain the favorable

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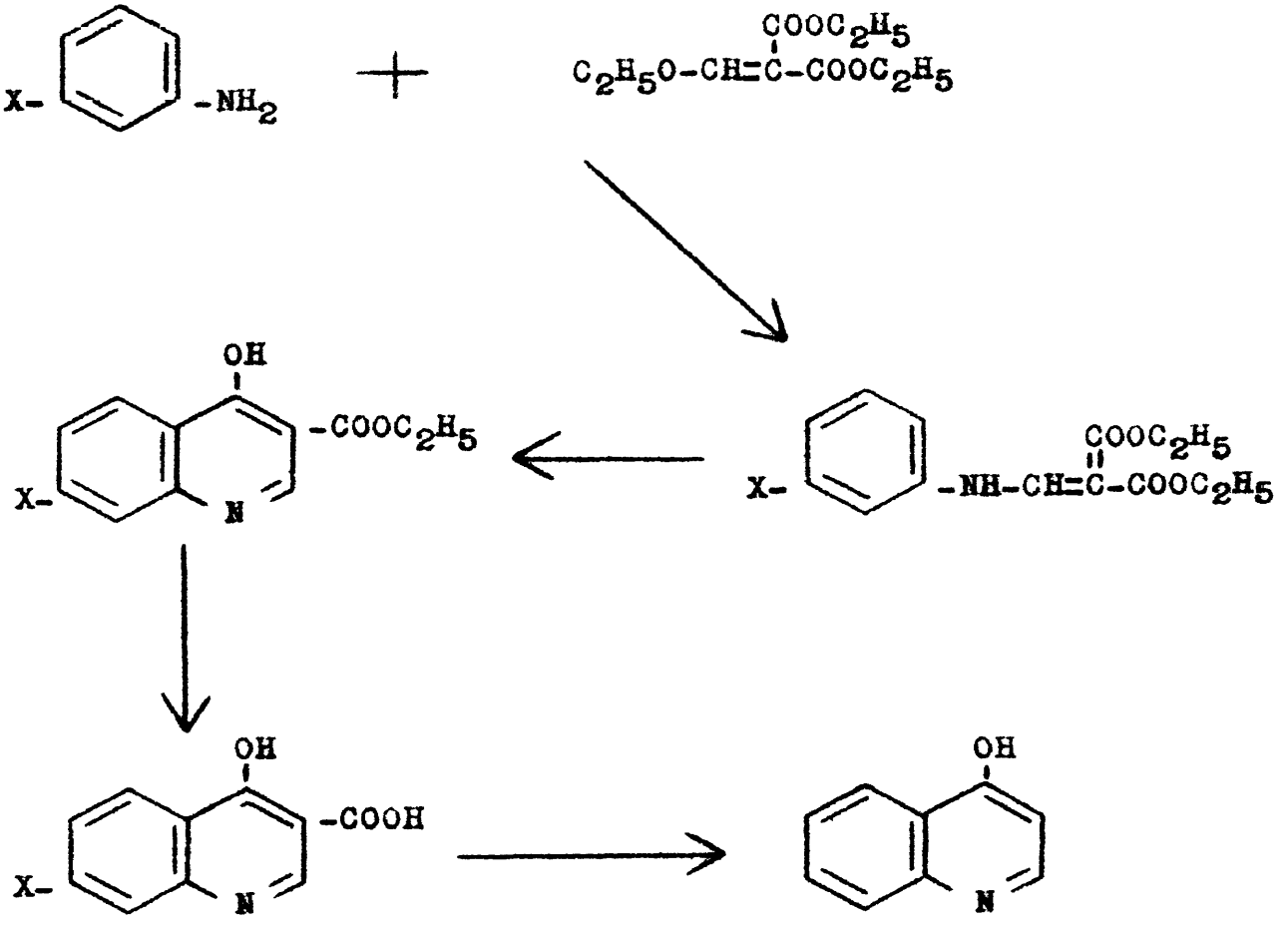
[28]Claisen, Ber., 36, 2729 (1903); Claisen and Haas, Ann., 297, 75 (1897).

[29]Gould and Jacobs, J. Am. Chem. Soc., 61, 2890 (1939).

[30]Price and Roberts, ibid., 68, 1204 (1946).


X-
-NH2
COOC2H5
C2H5O-CH=C-COOC2H5
OH
-COOC2H5
X-
N
X-
-NH-CH=C-COOC2H5
COOC2H5
OH
-COOH
X-
N
OH
N

Scheme L

cyclization of the ethyl α-carbethoxyanilinoacrylate. Dains had reported that phenylformamidine (from heating aniline and formanilid or aniline and ethyl ortho-formate) condensed with active methylene compounds.[31] With cyanoacetic ester he obtained ethyl α-cyano-β-anilinoacrylate (Scheme M, X=H). Price, Leonard, and Herbrandson[32], and Synder and Jones[33] investigated variations in making this compound. For instance, they condensed the ethyl ortho-formate with cyanoacetic ester and then condensed the resulting ethoxymethylenecyanoacetic ester with aniline or a substituted aniline to obtain the desired α-cyano compound. In this way, ethyl α-cyano-β-(m-chloroanilino)acrylate was prepared and cyclized to 3-cyano-4-hydroxy-7-chloroquinoline. The cyanoquinoline was hydrolyzed and decarboxylated to 4-hydroxy-7-chloroquinoline (Scheme M, X=Cl). The difficulty with this cyclization, however, was the high dilution necessary to avoid side reactions.

Dains had also reported that phenylformamidine reacted with malonic ester,[31] but at the temperature used in his experiment, the aniline (formed as a by-product) aminolyzed an ester group and consequently the compound obtained was ethyl α-carbanilido-β-anilinoacrylate. Price, Leonard,

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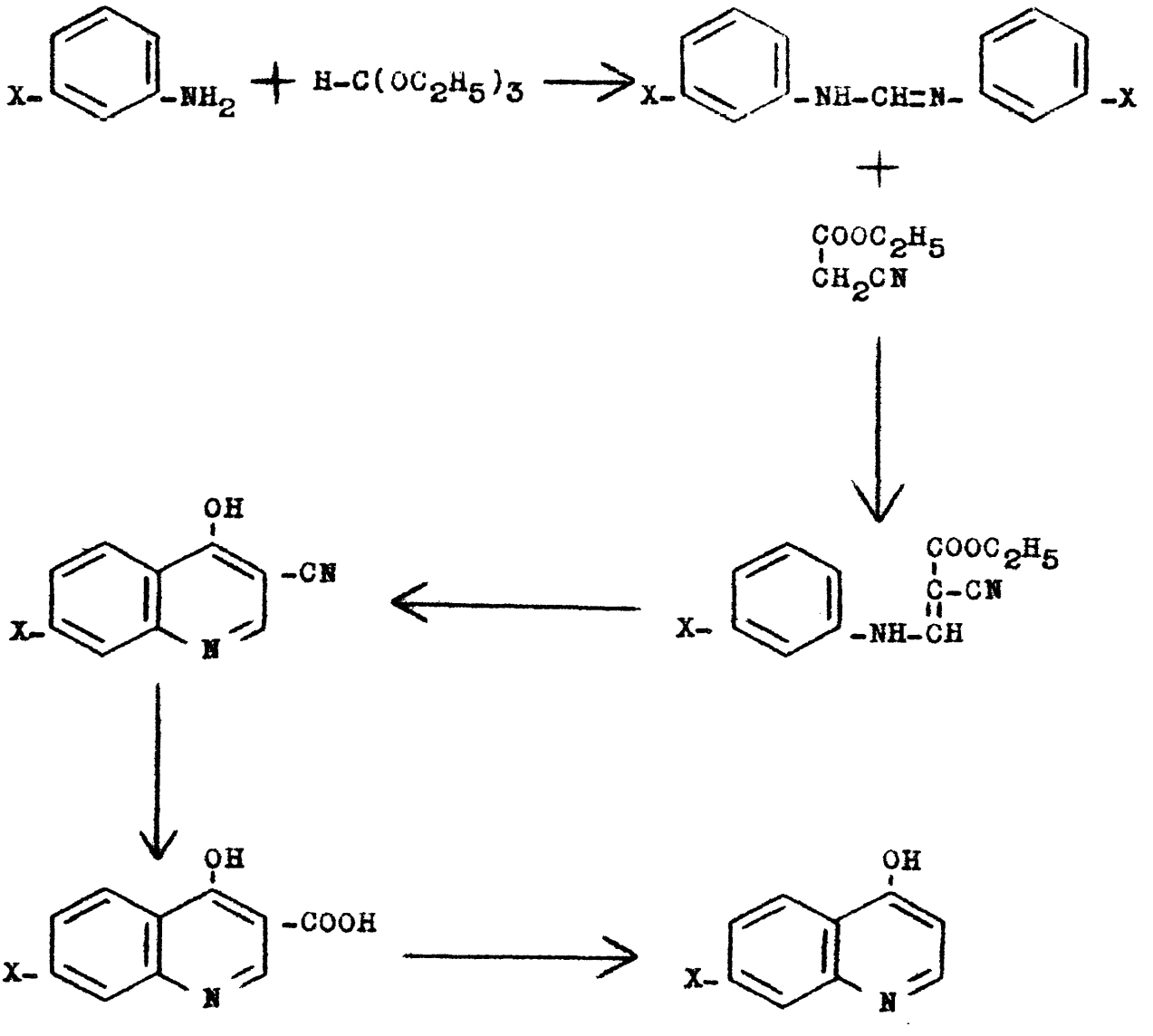
[31]Dains, Ber., 35, 2496 (1902); Univ. of Kansas Sci. Bull., 19, 215 (1930).

[32]Price, Leonard, and Herbrandson, J. Am. Chem. Soc., 68, 1251 (1948).

[33]Snyder and Jones, ibid., 68, 1253 (1946).



Scheme M

and Herbrandson repeated this work using m-chloroaniline as the starting material to secure their bis(m-chlorophenyl) formamidine.[32] The formamidine was treated with malonic ester to give ethyl α-(m-chlorocarbanilido)-β-(m-chloroanilino)acrylate. The acrylate was cyclized to 3-(m-chlorocarbanilido)-4-hydroxy-7-chloroquinoline, which upon hydrolysis and decarboxylation gave the desired 4-hydroxy-7-chloroquinoline (Scheme N).

Price and Roberts discovered, on the other hand, that by operating at a lower temperature, the condensation between ethyl malonate and bis(m-chlorophenyl) formamidine could be controlled to yield ethyl α-carbethoxy-β-(m-chloroanilino) acrylate and m-chloroaniline (Scheme O).[30] Roberts has reviewed the mechanism and favorable operating conditions for this type of reaction.[34]

4-Chloroquinolines Without Prior Introduction of A 4-Hydroxy Group

The major method of synthesizing 4-chloroquinolines without prior introduction of the 4-hydroxy group was discovered by Meisenheimer.[35] He oxidized quinoline to N-quinoline oxide with perbenzoic acid. When the oxide was treated with either phosphorous oxychloride or sulfuryl

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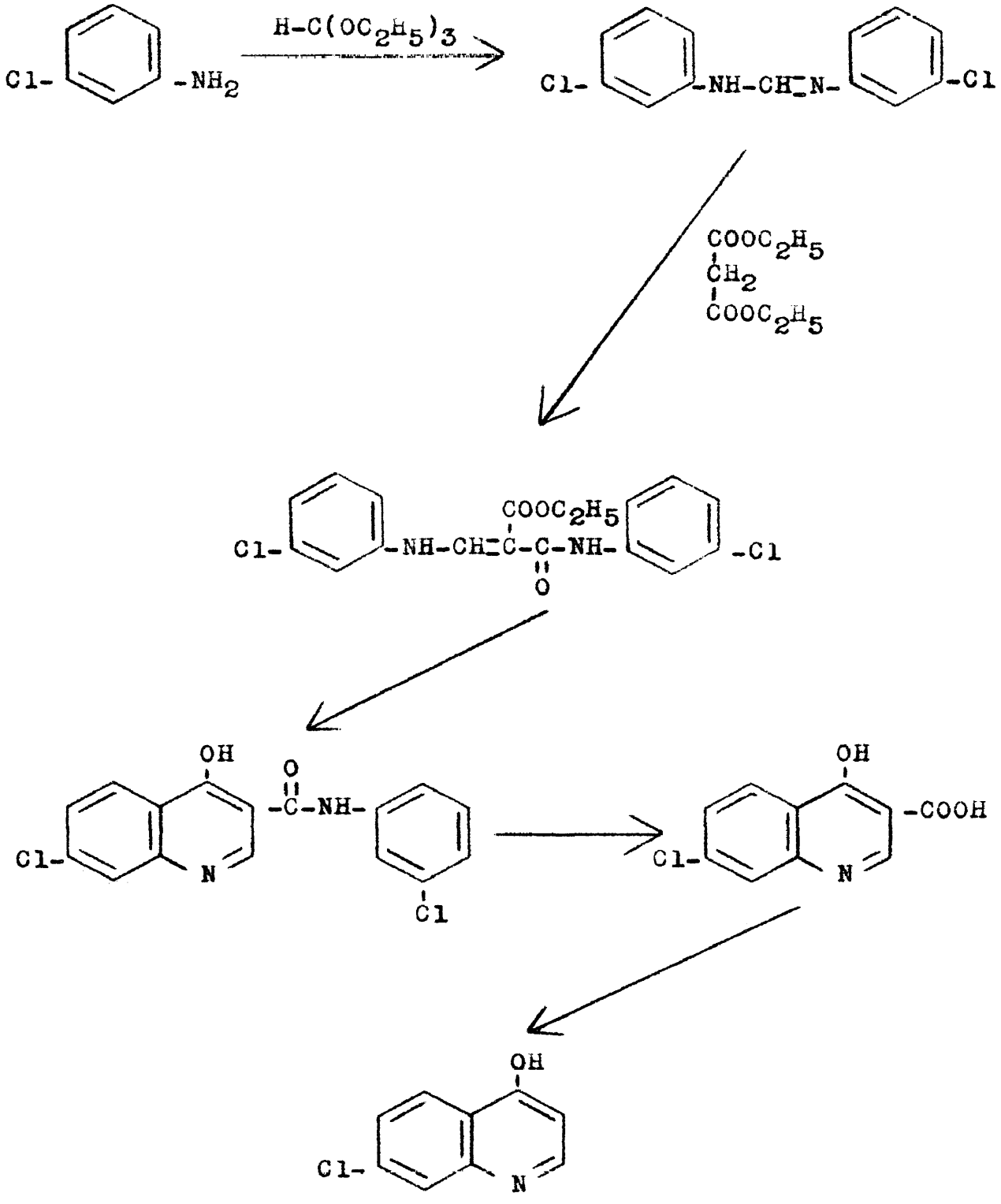
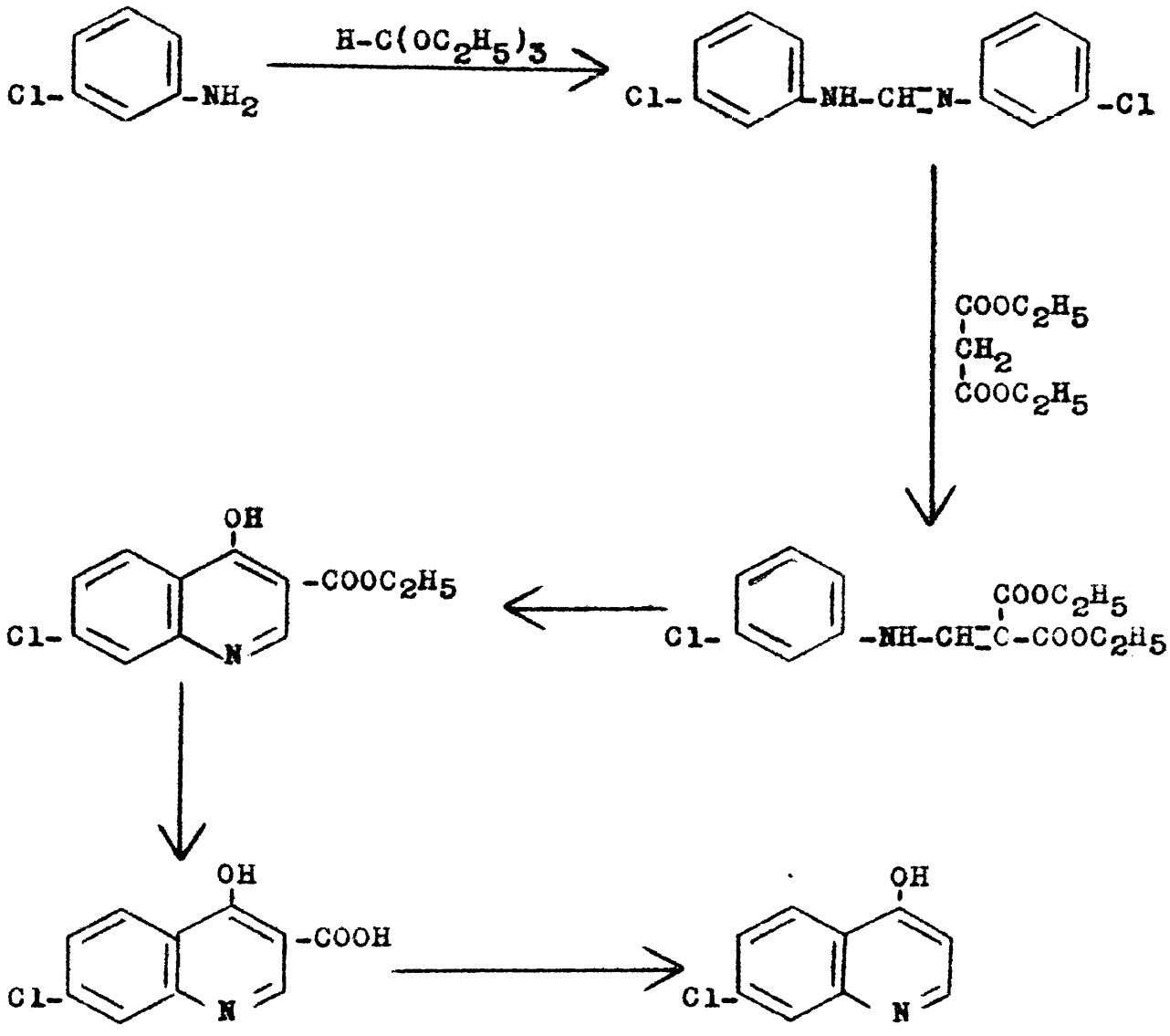
[34]Roberts, J. Org. Chem., 14, 277 (1949).

[35]Meisenheimer, Ber., 59B, 1848 (1926).



Scheme N


Cl-
-NH2
H-C(OC2H5)3
Cl-
NH-CH=N-
-Cl
COOC2H5
CH2
COOC2H5
OH
-COOC2H5
Cl-
N
Cl-
COOC2H5
-NH-CH=C-COOC2H5
OH
-COOH
Cl-
N
OH
Cl-
N

Scheme 0

chloride, some 4-chloroquinoline was obtained. Brobranski showed that the reaction products actually consisted of 62% of the 4-chloro compound and 38% of the 2-chloro compound (Scheme P).[8,36]

Although no details are given, the Meisenheimer reaction is reported as unsatisfactory for the production of DCQ from 7-chloroquinoline.[37]

Although the diazotization of 4-aminoquinoline can be used to prepare 4-hydroxyquinoline as was shown earlier, it can also be used to prepare 4-chloroquinoline directly. Wenzel diazotized 4-aminoquinoline with potassium nitrite in hydrochloric acid and obtained the 4-chloro compound (Scheme F).[38]

The last type of reaction in this category was the cyclization of N-tosyl-β-anilinopropionate with phosphorous pentachloride by Clemo and Perkin.[12] Although they believed that they had obtained N-tosyl-3-chlorodihydroquinoline, Backberg[13] showed that they really had obtained the N-tosyl-4-chlorodihydroquinoline. Elderfield and coworkers attempted to dehydrogenate this compound but they were not successful and decided further investigation was needed. The reactions are analogous to Scheme E.

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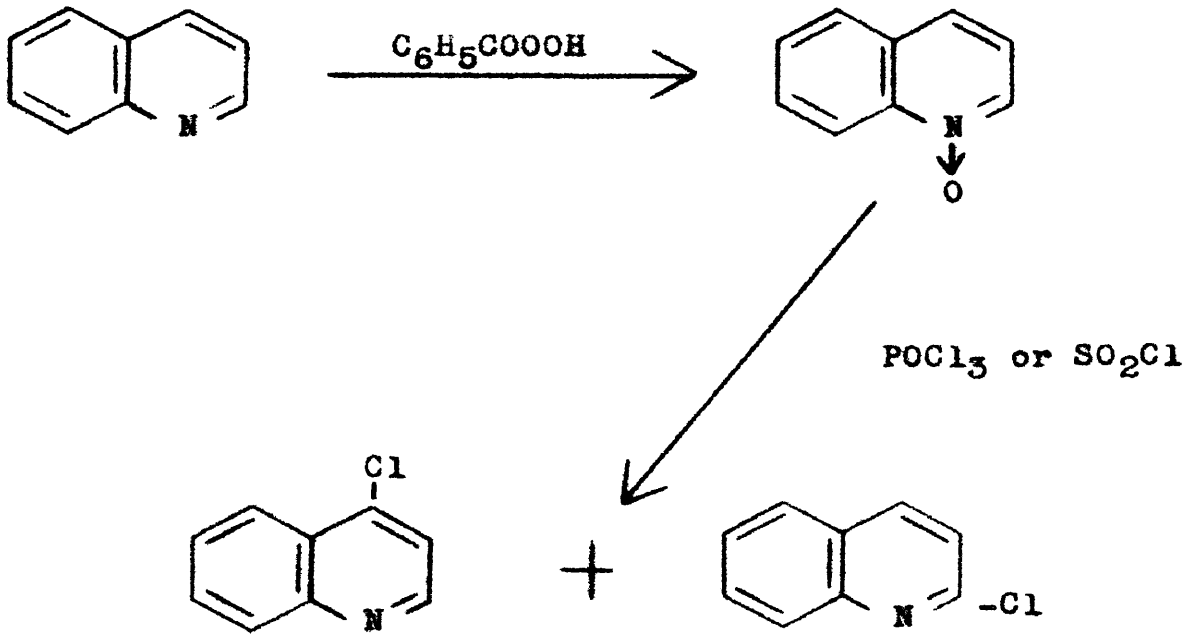
[36]Brobranski, Ber., 71, 578 (1938).

[37]Riegel, Albisetti, et al., J. Am. Chem. Soc., 68, 2685 (1946).

[38]Wenzel, Monatsh., 15, 459 (1872).



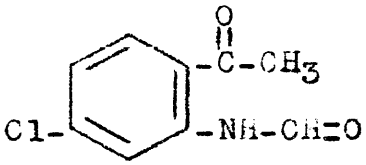
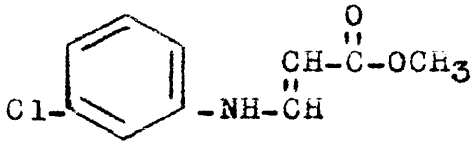
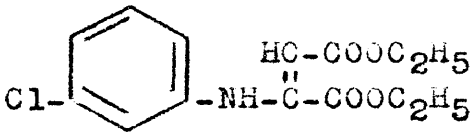
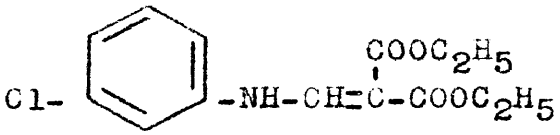
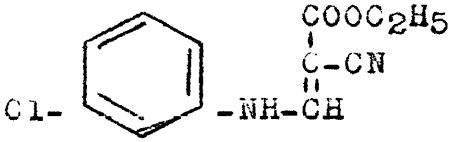
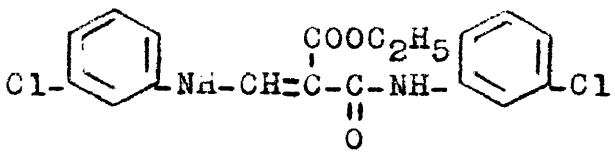
Scheme P

Summary

Tables I and II summarize ten methods that are applicable to the synthesis of 4,7-dichloroquinoline by way of a 4-hydroxy-7-chloroquinoline intermediate. In addition, the historical section outlines several other methods which have been tried but which were wholly unsuccessful. Table I itself is composed of those methods of synthesizing 4-hydroxyquinoline which have actually been extended to the synthesis of 4-hydroxy-7-chloroquinoline. Although the synthesis accomplished in the present work provides a sixth member for Table I, the cyclization step did not occur in high enough yield to offer any serious competition to the best of the other methods (Schemes L or O). The cyclization of 2-formamino-4-chloroquinoline, however, is the only one of the successful syntheses which theoretically precludes the possibility of any contamination with the 5-chloro isomer.

TABLE I

CYCLIZATIONS TO 4-HYDROXY-7-CHLOROQUINOLINE

Compound Cyclized	Scheme	Yield[a]	Isomer[b]	Dil.[c]	Ref.
	B (X=Cl)	19.2%	None Possible	67	This Work
	D (X=Cl)	40%	4/1	25	11
	J (X=Cl)	34%	1/1	6.7	3, 27
	L or O	80%	None Isolated	5.1	30
	M	40%	None Isolated	27	32,33
	N	58%	None Isolated	28	32

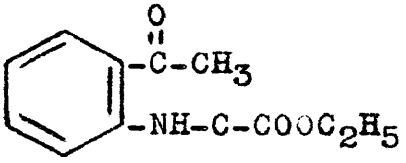
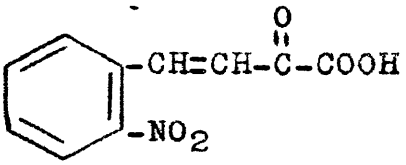
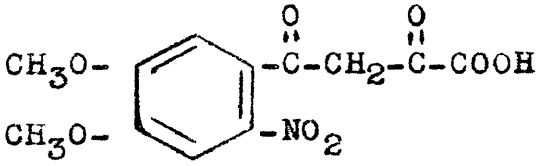
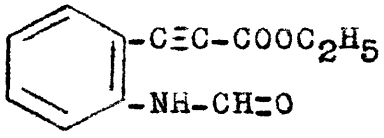
[a] Yield of direct product of cyclization.

[b] Ratio of 4-hydroxy-7-chloro to 4-hydroxy-5-chloro derivative.

[c] Milliliters of solvent per gram of compound cyclized.

TABLE II

CYCLIZATIONS NOT TRIED FOR 4-HYDROXY-7-CHLOROQUINOLINE

Compound Cyclized	Scheme	Yield[a]	Isomer[b]	Dil.[c]	Ref.
	G	Not Given	None Possible	27	7
	H	Not Given	None Possible	53	22
	I	46%	None Possible	21	23
	K	90%	None Possible	120	7

[a] Yield of direct product of cyclization.

[b] Position isomers if benzene ring were further substituted.

[c] Milliliters of solvent per gram of compound cyclized.

DISCUSSION

The object of the experimental part of this work was the continuation of the transfer of the methods of synthesizing 4-chloroquinoline to the synthesis of 4,7-dichloroquinoline. Although the logical intermediate, 4-hydroxy-7-chloroquinoline, has been synthesized by cyclization which involved a condensation at one of the carbon atoms of a benzene ring, no synthesis has previously been accomplished which involved only substituents attached to the ring. While this type of ring closure would involve a benzene derivative containing three substituents instead of two, it would remove the possibility of the formation of a position isomer. The method of Camps (Scheme B, where X would be Cl) was chosen for investigation. Since the key intermediate for this method is 2-amino-4-chloroacetophenone a study of the synthesis of this ketone was also undertaken.

Synthesis of 2-Amino-4-chloroacetophenone

The first reported attempt to prepare 2-amino-4-chloroacetophenone involved a Friedel-Crafts type of synthesis. Roberts and Turner treated p-chloroaniline with acetic anhydride in the presence of zinc chloride but was not able to isolate any of the desired product.[39] The recent search

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[39]Roberts and Turner, J. Chem. Soc., 1927, 1884.

for new antimalarials created interest in 4-hydroxy-7-chlorocinnolines and these could be conveniently prepared by the diazotization of the appropriate 2-amino-4-chloroacetophenone derivative. Leonard and Boyd described several methods for the synthesis of the parent compound.[40] In the first method, m-dichlorobenzene was acylated under Friedel-Craft conditions to give a 62% yield of 2,4-dichloroacetophenone and the dichloro compound was ammonolyzed under pressure to give an 11% yield of 2-amino-4-chloroacetophenone along with a good deal of the diamino compound (Scheme Q).

Several more important methods have been proposed for the synthesis of 2-amino-4-chloroacetophenone and all of these involve the preparation and reduction of 2-nitro-4-chloroacetophenone. Leonard and Boyd proposed a method starting with 2-nitro-4-chlorotoluene.[40] This compound was oxidized with potassium permanganate to 2-nitro-4-chlorobenzoic acid in 62% yield. The acid was converted into the acid chloride, which in turn was treated with a sodium ethyl acetoacetate solution to give the 2-nitro-4-chlorobenzoyl derivative of acetoacetic ester. The benzoyl compound was cleaved with sulfuric acid and alcohol to 2-nitro-4-chlorobenzoylacetic ester. Upon treatment with aqueous acid, 2-nitro-4-chloroacetophenone was obtained in 61% yield from the benzoic acid and 38% over-all yield from

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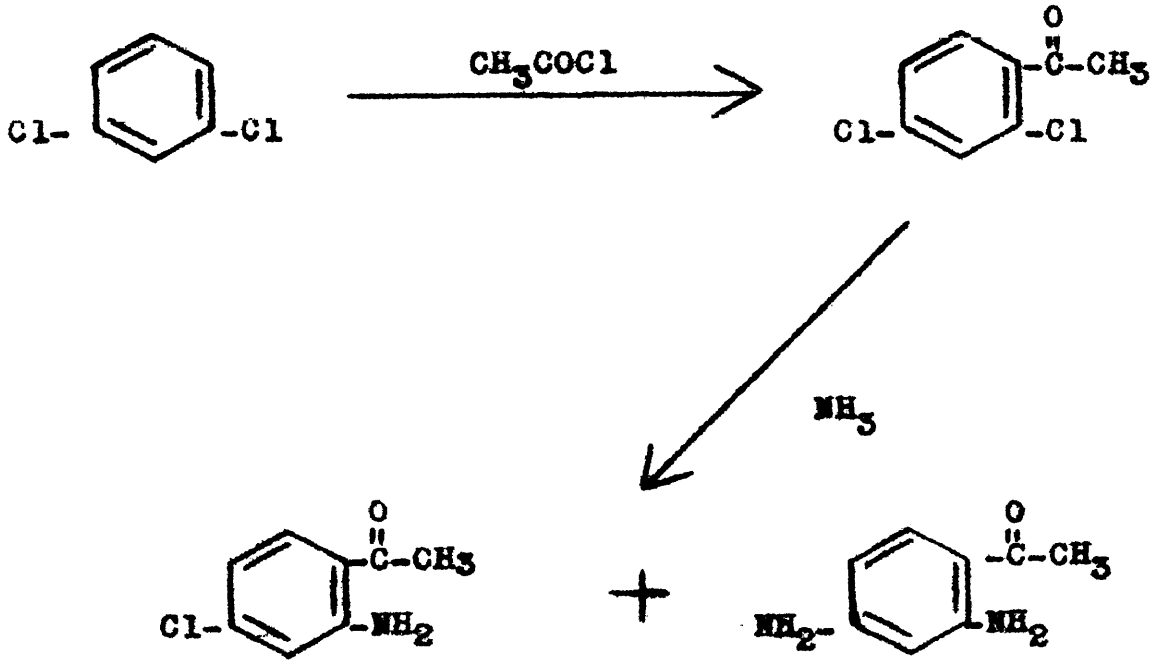
[40]Leonard and Boyd, J. Org. Chem., 11, 405 (1946).



Scheme Q

the toluene derivative. (The amount of pure ketone, however, was probably much less as the melting point was quite low.) The nitro compound was reduced to 2-amino-4-chloroacetophenone in 64.2% yield with platinum oxide in ethanol (Scheme R).

A very similar process was reported by the English workers, Atkinson and Simpson, who obtained a 29.6% yield of 2-nitro-4-chloroacetophenone from 2-nitro-4-chlorotoluene.[41] A variation in producing 2-nitro-4-chlorobenzoic acid was also tried. Diazotization of 2-nitro-4-chloroaniline and treatment with alkali cyanide and copper sulfate gave 2-nitro-4-chlorobenzonitrile. Hydrolysis of the nitrile gave the benzoic acid in about 40% over-all yield. These authors also described the use of iron powder and acetic acid for the reduction of the nitro compound to 4-chloro-2-amino-acetophenone in 84% yield.

Another synthesis of the ketone was accomplished by Kenneford and Simpson who employed chlorobenzene as the starting material.[42] A Friedel-Crafts reaction gave p-chloroacetophenone which was nitrated to 3-nitro-4-chloro-acetophenone. The nitro compound was reduced, acetylated, and nitrated to give a mixture of 2-nitro-4-chloro-5-acetamino-acetophenone and the 3-nitro-4-chloro-5-acetamino isomer. After separation, the removal of the acetyl group, the

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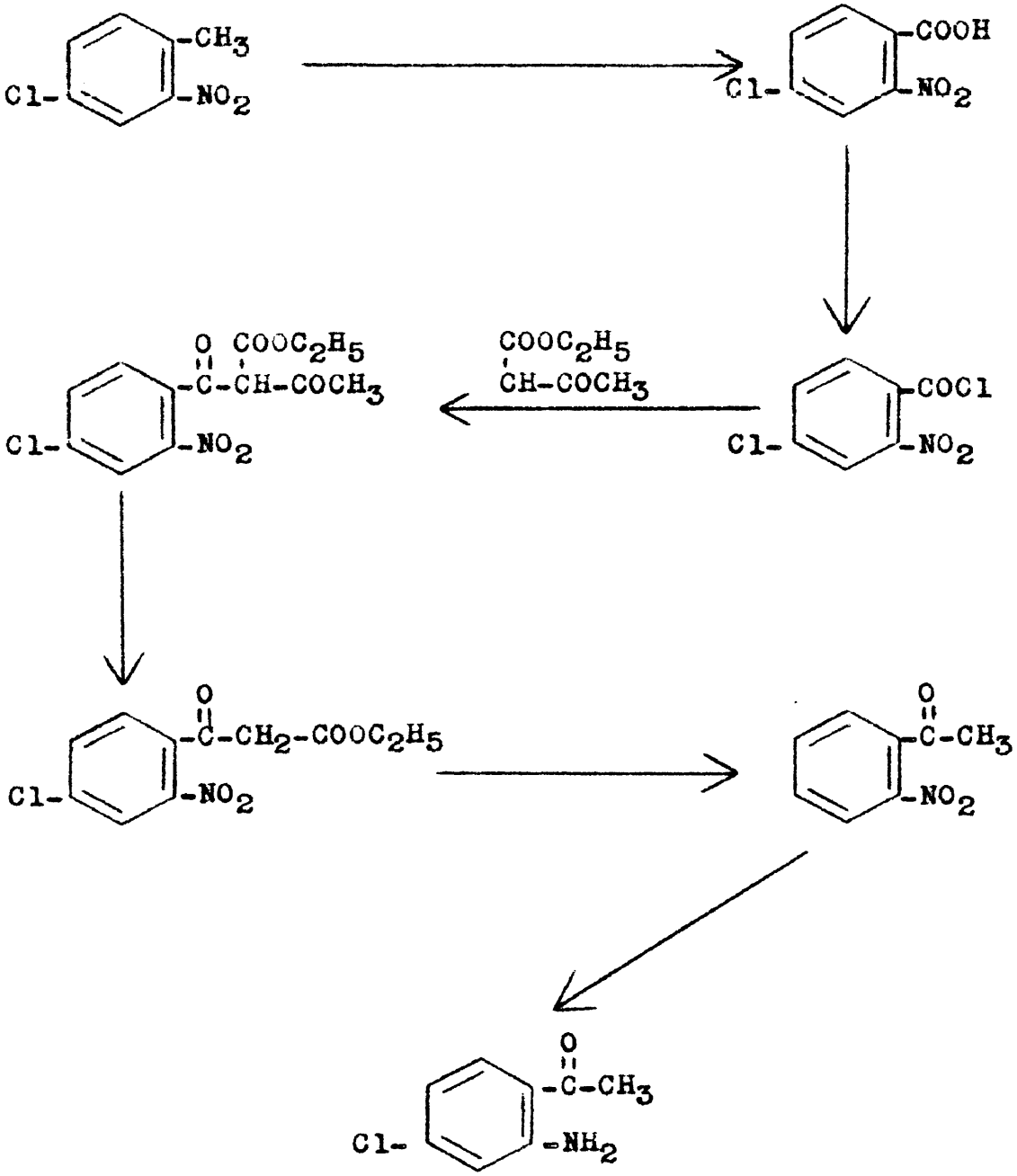
[41]Atkinson and Simpson, J. Chem. Soc., 1947, 232.

[42]Kenneford and Simpson, ibid., 1947, 227.



Scheme R

2-nitro derivative was deaminated by treatment with amyl nitrite and sulfuric acid to give 2-nitro-4-chloroacetophenone in undisclosed over-all yield (Scheme S).

Still another scheme advanced by Atkinson and Simpson made use of p-chloroanthranilic acid as the starting material.[41] The acid was treated with phthalic anhydride to give 2-phthalimido-4-chlorobenzoic acid, which in turn was treated with sodium malonate to give 2-phthalimido-4-chlorobenzoyl malonic ester. Treatment with hydriodic acid produced 2-amino-4-chloroacetophenone in 45.8% yield from the phthalimido acid. This represented about a 32% over-all yield (Scheme T).

The best methods of Leonard and Boyd and Atkinson and Simpson produced yields of 38% (with rather low melting point) and 29.6% of 2-nitro-4-chloroacetophenone respectively and their starting material was the nitro-chlorotoluene. These methods involved oxidation to the acid[43] and then a several step method of essentially replacing the hydroxy group of the acid with a methyl group. It seemed desirable to evolve a method whereby a compound very similar to the toluene derivative could be directly converted to the ketone. Since ethylbenzene is a readily available starting material, and since the synthesis of 2-nitro-4-chloroethylbenzene

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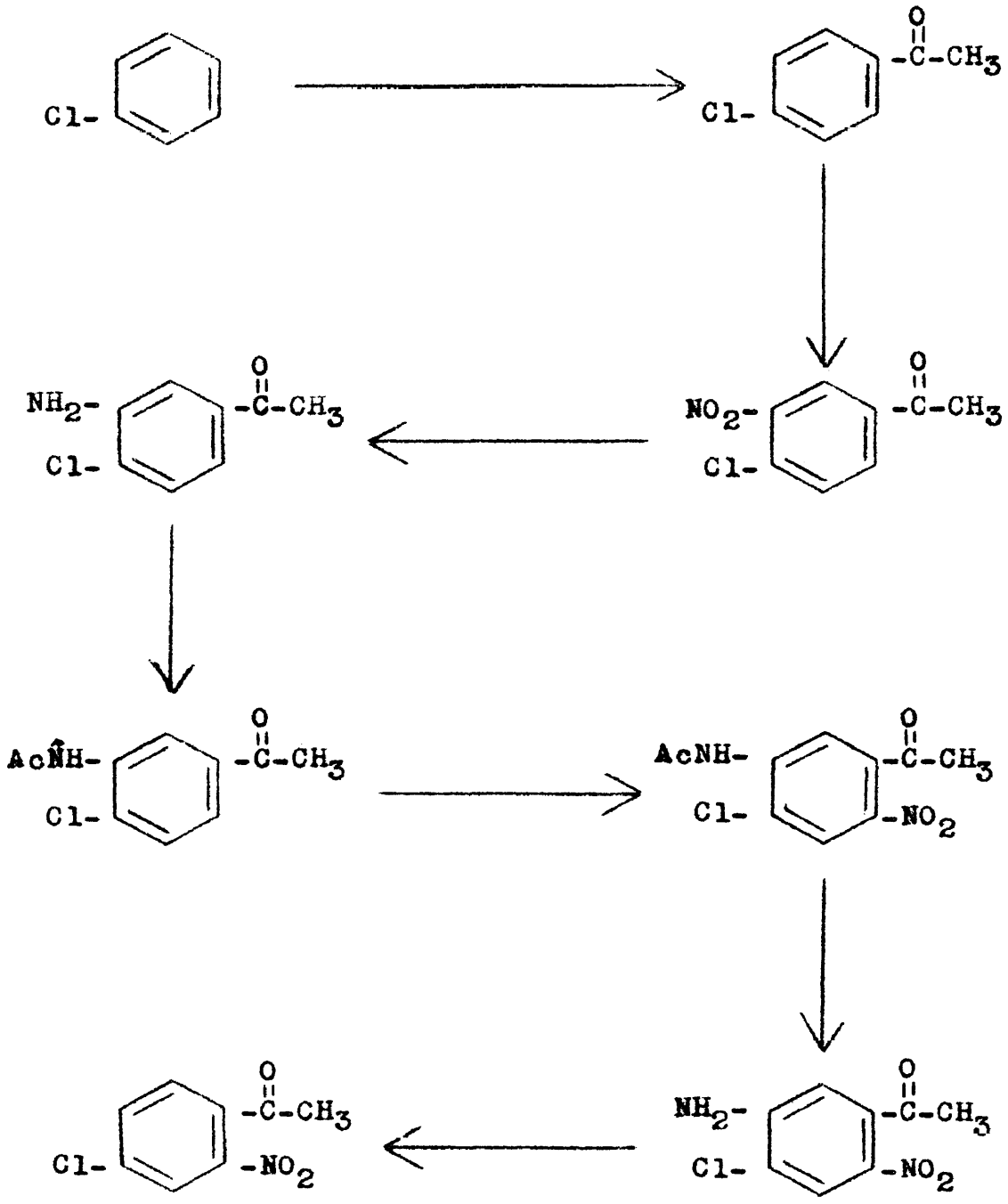
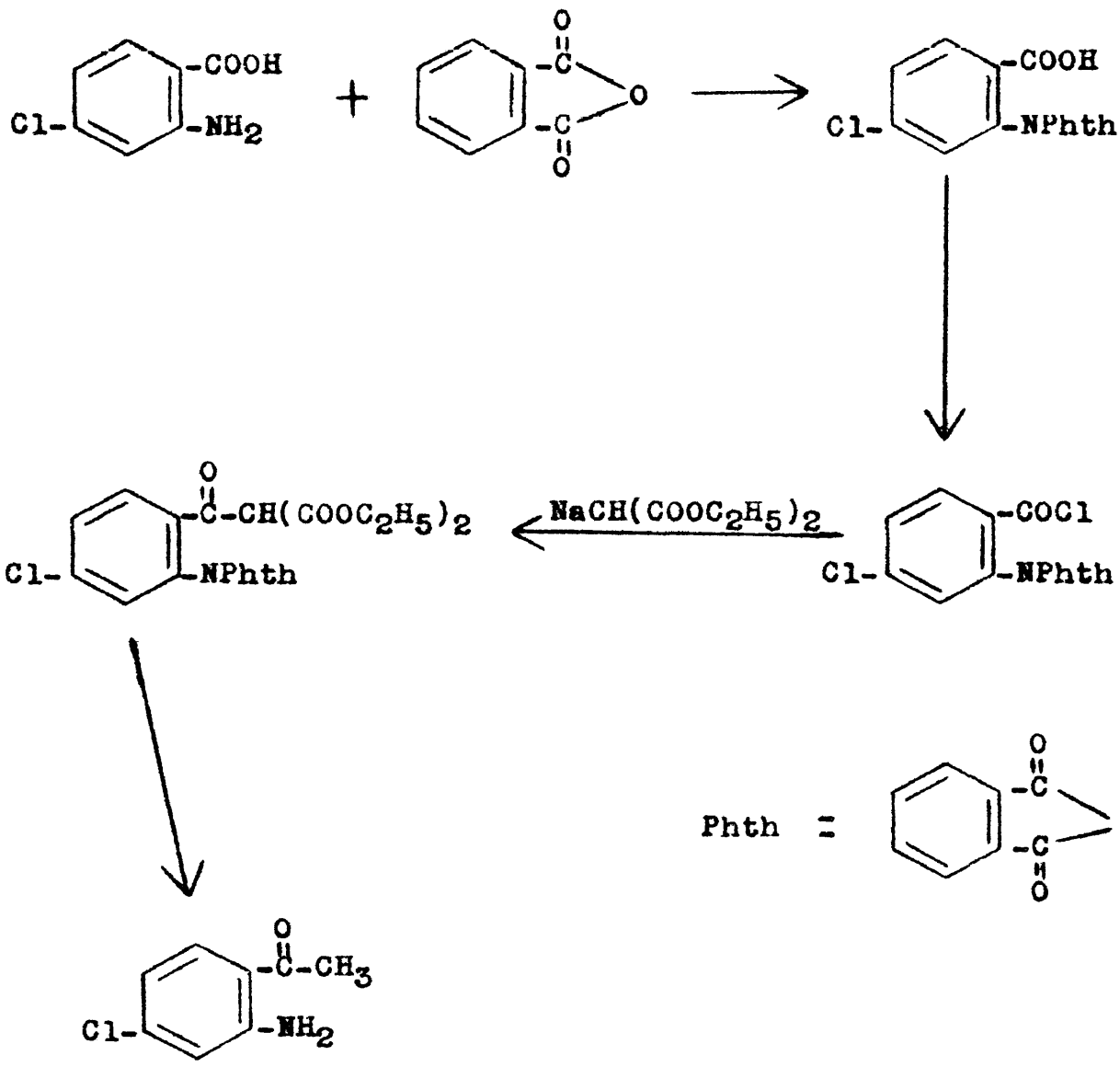
[43]Atkinson and Simpson describe the oxidation of 10 g. of material and state, "This result could not be reproduced on a larger scale."



Scheme S


Cl-
-COOH
-NH2
+
-C
O
-C
O
-COOH
-NPhth
-COCl
-NPhth
NaCH(COOC2H5)2
-C-CH(COOC2H5)2
-NPhth
-C-CH3
-NH2
Phth =
-C
-C
O

Scheme T

involves essentially the same steps as the synthesis of the toluene analogue, an investigation into the synthesis of 2-nitro-4-chloroethylbenzene and its conversion into the ketone was undertaken by us. The essential steps were dinitration of the ethylbenzene, selective reduction of the p-nitro group, replacement of the p-amino group with chloride, and lastly conversion of the ethyl group to the ketone. The sequence is shown in Scheme U.

Since o-nitro-p-dichlorobenzene is also a relatively inexpensive starting material, we attempted to use it in the synthesis of 2-nitro-4-chloroacetophenone. Although the reaction of sodium acetylide with alkyl halides has been well established by a large number of examples, no reaction was ever successful with aromatically bound halogen. It was felt, however, that perhaps an activated halogen such as in o-nitro-p-dichlorobenzene would produce the desired phenylacetylene. The acetylene, of course, could easily be hydrated to the ketone. The reaction was first tried with butyl bromide as the condensation was reported to give hexyne-1 in good yields.[44] A procedure which afforded hexyne-1 in 51.5% yield is described in the experimental section.

The reaction with sodium acetylide was repeated with p-nitrobromobenzene and with o-nitro-p-dichlorobenzene,

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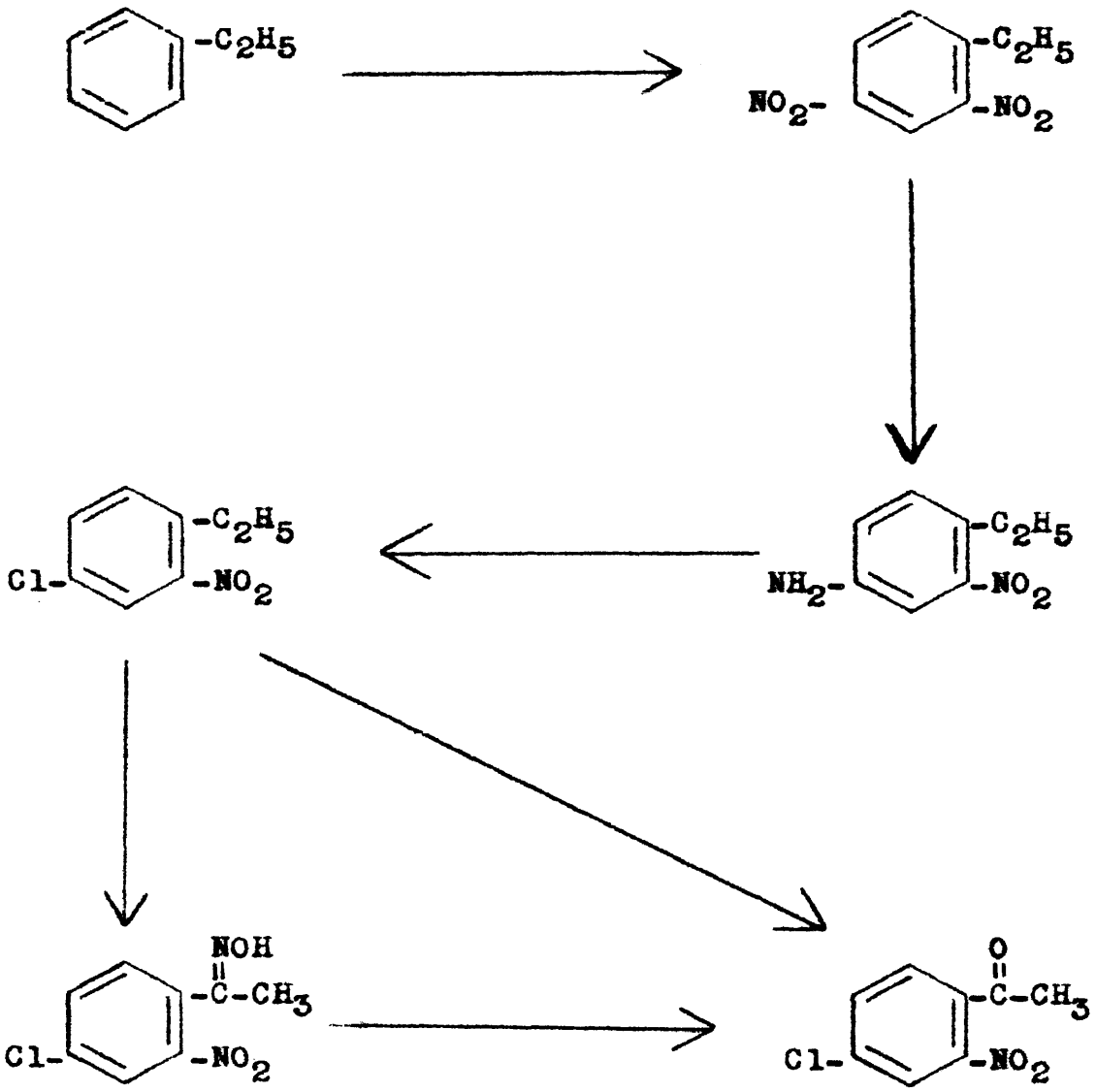
[44] Vaughn, Vogt, Hennion, and Nieuwland, J. Org. Chem., 2, 1 (1937).


-C2H5
NO2-
-C2H5
-NO2
-C2H5
NH2-
-NO2
-C2H5
Cl-
-NO2
NOH
-C-CH3
Cl-
-NO2
O
-C-CH3
Cl-
-NO2

Scheme U

the only change being the evaporation of the ether extracts and recrystallization of the solids from a 20% benzene in petroleum ether solvent. In both cases the starting materials were essentially quantitatively recovered. The temperature at which the reaction was conducted was increased by substituting dioxane as the solvent, but again only the starting material was recovered.

Dinitration of Ethylbenzene

The dinitration of ethylbenzene was first accomplished by Weissweiler[45] but Borsche was unable to repeat his work.[46] 2,4-Dinitroethylbenzene was also obtained as a by-product of the mononitration of ethylbenzene by Cline and Reid.[47] Ipatieff and Schmerling also mention the product[48] but none of these workers gives much detail for the reaction and none mentions his yield. From the facts available and from some preliminary experiments it became obvious that three factors are involved. First, a high temperature is required for the dinitration. Second, adding the reactants in the cold and then heating up the mixture results in a great deal of oxidation and the reaction tends to become quite violent. Third, if the ethylbenzene is dinitrated rapidly at elevated tempera-

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[45]Weissweiler, Monatsh., 21, 40 (1900).

[46]Borsche, Ann., 386, 365 (1912).

[47]Cline and Reid, J. Am. Chem. Soc., 49, 3150 (1927).

[48]Ipatieff and Schmerling, ibid., 59, 1056 (1937).

ture, the stability of the dinitro product prevents the formation of significant quantities of oxidation product. A convenient method for the production of 2,4-dinitroethylbenzene on a rather large scale was evolved. The method affords yields of either 73% or 91% depending on the mode of isolation of the final product.

Selective Reduction of 2,4-Dinitroethylbenzene

The selective reduction of one nitro group of dinitrobenzene homologues has classically been carried out with hydrogen sulfide and ammonia. Schultz,[49] and Cline and Reid[47] have used this method on 2,4-dinitroethylbenzene. The latter have shown that only a very small amount of the 2-amino compound is formed from either 2,4-dinitrotoulene or 2,4-dinitroethylbenzene and that the amount of 2-amino compound formed in the case of the ethylbenzene derivative is so small it could not be directly isolated. Cline and Reid have also pointed out that the isomer free 2-nitro-4-aminoethylbenzene melts at 45° and its acetyl derivative melts at 110°. Since they did not give their yields, however, their experiment was repeated. The amount of 2-nitro-4-aminoethylbenzene hydrochloride isolated corresponded to 52.7% of the calculated quantity.

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[49]Schultz, Ber., 42, 2634 (1909).

Hodgson and Birtwell reported some experiments in the selective reduction of various dinitro compounds and came to the conclusion that methanol was a superior solvent to ethanol and that sodium sulfide buffered with sodium bicarbonate was superior to ammonia and hydrogen sulfide.[50] The application of these ideas to our work on the monoreduction of dinitroethylbenzene produced a method providing an increased yield of substantially pure product. Thus 2-nitro-4-aminoethylbenzene hydrochloride was produced in 79% yield: the free base melted sharply at 45° and the acetyl derivative melted at 110.5-111° in good agreement with the constants reported by Cline and Reid for the isomer free compound.

Synthesis of 2-Nitro-4-chloroethylbenzene

Replacement of the amino group in 2-nitro-4-aminoethylbenzene by a chloro group was accomplished by us in 46% yield by the standard Sandmeyer conditions. The reaction was very difficult to handle, however, due to an excessive amount of foaming during the diazotization. A much smoother reaction and also a higher yield was obtained by use of a procedure adapted from Hodgson and Walker.[51]

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[50] Hodgson and Birtwell, J. Chem. Soc., 1944, 75; 1945, 663.

[51] Hodgson and Walker, ibid., 1933, 1620.

The procedure involved the use of a glacial acetic acid solvent and afforded a diazotization that could be conducted at slightly below 15° with no foaming. The use of this method of diazotization increased the yield of 2-nitro-4-chloroethylbenzene to 63%. The compound is a pale yellow liquid which distilled at 133-135°/20 mm. Both methods of diazotization are described in the experimental section.

Ketonization of 2-Nitro-4-chloroethylbenzene

Two general methods for the conversion of 2-nitro-4-chloroethylbenzene to 2-nitro-4-chloroacetophenone were investigated. The first method involved an oximation at the α-carbon followed by hydrolysis of the oxime to the ketone. The second method involved the possibility of a direct oxidation at the α-carbon to produce the ketone in one step.

Ford-Moore and Rydon have investigated the oximation of o-nitroethylbenzene and their highest yield of the oxime (48%) was obtained by the use of tertiary butyl nitrite as the oximating agent.[52] By applying this method to 2-nitro-4-chloroethylbenzene a yield of 39.4% of 2-nitro-4-chloroacetophenone oxime was obtained. Hydrolysis of the oxime, however, afforded the ketone in only 68.5% yield; the over-all yield of ketone was thus about 28%.

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[52]Ford-Moore and Rydon, J. Chem. Soc., 1946, 679.

The oxidation of compounds such as o-nitrotoluene to o-nitrobenzaldehyde by chromium trioxide in the presence of acetic anhydride and acetic acid[53,54] suggested the second avenue of approach. Application of this method to 2-nitro-4-chloroethylbenzene afforded a 55% yield of the ketone in one step. The ketone and the oxime prepared from it did not depress the melting points of the corresponding compounds produced via the oximation reaction.

Reduction of 2-Nitro-4-chloroacetophenone

Catalytic reduction of 2-nitro-4-chloroacetophenone by hydrogen has not produced as high yields of 2-amino-4-chloroacetophenone as has the use of metallic reductants. Leonard and Boyd secured the amine in 64.2% yield by the use of hydrogen and a platinum oxide catalyst. In our work, the use of an alcoholic solution of stannous chloride afforded the amine in 79.5% yield. A similar high yield of amine has also been accomplished by the use of iron powder and acetic acid.[41]

The formylation of 2-amino-4-chloroacetophenone was easily accomplished by a simple reflux procedure with 90% formic acid.

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[53]Thiele and Winter, Ann., 311, 353 (1900).

[54]Blatt, "Organic Synthesis," Vol. II, John Wiley and Sons, New York City, 1943, p. 441.

Cyclization of 2-Formamido-4-chloroacetophenone

Cyclization of o-formamidoacetophenone to 4-hydroxyquinoline in the presence of dilute alkali and a trace of alcohol was first accomplished by Camps who obtained 8.5 g. (68.5%) of the quinoline from 14 g. of starting material.[7] Brobranski repeated the experiment (ostensibly under the same conditions) but was only able to secure an amount of hydroxyquinoline corresponding to a yield of 25.8%. Cyclization of 2-formamido-4-chloroacetophenone has now also been accomplished and the procedure is described in the experimental section. Although the quantity of 4-hydroxy-7-chloroquinoline that was isolated corresponded to a yield of 19.2% of the calculated quantity, a considerable amount of 2-amino-4-chloroquinoline was recovered during the steam distillation. The yield of 4-hydroxy-7-chloroquinoline based on recovered material was 89.2%. It is possible that the 8.5 g. of 4-hydroxyquinoline found in the article by Camps was a misprint, as 3.5 g. would represent a yield of 28% in reasonable agreement with Brobranski and ourselves.

That the alkali soluble compound formed in the cyclization of 2-formamido-4-chloroacetophenone was actually 4-hydroxy-7-chloroquinoline was shown by the fact that it did not depress the melting point of a sample prepared by the hydrolysis of an authentic sample of 4,7-dichloroquinoline. The hydrolysis was conducted according to the directions of

Brobranski for the hydrolysis of 4-chloroquinoline.[8] A sample of 4,7-dichloroquinoline prepared from the alkali soluble compound by treatment with phosphorous oxychloride according to the directions of Surrey and Hammer[3] also failed to depress the melting point of the authentic sample.

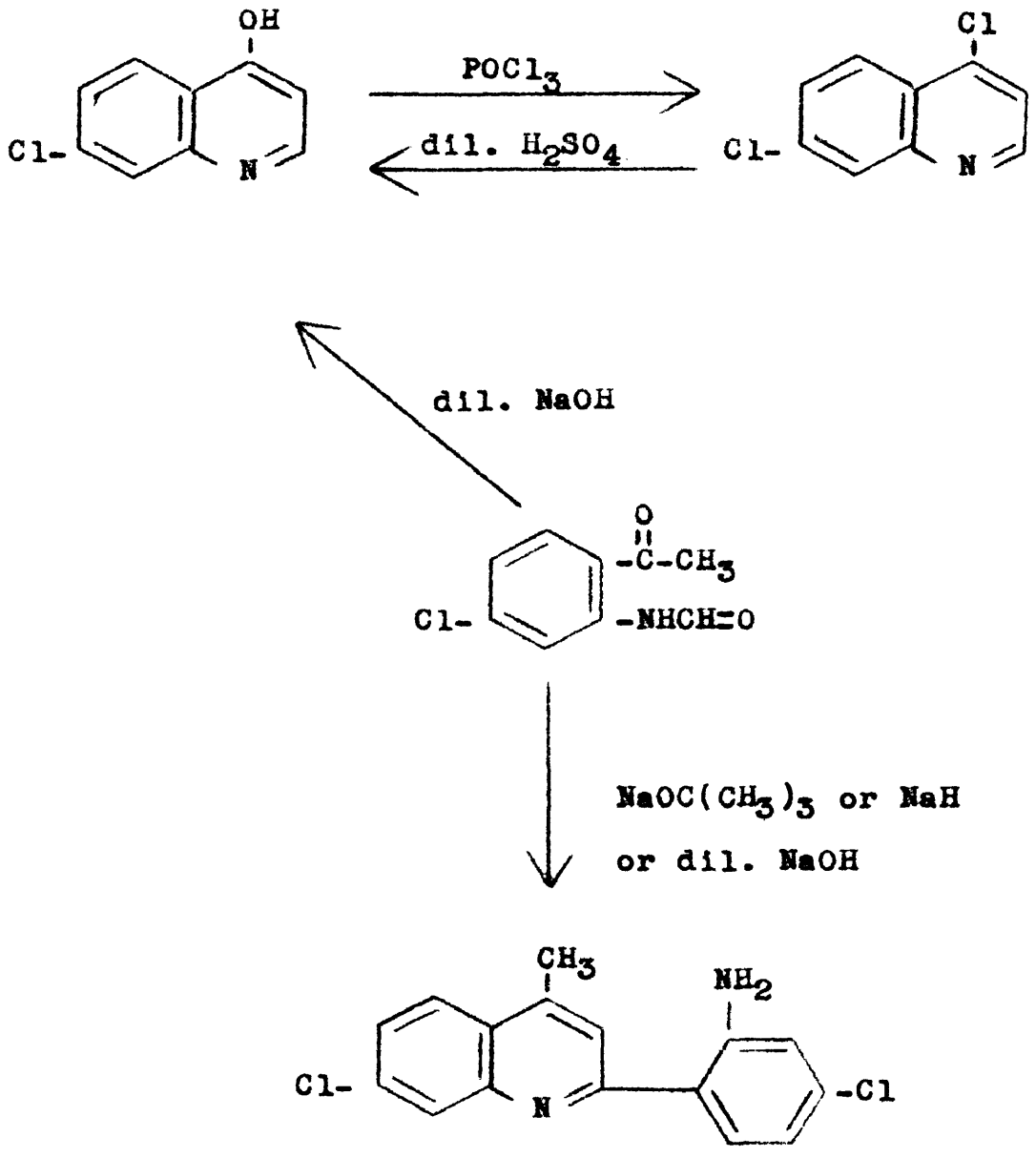
The presence of a small amount of alcohol in the cyclization of the 2-formamido-4-chloroacetophenone seems to be necessary for the reaction as the reaction conducted without it (and with or without the presence of enough dioxane to solubilize the starting material) failed to produce the hydroxyquinoline.

Camps also isolated a by-product in his cyclization of o-formamidoacetophenone. The compound, a yellow amine, was easily separated from 4-hydroxyquinoline because it was insoluble in alkali. He demonstrated that the compound was isoflavaniline, 2-(2-aminophenyl)-4-methylquinoline. It was not surprising, therefore, that the cyclization of 2-formamido-4-chloroacetophenone produced a small amount of a yellow compound which was insoluble in alkali and not volatile with steam. The compound melted at 170-171° and contained nitrogen and chlorine. The results of an elementary analysis were consistent with a formula of $C_{16}H_{12}Cl_2N_2$. By analogy with the compound obtained by Camps, the compound is believed to be 2-(2-amino-4-chlorophenyl)-4-methyl-7-chloroquinoline. The formyl and acetyl derivatives of this compound were also prepared.

Other alkaline condensing agents were tried in the attempt to improve the cyclization of 2-formamido-4-chloroacetophenone to 4-hydroxy-7-chloroquinoline. Sodium hydride suspended in benzene was apparently unreactive as a subsequent steam distillation afforded only the hydrolysis product. Sodium hydride in boiling dioxane or sodium tertiary butoxide in boiling tertiary butyl alcohol, however, both produced the dichloro-isoflavaniline in yields of 58.5% and 86.5%, respectively. None of these reagents gave the desired alkali-soluble hydroxyquinoline.

In addition to the alkaline condensing agents, various acidic reagents were also tried in attempted cyclization. With refluxing benzene as the solvent, phosphorous pentoxide, dry hydrogen chloride, and boron trifluoride failed to produce any of the hydroxyquinoline. Simple fusion or heating to 200° in an inert medium also failed to provide the hydroxy compound.

The 4-hydroxy-7-chloroquinoline prepared by the cyclization in dilute sodium hydroxide was easily converted to 4,7-dichloroquinoline by the use of phosphorous oxychloride. The conversion was accomplished in 81% yield. The 4,7-dichloroquinoline prepared in this manner did not depress the melting point of an authentic sample.


OH
Cl-
N
POCl3
dil. H2SO4
Cl
Cl-
N
dil. NaOH
O
-C-CH3
Cl-
-NHCH=O
NaOC(CH3)3 or NaH
or dil. NaOH
CH3
NH2
Cl-
N
-Cl

Scheme V

EXPERIMENTAL

Trial preparation of hexyne-1.

A 250 ml. portion of liquid ammonia from a commercial cylinder was placed in a dropping funnel which was surrounded by a cooling jacket containing dry ice and cellosolve. A total of 22.5 g. (0.98 mole) of sodium was added to the liquid ammonia in small pieces. A second 250-ml. portion of liquid ammonia was placed in a 1-l. three-necked flask equipped with a gas inlet tube and a mechanical stirrer. Commercial acetylene was led through water and sulfuric acid scrubbers and finally into the flask. The solution of sodium in liquid ammonia was slowly added to the flask during the passage of the acetylene. The addition of the sodium solution was completed in an hour but the passage of the acetylene was continued a few minutes longer. From another dropping funnel, 104 g. (0.76 mole) of redistilled butyl bromide was slowly to the flask. A condenser filled with dry ice and cellosolve was fitted on the flask and the cooling bath was removed from around the flask. The liquid ammonia began to boil and the boiling and refluxing was allowed to continue for two hours. A condenser containing liquid ammonia was placed atop the first condenser and 158 ml. of water was slowly added to the flask. The whole reaction mixture was siphoned into a 2-l. separatory funnel and the organic layer was taken up with ether. The ether

solution was washed several times with water and dried over calcium chloride. After the ether was carefully distilled off, a 32 g. (51.5%) fraction of hexyne-1 distilling at 70-72° was obtained. The alkyne gave a white mercury derivative melting at 96.5° (Vaughn, et al.,[44] 96.2-96.5°). Another portion of the alkyne was converted to methyl butyl ketone which was identified through its 2,4-dinitrophenylhydrazone.

Attempted preparation of phenylacetylenes in liquid ammonia.

p-Nitrobromobenzene and o-nitro-p-dichlorobenzene were substituted for the butyl bromide in the experiment described above. The ether extraction was eliminated, however, and the solid products were recrystallized from a benzene-petroleum ether solvent. In both cases the starting material was essentially quantitatively recovered.

Attempted preparation of phenylacetylenes in dioxane.

A 125-ml. portion of liquid ammonia was placed in a dropping funnel which was surrounded by a cooling jacket containing dry ice and cellosolve. A total of 11.3 g. (0.49 mole) of sodium metal was added to the ammonia in small pieces. A second portion of 125 ml. of liquid ammonia was placed in a 1-l. three-necked flask equipped as in the previous experiment. The passage of the acetylene was begun and the sodium in ammonia solution was slowly added to the flask. After the passage of the acetylene was completed, a dry ice-cellosolve condenser was fixed on the flask and

250 ml. of purified dioxane was slowly added. A heating mantle was substituted for the cooling bath and the condenser was removed. With the gentle application of heat, the ammonia slowly evaporated. Eventually the mixture was brought up to room temperature and 77 g. (0.38 mole) of p-nitrobromobenzene was added. After twelve hours of agitation the mixture was slowly diluted with 100 ml. of water and then poured into another flask containing 1500 ml. of water. The solid was filtered off and recrystallized from a 20% benzene in petroleum ether solution. The solid, which weighed 74 g., did not depress the melting point of the starting material and represented a substantially complete recovery of starting material. The experiment was repeated with o-nitro-p-dichlorobenzene with the same negative result.

2,4-Dinitroethylbenzene.

The mixed acid for the nitration was prepared by slowly adding 510 ml. of concentrated nitric acid (d. 1.42) to 1020 ml. of concentrated sulfuric acid (d. 1.84) in a 3-l. three-necked flask equipped with a condenser, a nichrome Hirshberg stirrer, a thermometer, and a dropping funnel. The stirrer was started and 306 ml. (265 g., 2.5 moles) of ethylbenzene was added to the mixed acid. The ethylbenzene was first added at a fairly rapid rate, but when the temperature of the mix reached 105° the rate of addition was slowed

down; the rest of the ethylbenzene was added at such a rate as to maintain the temperature at 110 ± 2°. (A regular house fan played on the flask decreased the time of addition from about three hours to about one hour. The fan was removed after the addition was complete.) The mixture was stirred for an additional half-hour, although it was not allowed to cool below 75°. When the agitation was finally stopped, the organic layer rose to the top. The bilayered mixture (still at 75°) was poured into a sturdy separatory funnel[51] and allowed to cool for a few hours. The lower layer was carefully drawn off, poured into a very large amount of water and discarded. The crude dinitroethylbenzene in the separatory funnel was shaken with about 500 ml. of cold water. A liter of ether was added to the mixture and the whole was shaken again. After the lower aqueous layer was drawn off and discarded, the remaining ether layer was washed twice with water, four times with 250-ml. portions of saturated sodium bicarbonate solution, and finally twice with water. (The wash water should be neutral at this point.) After the ethereal layer was dried over anhydrous sodium sulfate or anhydrous magnesium sulfate (not calcium chloride), the ether was removed on the steam bath under the pressure of a water aspirator. The dinitro compound was distilled

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[51] If the temperature if allowed to fall much below 75° an emulsion is formed when the mixture is poured into the separatory funnel.

under vacuum from a Claisen type flask and the fraction distilling at 122-123°/0.6 mm. was taken. The yield of 2,4-dinitroethylbenzene by this method was 356 g. (73%) of a yellow oily material whose refractive index was n^{25}_D 1.5659. Other distillation temperatures are 160-163°/6.5 mm. and 150-153°/4.5 mm.

It was possible to increase the yield by allowing the reaction mixture to cool thoroughly, pouring it into a large amount of ice water, extracting with a large amount of ether and then proceeding as before. By this method 443 g. (91%) of the dinitroethylbenzene was obtained. The convenience of the first method, however, probably compensates for the reduced yield.

Analysis: Calculated for $C_8H_8N_2O_4$: C, 49.00; H, 4.11; N, 14.28. Found: C, 49.17, 49.27; H, 4.12, 4.23; N, 14.03, 14.05.

2-Nitro-4-aminoethylbenzene.

(A) Via reduction with hydrogen sulfide and ammonia. A solution of 190 g. (0.98 mole) of 2,4-dinitroethylbenzene in 555 g. of 95% ethanol and 555 g. of concentrated ammonia was treated with gaseous hydrogen sulfide for half an hour and then boiled. After the saturating and boiling had been repeated three times, the reaction-solution was poured onto ice. The resulting precipitate was filtered off and treated with 800 ml. of boiling 3N hydrochloric acid. The hot solution was decanted from the oil, treated with decolorizing

carbon, filtered, and allowed to cool. The crystalline hydrochloride was filtered off, washed with 200 ml. of ice 3N hydrochloric acid, and dried under vacuum. The yield of light tan 2-nitro-4-aminoethylbenzene hydrochloride was 104 g. (52.7%). The free amine was prepared by treating the salt with dilute base and ice. It melted at 45° after several recrystallization from dilute ethanol.

(B) Via reduction with sodium sulfide in methanol. In a 5-l. three-necked flask equipped with a reflux condenser, an efficient stirrer, and a dropping funnel, 360 g. (1.5 moles) of sodium sulfide nonahydrate and 126 g. (1.5 moles) of sodium bicarbonate were dissolved in 600 ml. of warm distilled water. The stirrer was started and a liter of methanol was rapidly added. A white precipitate of inorganic salts formed during the addition of the methanol. The mixture was heated to reflux, whereupon a solution of 98 g. (0.5 mole) of 2,4-dinitroethylbenzene in 500 ml. of methanol was slowly added through the dropping funnel over a period of about two hours. During the addition, the reaction mixture turned a deep red. After the dinitro compound had all been added, the refluxing was continued for half an hour. An 800-ml. portion of water was then added and the methanol was distilled off. The dark mixture remaining in the flask was extracted with four 500-ml. portions of benzene. The benzene layers were combined and washed three times with 500 ml. of water. The benzene solution was then stirred with 10 g. of decolorizing carbon

and filtered. The pale yellow solution was placed in a three-necked flask equipped with a glass stirrer and an azeotrope trap. With the aid of the trap, the water was removed from the solution. After the solution cooled, dry hydrogen chloride was bubbled in until precipitation was complete. The mixture was filtered through a sintered glass funnel and the precipitate was dried in a vacuum desiccator under constant suction. The very pale yellow 2-nitro-4-aminoethylbenzene hydrochloride weighed 80 g. (79%). The hydrochloride crystallized in very light colored plates from hot butyl alcohol to which enough 60-80° petroleum ether was added to produce cloudiness. That the product was relatively free from isomer was demonstrated by the melting point of the free base and the acetyl derivative which were prepared from the hydrochloride. The free base was obtained by treatment of the hydrochloride with dilute alkali and ice. The yellow-orange amine was filtered off and recrystallized from dilute alcohol. The product melted sharply at 45°. (Cline and Reid[47] found that the melting point of the substantially isomer free amine was 45°.) The amine was also distilled at 145-147°/3.5 mm. and it crystallized upon standing as large yellow-orange plates melting at 45°. The acetyl derivative of 2-nitro-4-aminoethylbenzene was prepared from the hydrochloride by treatment with acetic anhydride and base.[52] It

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[52]Shriner and Fuson, "The Systematic Identification of Organic Compounds", Second Edition, John Wiley and Sons, Inc., New York, 1940, p. 146.

melted sharply at 110.5-111° after a single recrystallization from dilute alcohol. (Cline and Reid found that the melting point of the substantially isomer-free acetyl derivative was 110°.)

Analysis: Calculated for $C_8H_{10}N_2O_2 \cdot HCl$: C, 47.41; H, 5.47; N, 13.83. Found: C, 47.38, 47.57; H, 5.74, 5.74; N, 13.87, 13.97.

2-Nitro-4-chloroethylbenzene.

(A) Via diazotization in aqueous medium. Eighty-one grams (0.4 mole) of 2-nitro-4-aminoethylbenzene was dissolved in a mixture of 335 ml. of hot water and 16 ml. of concentrated hydrochloric acid. The solution was stirred and cooled rapidly to a temperature slightly below 4°. (The amine hydrochloride crystallized out during the cooling.) A solution of 28.8 g. (0.42 mole) of sodium nitrite in 70 ml. of water was added dropwise to the stirred suspension of amine hydrochloride at such a rate as to maintain the temperature at slightly below 4°. The addition of nitrite was stopped when the red diazonium salt solution produced a blue color when tested on starch iodide paper five minutes after the last addition of nitrite. The cold diazonium salt solution was used directly in the next step.

To a solution of 125 g. (0.5 mole) of cupric sulfate pentahydrate and 40 g. (0.67 mole) of sodium chloride in 400 ml. of water at 65° was added 26.5 g. (.25 mole) of sodium bisulfite dissolved in a minimum amount of water. After the mixture cooled, the cuprous chloride was filtered off, washed with

water and suspended in a solution composed of 150 ml. of concentrated hydrochloric acid and 200 ml. of water. The cold diazonium solution was added to the stirred cuprous chloride suspension at such a rate as to maintain the temperature at 25-30°. The mixture was then heated on a steam bath for 15 minutes. After cooling, the mixture was diluted with an equal volume of water and the oil was removed by means of a separatory funnel. The aqueous material was extracted with 200 ml. of benzene and the extract was combined with the oil. The benzene solution was washed with water and 10% sodium bicarbonate solution. After the benzene was removed, vacuum distillation of the residue afforded 34 g. (46%) of 2-nitro-4-chloroethylbenzene, a pale yellow liquid which distilled at 133-135°/20 mm. and whose refractive index was n^{20}_D 1.5515.

(B) Via diazotization of acetic acid medium. To 6 l. of glacial acetic acid contained in a 12-l. three-necked flask equipped with a glass paddle stirrer, a reflux condenser, and a dropping funnel was added 405 g. (2 moles) of 2-nitro-4-aminoethylbenzene hydrochloride (or 332 g. of the free base). The acid for diazotization was prepared by slowly dissolving 254 g. (3.7 moles) of sodium nitrite in 1.8 l. of concentrated sulfuric acid. (Although this was an excess of nitrite, it was not all used.) The mixed acid was slowly added to the stirred amine-acetic acid mixture at such a rate as to maintain

the temperature below 15°. The solid gradually dissolved and the mixture turned a deep red. (When the nitrite solution clogged the opening in the dropping funnel due to precipitation of sodium sulfate, it was helped through the opening with a piece of stiff nichrome wire.) The completeness of diazotization was determined by adding a few drops of the mixture to a few drops of water and testing this solution with starch iodide paper for an instantaneous blue color. At least half an hour was allowed between tests with no addition of nitrite before the diazotization was considered complete. When the diazotization was finally complete, the flask was surrounded by an ice bath until further use.

To a solution of 750 g. (3 moles) of cupric sulfate and 240 g. (4.1 moles) of sodium chloride in 2.2 l. of water at 65° was added a solution of 190 g. (1.5 moles) of sodium bisulfite and 108 g. of sodium hydroxide in 1.2 l. of water. After the mixture cooled, the cuprous chloride was filtered off, washed with water and suspended in 3.75 l. of concentrated hydrochloric acid. The cold diazonium solution was added to the rapidly stirred cuprous chloride solution by means of a dropping funnel. After standing over-night, the mixture was poured into an equal volume of water and extracted with benzene. The dilution and extraction was conveniently accomplished by placing 3 l. of water in each of three

separatory funnels and adding one third of the reaction mixture to each funnel. The mixture in each funnel was extracted twice with 1 l. of benzene and one last liter of benzene was passed through all three funnels. The combined benzene extract was washed with water, sodium carbonate solution and then water again. The solution was filtered, and the benzene was removed under the pressure of a water aspirator. Vacuum distillation of the residue afforded 232 g. (63%) of 2-nitro-4-chloroethylbenzene, a pale yellow liquid which distilled at 133-135°/20 mm. and whose refractive index was n^{20}_D 1.5515.

Analysis: Calculated for $C_8H_8NO_2Cl$: C, 51.77; H, 4.35; N, 7.55. Found: C, 51.94, 52.05; H, 4.50, 4.70; N, 7.72, 7.70.

2-Nitro-4-chloroacetophenone via oximation.

Tertiary butyl nitrite. A solution of 76 g. of sodium nitrite in 300 ml. of water was placed in a 1-l. three-necked flask equipped with a glass stirrer, a thermometer, and a dropping funnel whose tip reached to the bottom of the flask. The solution was cooled below 0° with ice and salt. A solution of composed 72 g. (0.97 mole) of tertiary butyl alcohol, 27.2 ml. of concentrated sulfuric acid, and 20 ml. of water was also cooled below 0° and then slowly added to the nitrite solution by means of the dropping funnel. The reaction mixture was maintained at 0° during the entire addition. After the addition was completed, the mixture was allowed to stand until two distinct layers were formed. Both

layers were carefully decanted from the precipitate of sodium sulfate and placed in a separatory funnel. After the lower aqueous layer was drawn off and discarded, the remaining layer was washed with several 10-ml. portions of a solution composed of 1 g. of sodium bicarbonate, 12.5 g. of sodium chloride, and 50 ml. of water. The pale yellow liquid was dried over anhydrous sodium sulfate and distilled to give 76.5 g. (76%) of tertiary butyl nitrite (b.p. 65-66°). The compound was kept in an ice-box and it was used within 24 hours of its preparation.

Oximation of 2-nitro-4-chloroethylbenzene. Five grams (0.22 mole) of sodium wire was added to 1-l. of dry tertiary butyl alcohol which was contained in a 2-l. flask equipped with a stirrer and a condenser protected by a calcium chloride tube. After the wire was dissolved with the aid of heat and stirring, 750 ml. of the sovent was removed by distillation. When the remaining white paste cooled to room temperature, 37 g. (0.20 mole) of 2-nitro-4-chloroethylbenzene and 22.5 g. of tertiary butyl nitrite were added to the flask. The reaction mixture was stirred over-night at room temperature, diluted with 200 ml. of water and finally subjected to a steam distillation. When all of the butanol had passed over, the receiver was changed and a pale oil appeared in the steam distillate. The oil was extracted with benzene. Subsequent removal of the benzene

and distillation of the oil afforded 6.0 g. of starting compound.

The residue remaining in the flask after the steam distillation consisted of a brown solution and an oil. The brown solution was decanted and the oil was leached with two 100-ml. portions of 25% sodium hydroxide solution. The alkaline leachings and the original brown solution were combined and saturated with carbon dioxide (dry ice). The precipitate was filtered off, washed with water and recrystallized from dilute alcohol. By this method 16.5 g. of 2-nitro-4-chloroacetophenone was obtained in the form of white needles melting at 153.2-153.8°. This quantity represented a yield of 39.4% of the calculated amount, or a yield of 45% based on recovered starting material. The oxime obtained by this method did not depress the melting point of the sample obtained by the oximation of the ketone which was prepared by the oxidation of 2-nitro-4-chloroethylbenzene.

Hydrolysis of 2-nitro-4-chloroacetophenone oxime. A mixture of 16.5 g. (0.077 mole) of the oxime prepared in the preceeding paragraph, 20 ml. of water, and 10 ml. of concentrated sulfuric acid was stirred for three hours under reflux. After cooling, the reaction mixture was extracted with several portions of ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the ether and recrystallization of the residue from dilute alcohol afforded 10.5 g.

(68.5%) of 2-nitro-4-chloroacetophenone melting at 55.5-55.7°. The over-all yield from the ethylbenzene derivative was about 28%. The ketone made by this method did not depress the melting point of the ketone prepared by the oxidation of 2-nitro-4-chloroethylbenzene.

2-Nitro-4-chloroacetophenone via direct oxidation.

In a three-necked flask equipped with a thermometer, a glass stirrer, a condenser and a dropping funnel were placed 70 g. (0.378 mole) of 2-nitro-4-chloroethylbenzene, 590 ml. of glacial acetic acid, and 580 ml. of acetic anhydride. After the stirred solution was cooled below 15° with an ice bath, 88 ml. of concentrated sulfuric acid was slowly added through the dropping funnel. When the addition of the acid was complete, the solution was cooled to 5° and 104 g. of chromium trioxide was added in small portions over a period of an hour. After twenty additional minutes of stirring at 5°, the green solution was slowly warmed to 35° and stirred at this temperature for fifteen minutes. At this time a precipitation occurred and stirring was stopped. The green mixture was poured onto 2 kg. of ice and the dark green residue in the flask was rinsed into the mixture with some cold water. After standing for several hours, the mixture was extracted twice with 1 l. of ether-benzene solution (1:1). The extract was washed with several portions of water, then with 2% sodium carbonate solution and finally with water again. The solvent was removed and

the residue was distilled under vacuum. The first fraction distilled at 78-80°/2 mm. and afforded 7.4 g. of starting material. The second fraction distilled at 118-120°/1 mm. and afforded 37 g. (65%) of 2-nitro-4-chloroacetophenone which subsequently crystallized in the receiver. Recrystallization of the ketone from dilute ethanol gave colorless needles, which melted at 55.5-55.7°. (Atkinson and Simpson,[41] 55-56°; Leonard and Boyd,[40] 44°.) The ketone is soluble in alcohol, ether, and benzene; insoluble in petroleum ether.

Analysis: Calculated for $C_8H_6ClNO_3$: C, 48.54; H, 3.03; N, 7.02. Found: C, 48.45, 48.24; H, 3.21, 3.20; N, 7.13,7.06.

2-Nitro-4-chloroacetophenone 2,4-dinitrophenylhydrazone.

One-tenth gram of 2-nitro-4-chloroacetophenone was added to 15 ml. of a reagent prepared from 1.0 g. of 2,4-dinitrophenylhydrazine, 1.5 ml. of concentrated hydrochloric acid, and 100 ml. of methanol. After the solution had been warmed for a few minutes, 7.5 ml. of 6N hydrochloric acid was added. The copious yellow precipitate was filtered off and recrystallized twice frommethanol. The compound crystallized in the form of yellow plates which melted at 193.4-193.6°.

Analysis: Calculated for $C_{14}H_{10}N_5O_6Cl$: C, 44.28; H, 2.66; N, 18.45. Found: C, 44.46, 44.47; H, 3.22, 3.04; N, 18.77, 18.44.

2-Nitro-4-chloroacetophenone oxime.

A sample of the ketone produced via the oxidation of 2-nitro-4-chloroethylbenzene was treated with hydroxylamine

hydrochloride, alkali, and alcohol.[53] Several recrystallizations of the precipitate from benzene-petroleum ether (60-80°) afforded the oxime in the form of colorless plates which melted at 153.2-153.4°. The oxime prepared in this manner did not depress the melting point of the compound prepared by the oximation of 2-nitro-4-chloroethylbenzene.

Analysis: Calculated for $C_8H_7ClN_2O_3$: C, 44.77, H, 3.29; N, 13.06. Found: C, 44.83, 44.67; H, 3.41, 3.55; N, 13.27, 13.24.

2-Amino-4-chloroacetophenone.

A solution of 17.3 g. (0.087 mole) of 2-nitro-4-chloroacetophenone in 97 ml. of 95% alcohol was heated in a 500-ml. flask equipped with a glass stirrer, a condenser, and a dropping funnel. When refluxing commenced, a solution composed of 62 g. (0.275 mole) of stannous chloride dihydrate, 60 ml. of concentrated hydrochloric acid and 69 ml. of 95% alcohol was gradually added to the contents of the flask. After the addition was complete (45 minutes), the refluxing was continued for an hour and a half whereupon the condenser was turned down and the alcohol removed. The amino ketone was isolated in two ways:

(a) Upon cooling the above solution, 18.8 g. of the tin complex precipitated in the form of course white needles.

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[53]Reference 52, Procedure 34B.

The precipitate was filtered off, washed with ice cold hydrochloric acid (1:1), and finally stirred for two hours with a solution of 11 g. of sodium hydroxide in 11 ml. of water. Recrystallization of the new precipitate gave 9.7 g. (66.5%) of 2-amino-4-chloroacetophenone. The amino ketone crystallized in the form of white needles which melted at 92-93° (Atkinson and Simpson[41], 91-93°).

(b) The solution from which the alcohol had been removed was treated with 50% sodium hydroxide until a pH of about 12 was reached and then the mixture was subjected to a steam distillation. The amine steam distilled and crystallized readily in the distillate. Filtration of the distillate and recrystallization of the precipitate from dilute alcohol afforded 11.6 g. (79.5%) of 2-amino-4-chloroacetophenone (m.p. 92-93°).

2-Acetamido-4-chloroacetophenone.

2-Amino-4-chloroacetophenone and five times its weight of acetic anhydride were heated under reflux conditions for fifteen minutes. The solution was cooled, poured into ice water, and allowed to come to room temperature. The precipitate was filtered off, washed thoroughly with water and recrystallized from dilute alcohol. The acetyl derivative crystallized as white needles which melted at 152-153° (Leonard and Boyd[40], 152-153°).

2-Formamido-4-chloroacetophenone.

A mixture of 16.3 g. (0.0825 mole) of 2-amino-4-chloroacetophenone and 80 g. of 90% formic acid was heated under reflux for ten minutes. The solution was cooled and poured onto 100 ml. of ice water. The white precipitate was filtered off and recrystallized from dilute alcohol. The yield was 17.2 g. (91%) of 2-formamido-4-chloroacetophenone in the form of white needles which melted at 124.2-124.8°.

Analysis: Calculated for $C_9H_8ClNO_2$: C, 54.70, H, 4.08; N, 7.02. Found: C, 54.90, 55.06; H, 4.11, 4.12; N, 7.22, 7.19.

2,4-Dinitrophenylhydrazone of 2-amino-4-chloroacetophenone and its formyl derivative.

Two-tenths gram of 2-formamino-4-chloroacetophenone was added to 15 ml. of a reagent prepared from 1.0 g. of 2,4-dinitrophenylhydrazine, 1.5 ml. of concentrated hydrochloric acid, and 100 ml. of methanol. After the ketone was dissolved by gentle warming, the solution was cooled in an ice bath, diluted by the addition of 10 ml. of 6N hydrochloric acid, and finally allowed to stand for several hours. The copious precipitate which subsequently formed was filtered off and washed with 50% methanol. (The precipitate changed from a bright yellow to a deep red color during the washing procedure). Several recrystallizations of the compound from toluene-petroleum ether mixture afforded very fine red crystals which melted at 257-258°. Elementary analysis of the compound

revealed that the formyl group had been lost during the reaction as the analysis agreed very well with the calculated values for 2-amino-4-chloroacetophenone 2,4-dinitrophenylhydrazone.

Analysis: Calculated for $C_{14}H_{12}ClN_5O_4$: C, 48.08; H, 3.46; N, 20.03. Found: C, 47.85, 47.95; H, 3.64, 3.69; N, 20.00, 19.70.

A small sample of the above compound and 20 ml. of 90% formic acid were heated under reflux for ten minutes. The solution was cooled, poured into an equal volume of ice water and allowed to stand for an hour. The precipitate was filtered off and washed with ice cold water. Several recrystallizations of the precipitate from a toluene-petroleum ether mixture afforded 2-formamido-4-chloroacetophenone 2,4-dinitrophenylhydrazone in the form of fine orange-red crystals which decomposed at 190-191°.

Analysis: Calculated for $C_{15}H_{12}ClN_5O_5$: C, 47.70; H, 3.23; N, 18.54. Found: C, 48.07, 48.09; H, 3.42, 3.47; N, 18.57, 18.76.

4-Hydroxy-7-chloroquinoline.

A mixture of 26.7 g. (0.135 mole) of 2-formamido-4-chloroacetophenone, 1.6 ml. of water, and 150 ml. of ethanol was heated in a 2-l. flask equipped with a condenser and a stirrer. When the reflux temperature was reached, a solution of 9.6 g. of sodium hydroxide in 20 ml. of water was added to

the flask. The stirring and refluxing was continued for three hours and then the contents of the flask were subjected to a steam distillation. Filtration of the cooled steam distillate afforded 16.1 g. (70%) of 2-amino-4-chloroacetophenone (m.p. 92-93°).

The material remaining in the distillation flask was reduced to a volume of 50 ml. and filtered. The precipitate was recrystallized from dilute alcohol and afforded 1.8 g. (8.8%) of lemon yellow cottony fibers (m.p. 170-171°) which by analogy with Camps[7] compound is believed to be 2-(2-amino-4-chlorophenyl-4-methylquinoline. The filtrate was treated with small drops of concentrated hydrochloric acid until a pH of 8 was reached. Filtration and recrystallization of the resulting precipitate from 2 l. of water afforded 4.6 g. of 4-hydroxy-7-chloroquinoline in the form of long white fibers which melted at 280-282° (Surrey and Hammer[3] 277-279°; Price and Roberts[30] 270-272°). The yield of hydroxyquinoline corresponded to 19.2% of the calculated quantity and 89.2% of the quantity of amino ketone consumed. The compound prepared in this manner did not depress the melting point of a sample prepared by the hydrolysis of an authentic sample of 4,7-dichloroquinoline.

Analysis: Calculated for C_9H_6ClNO: C, 60.18; H, 3.37; N, 7.81. Found: C, 60.22, 60.12; H, 3.36, 3.36; N, 7.91, 7.80.

2-(2-Amino-4-chlorophenyl)-4-methyl-7-chloroquinoline.

(a) Two grams of sodium wire was added to 250 ml. of dry tertiary butyl alcohol which was contained in a 1-l. flask equipped with a stirrer and a condenser which was protected by a calcium chloride tube. After the wire was dissolved with the aid of heat and stirring, the condenser was turned down and 100 ml. of the alcohol was removed. The condenser was replaced and a solution of 6.0 g. (0.03 mole) of 2-formamido-4-chloroacetophenone in 300 ml. of dry tertiary butyl alcohol was added. The solution was stirred for one hour under reflux conditions whereupon the condenser was turned down again and an additional 350 ml. of alcohol was removed by distillation. When this amount of alcohol was removed a copious yellow solid precipitated from the reaction solution. The reaction mix was cooled and diluted with an equal volume of water. When the precipitate was filtered off and recrystallized from dilute alcohol, 4.0 g. (86.5%) of yellow cottony fibers of 2-(2-amino-4-chlorophenyl)-4-methly-7-chloroquinoline was obtained. The compound melted at 170-171° and did not depress the melting point of the by-product of the 4-hydroxy-7-chloroquinoline synthesis.

(b) To a solution of 6.0 g. (0.03 mole) of 2-formamido-4-chloroacetophenone in 250 ml. of dry dioxane, contained in a flask equipped with a stirrer and a condenser which was protected by a calcium chloride tube, was added 0.9 g. (0.036 mole) of sodium hydride. The mixture was stirred and

heated under reflux conditions for one hour. After the solution had cooled, 10 ml. of water was very carefully added dropwise. The dioxane was removed by steam distillation and the yellow precipitate was filtered off and recrystallized from dilute alcohol. By this reaction 2.7 g. (58.5%) of the same yellow lepidine was obtained. The compound did not depress the melting point of the compound produced in (a). The steam distillate afforded a small amount of the hydrolyzed starting material.

Analysis: Calculated for $C_{16}H_{12}Cl_2N_2$: C, 63.38; H, 3.99; N, 9.23. Found: C, 63.34, 63.30; H, 4.20, 4.23; N, 9.17, 9.22.

2-(2-Formamido-4-chlorophenyl)-4-methyl-7-chloroquinoline.

2-(2-Amino-4-chlorophenyl)-4-methyl-7-chloroquinoline and five times its weight of 90% formic acid were heated under reflux conditions for fifteen minutes. The solution was cooled, poured into ice water and allowed to come to room temperature. The precipitate was filtered off, washed thoroughly with water, and recrystallized from dilute alcohol. The formyl derivative crystallized as white cottony fibers which melted at 233-234°.

Analysis: Calculated for $C_{17}H_{12}Cl_2N_2O$: C, 61.64; H, 3.66; N, 8.46. Found: C, 61.69, 61.58; H, 3.62, 3.78; N, 8.42, 8.23.

2-(2-Acetamido-4-chlorophenyl)-4-methyl-7-chloroquinoline.

2-(2-Amino-4-chlorophenyl)-4-methyl-7-chloroquinoline and five times its weight of acetic anhydride were heated under reflux conditions for fifteen minutes. The solution was cooled, poured into ice water, and allowed to come to room temperature. The precipitate was filtered off, washed thoroughly with water, and recrystallized from dilute alcohol. The acetyl derivative crystallized as white cottony fibers which melted at 244-245°.

Analysis: Calculated for $C_{18}H_{14}Cl_2N_2O$: C, 62.62; H, 4.12; N, 8.12. Found: C, 62.67, 62.94; H, 4.16, 4.21; N, 8.11, 8.31.

Hydrolysis of 4,7-dichloroquinoline.

A mixture of 3 g. of an authentic sample of 4,7-dichloroquinoline (Winthrop), 12 ml. of distilled water, and 2 drops of 25% sulfuric acid was sealed in a glass tube which had about three times the volume of the mixture. The tube was maintained at a temperature of 150° for six hours in a metal bomb partially filled with water. When the bomb cooled, the tube was removed and the contents was dissolved in 20 ml. of 3N sodium hydroxide. The very small amount of insoluble material was removed by filtration and the filtrate was brought to a pH of 8 with 3N hydrochloric acid. The copious white precipitate was filtered off and recrystallized from about 1.5 l. of water. The yield was 2.7 g. (98%) of 4-hydroxy-7-chloroquinoline in the form of long white fibers.

The compound obtained in this manner melted at 280-282° and did not depress the melting point of the 4-hydroxy-7-chloroquinoline prepared by cyclizing 2-formamido-4-chloroacetophenone.

4,7-Dichloroquinoline.

A sample of the 4-hydroxy-7-chloroquinoline prepared by cyclizing 2-formamido-4-chloroacetophenone was converted to 4,7-dichloroquinoline according to the method of Surrey and Hammer.[3] A mixture of 17 g. (0.95 mole) of 4-hydroxy-7-chloroquinoline and 55 ml. of phosphorous oxychloride was heated under reflux for two hours. The excess oxychloride was distilled off under reduced pressure and the residue was poured onto ice. The solution was made alkaline with ammonium hydroxide and then extracted with methylene chloride. After the extract was dried over magnesium sulfate, removal of the solvent and vacuum distillation of the residue afforded 15.1 g. (81%) of 4,7-dichloroquinoline (b.p. 150-152°/12 mm.). The distillate crystallized in the receiver and a recrystallization from 80% ethanol afforded the dichloro compound in the form of long white needles which melted at 85.2-85.4° (Surrey and Hammer[3], 83.5-84.5°). The compound prepared in this manner did not depress the melting point of an authentic sample (Winthrop) of 4,7-dichloroquinoline.

Analysis: Calculated for $C_9H_5Cl_2N$: C, 54.58; H, 2.55; N, 7.07. Found: C, 54.61, 54.60; H, 2.62, 2.65; N, 7.00, 7.07.