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Some Reactions of 4-Chlorocinnoline

F. H. Kruse

Kruse — Some Reactions of 4-Chlorocinnoline

SOME REACTIONS OF 4-CHLOROCINNOLINE

By

F. H. Kruse

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I. INTRODUCTION

Until recently the chemistry of the cinnoline ring system has not been investigated extensively. The late work of Simpson, Schofield and co-workers[1] has shown some of the possibilities of the cinnoline ring system. However, the difficulty in synthesis of the intermediates leading to the cinnolines has been a principal deterring factor in their development. The discovery of the cinnoline ring dates back to 1883[2] and the preparation of 4-chlorocinnoline first took place in 1897 as reported by Busch and Rast[3].

Studies made on 4-chlorocinnoline by Busch, Rast and others indicated a high order of reactivity of the chlorine atom in the 4-position; similar to that of the chlorine atom in 4-chloroquinoline. Many of the reactions reported for 4-chloroquinoline have been shown to be equally successful with 4-chlorocinnoline. But, the formation of 4-cinnolyl organo-metallic compounds from 4-chlorocinnoline and the condensation of 4-chlorocinnoline with sodio salts of appropriate compounds have not been studied.

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[1]Simpson, Schofield, et al. A series of papers on cinnolines, the first: J. Chem. Soc. 353 (1942). (See Bibliography)

[2]Richter, Ber. 16, 677 (1883)

[3]Busch and Rast, ibid., 30, 521 (1897)

A. THE PROBLEM

This problem involves the preparation of 4-chlorocinnoline by the method of Borsche and Herbert[4] and Busch and Rast[3], and the study of further replacement reactions of the chlorine atom in the 4-position. The problem can be subdivided into two sections: (1) the preparation of the 4-cinnolyl Grignard reagent and the corresponding lithium compound and (2) the study of some condensation reactions of 4-chlorocinnoline.

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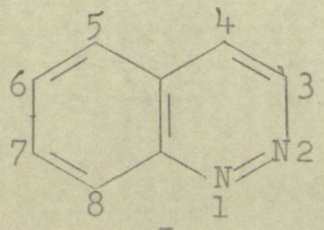
[4] Borsche and Herbert, Ann. 546, 293 (1941); C. A. 35, 4382[1] (1941)

II. REVIEW OF THE LITERATURE

A. Cinnolines in General

Cinnoline, (I), is an aromatic binuclear nitrogen heterocycle containing two adjacent nitrogen atoms. It can be described as a benzene and a pyridazine ring, (II), condensed in the ortho position. The cinnoline ring is also closely related to quinoline, whose numbering system it follows. It is the least well known member of the family of benzodiazines; the others being phthalazine, (III), quinoxaline, (IV), and quinazoline, (V).



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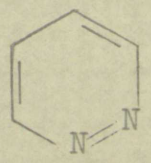

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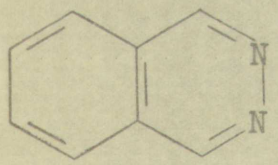

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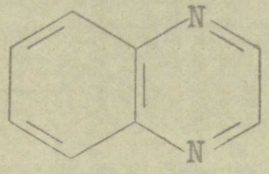

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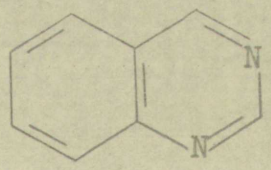
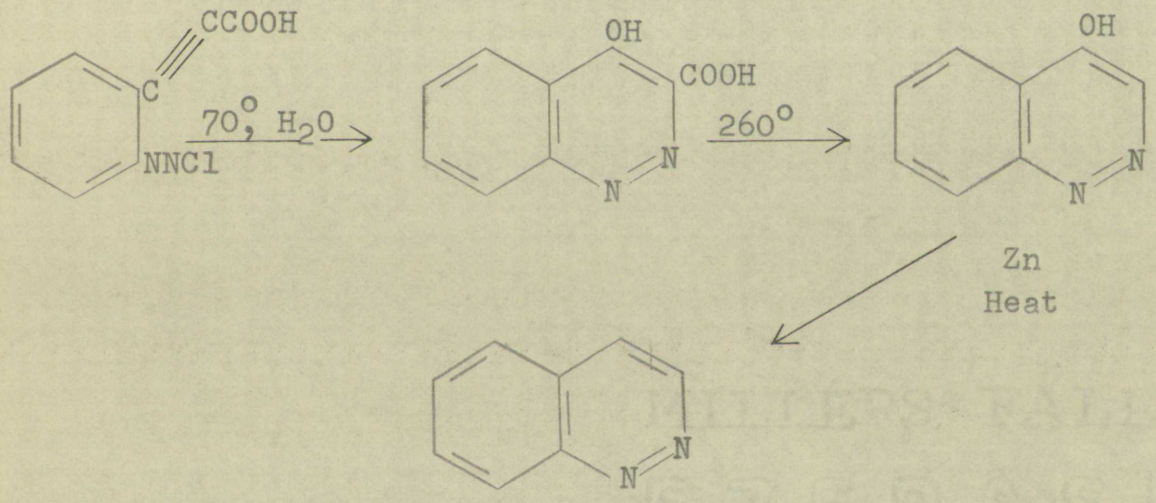


V

The reason that cinnoline and its derivatives are not well known is no doubt the lack of a convenient method of preparation in contrast to the isomeric phthalazines which

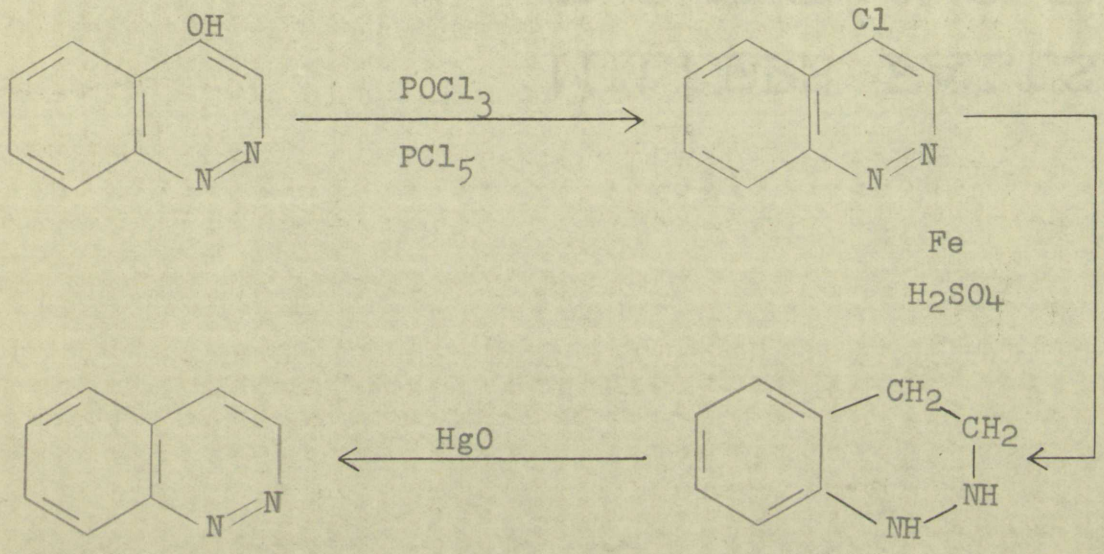
are readily accessible and have in consequence been widely studied. Presently, there are three general methods of preparation and a number of special reactions yielding various cinnolines.

The first synthesis of a cinnoline was reported by von Richter in 1883[2], while studying the reactions of diazotized o-aminophenylpropiolic acid. He heated the diazonium salt in water at 70° and on cooling obtained crystals of 4-hydroxycinnoline-3-carboxylic acid in nearly quantitative yield.



When the acid was heated above the melting point, carbon dioxide evolved and a good yield of 4-hydroxycinnoline resulted. Distillation of the 4-hydroxycinnoline with zinc dust yielded a small amount of basic oil which was not characterized, but was assumed to be cinnoline. This synthesis

of 4-hydroxycinnoline was later repeated by Busch and Klett[5]. Five years later Busch and Rast[3] successfully prepared free cinnoline via 4-hydroxycinnoline and 4-chloro-cinnoline:



The mechanism of the Richter reaction has been recently investigated by Schofield and Swain[6].

One of the more promising cinnoline syntheses, known as the Widman-Stoermer reaction, involves the diazotation of o-aminoaryl ethylenes, followed by cyclization[7,8]:

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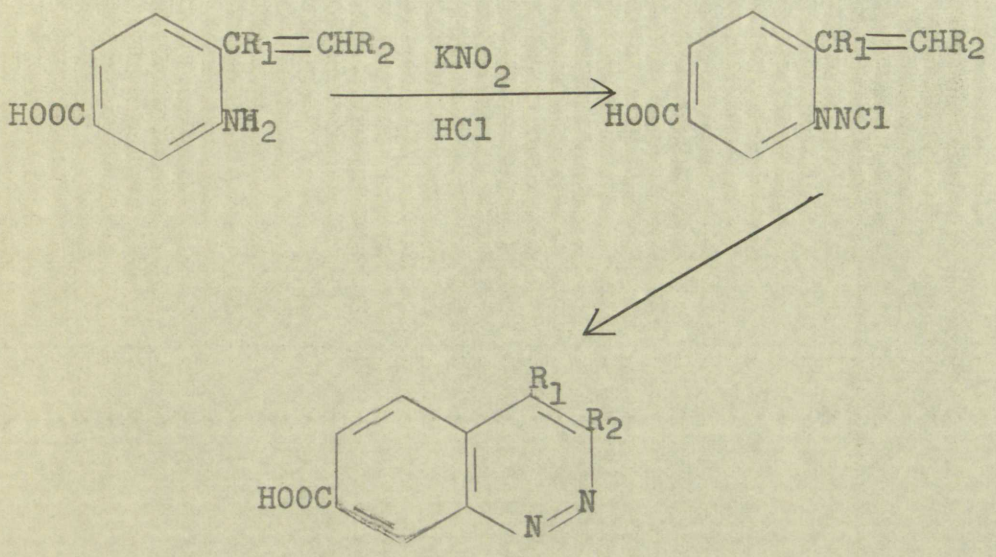
[5]Busch and Klett, Ber. 25, 2847 (1892)

[6]Schofield and Swain, J. Chem. Soc. 2393 (1949)

[7]Widman, Ber. 17, 722 (1884)

[8]Widman, ibid., 42, 4216 (1909)



This reaction has been studied and extended by Stoermer[9,10] and Simpson[11,12,13] to prepare a large number of substituted cinnolines. The groups R_1 and R_2 have a strong directing effect on the course of the reaction. Simpson has correlated recent and earlier experiments to summarize the effects of these groups on ring closure.

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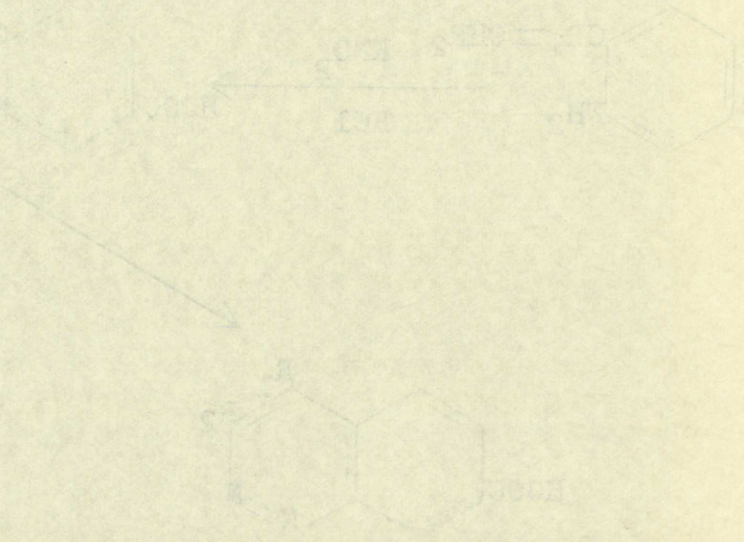
[9]Stoermer and Fincke, Ber. 42, 3115 (1909)

[10]Stoermer and Gaus, ibid., 45, 3104 (1912)

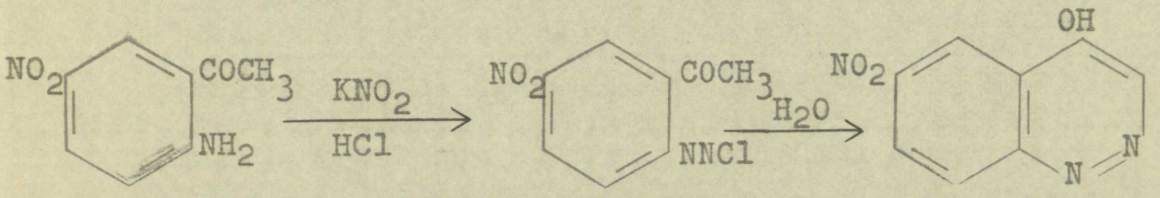
[11]Simpson and Stephenson, J. Chem. Soc. 353 (1942)

[12]Simpson, ibid., 447 (1943)

[13]Simpson and Schofield, ibid., 520 (1945)



A third approach was discovered by Borsche and Herbert[4] while studying the reactions of o-substituted acetophenones. If an o-aminoacetophenone is diazotized and the diazonium salt allowed to stand, or hydrolyzed at 60-70°, a 4-hydroxycinnoline is formed:



Koelsch[14] showed that other o-amino aryl-alkyl ketones could be employed in this synthesis, as did Leonard and Boyd[15] and Keneford and Simpson[16] in the preparation of a number of 4-hydroxy-3-substituted cinnolines. Simpson has also discussed the mechanism of this reaction and summarized the effect of other groups on the phenyl ring of the ketone[17].

A number of less important, or 'special', methods have been reported. In most of these the formation of the cinnoline was incidental to the main purpose of the investi-

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[14]Koelsch, J. Org. Chem. 8, 295 (1943)

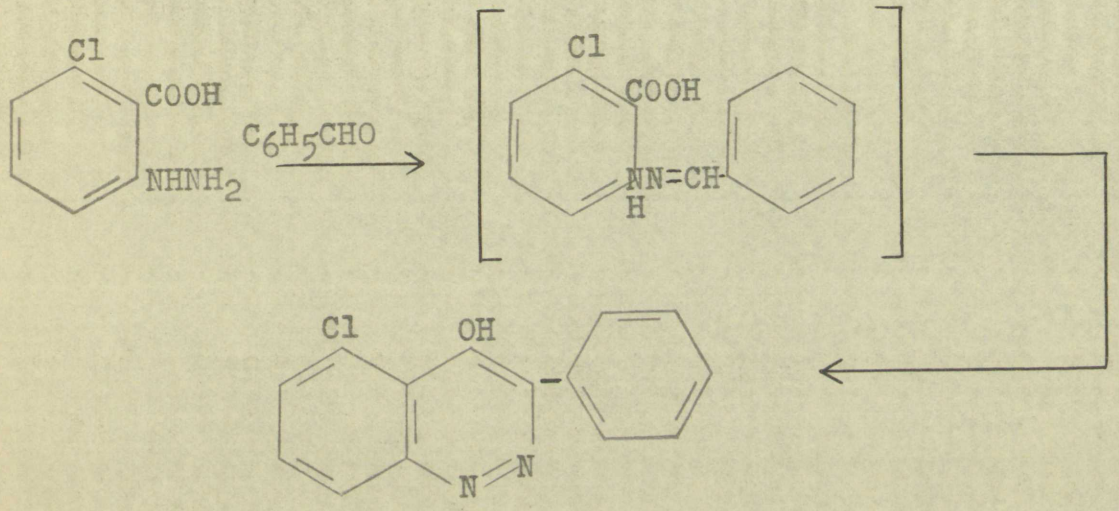
[15]Leonard and Boyd, ibid., 11, 419 (1946)

[16]Keneford and Simpson, J. Chem. Soc. 2318 (1948)

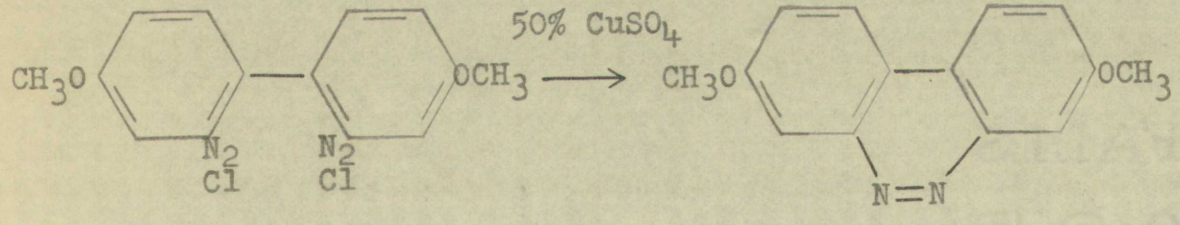
[17]Simpson and Schofield, ibid., 1170 (1948)

gation. The more important are as follows:

A. From hydrazines and substituted hydrazines. Pfannstiel and Janecke[18] prepared 5-chloro-4-hydroxy-3-phenyl cinnoline:



B. From diazo compounds. Representative of this method of synthesis is the reaction resulting in 3,8-dimethoxybenzo(c)cinnoline[19]:



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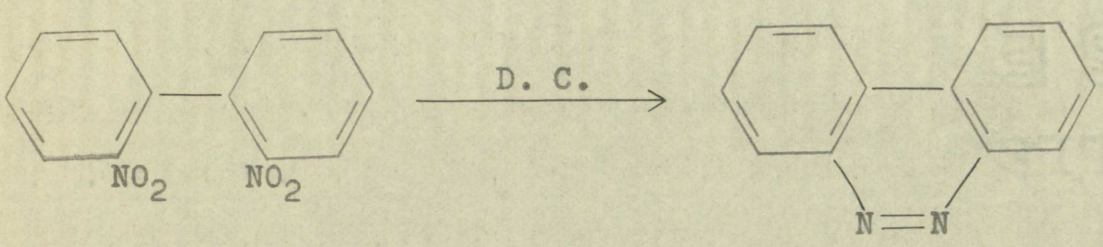
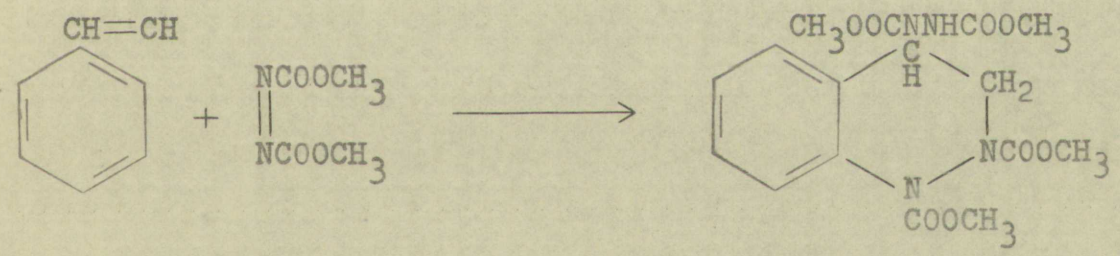
[18]Pfannstiel and Janecke, Ber. 75B, 1096 (1942)

[19]Hata, Tatematsu and Kubota, Bul. Chem. Soc. Japan 10, 425 (1935); C.A. 30, 10563 (1936).

C. By reduction of 2,2'-dinitrobiphenyls. The electrolytic reduction of 2,2'-dinitrobiphenyl gave a 95% yield of benzo(c)cinnoline[20].



D. From styrene by a Diels-Alder condensation. Only one example of this synthesis is known, that being the formation of the following tetrahydro cinnoline from the condensation of styrene and dimethyl azodicarboxylate[21].



The fine review article by Leonard[22] lists more

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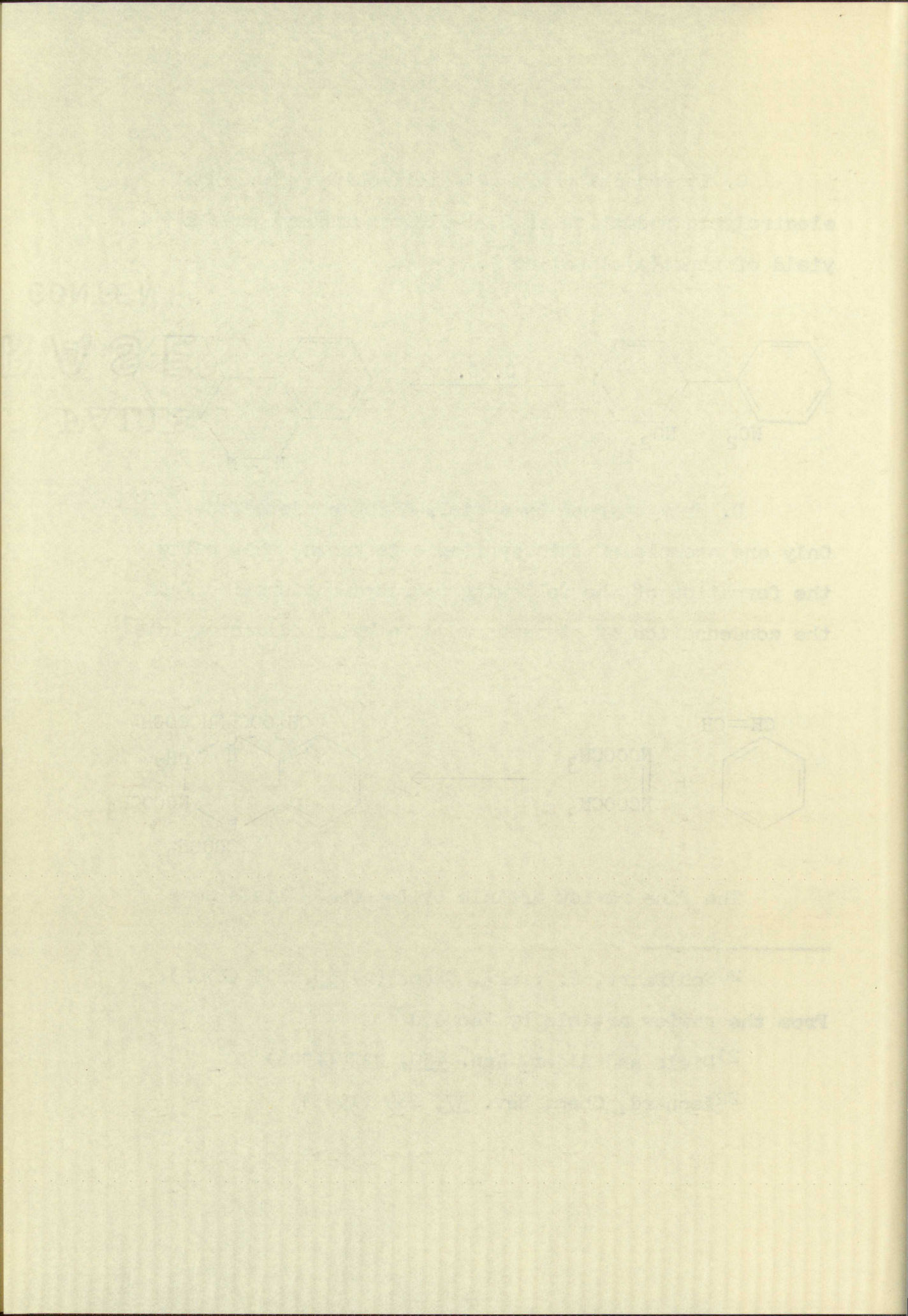
[20]Wohlfahrt, J. prakt. Chem. (2) 65, 295 (1902); From the review article by Leonard[22]

[21]Diels and Alder, Ann. 450, 237 (1926)

[22]Leonard, Chem. Rev. 37, 269 (1945)



examples of the preceding special preparations and Leonard, Boyd and Herbrandson[23] report a number of attempted syntheses of cinnolines.

Practically all cinnolines are solids, cinnoline itself melting at 39°. Cinnolines in general are described as colored compounds; but, little work on their absorption spectra has been done[24,25]. Calderbank and LeFevre[25] have carried out dipole moment studies on benzo(c)cinnoline and benzo(c)cinnoline oxide.

The following chemical properties of the cinnolines will be discussed in the order: salt formation, oxidation, reduction, substitution, replacement, and miscellaneous.

Cinnoline is a strong base (though not as strong as quinoline or quinazoline - see Simpson[26] and Albert[27]) and forms stable salts with strong acids. It forms an addition compound with methyl iodide[3]. Most substituted cinnolines react similarly.

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[23]Leonard, Boyd and Herbrandson, J. Org. Chem. 12, 47 (1947)

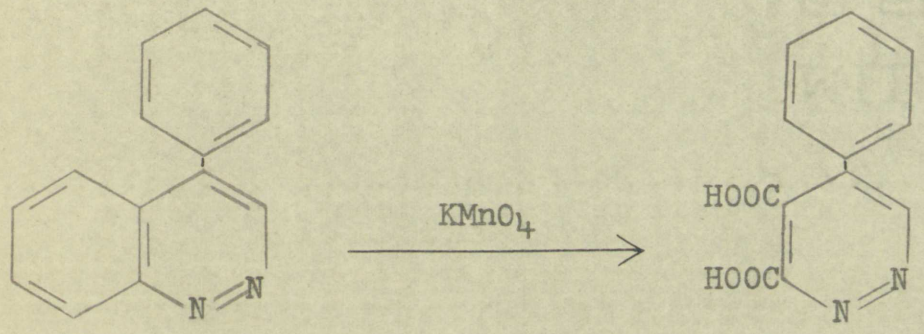
[24]Ramart-Lucas and Biquard, Bull. Soc. Chim. (5) 3, 430 (1936); C.A. 30, 4092[9] (1936)

[25]Calderbank and LeFevre, J. Chem. Soc. 1949 (1948)

[26]Simpson, et al., ibid., 1356 (1949)

[27]Albert, Goldacre and Phillips, ibid., 2240 (1948)

The nitrogen-containing ring in cinnoline is stable to oxidation. Stoermer[9,10] has oxidized some substituted cinnolines with potassium permanganate and obtained substituted pyridazines:



N-oxides of cinnolines are known, usually obtained by partial reduction of 2,2'-dinitrobiphenyls[28,29,30].

Reduction of the cinnoline ring under mild conditions produces 1,2-dihydrocinnolines[31,32]. More vigorous conditions (zinc or iron and hydrochloric acid) frequently cause cleavage of the nitrogen-nitrogen bond. Neber[32] has used

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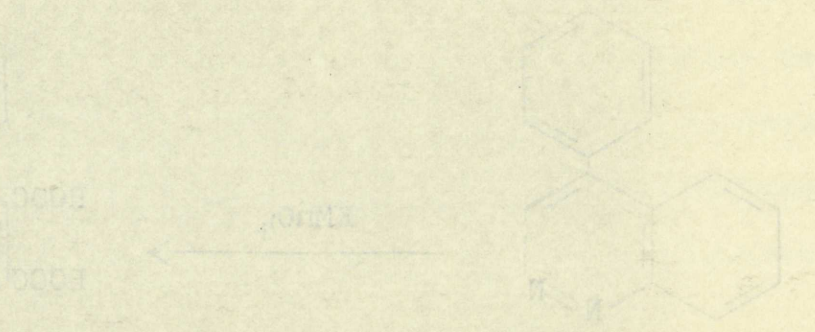
[28]Ullmann and Dieterle, Ber. 37, 23 (1904)

[29]Sako, Bull. Chem. Soc. Japan 2 393 (1934); C.A. 29, 10837 (1935)

[30]Atkinson and Simpson, J. Chem. Soc. 1649 (1947)

[31]Duval, Bull. Soc. Chim. (4) 7, 485 (1910); C.A. 4, 2304 (1910)

[32]Neber, et al., Ann. 471, 113 (1929)



phosphorus and hydriodic acid to reduce 4-hydroxycinnoline to the tetrahydro derivative, and 3-hydroxycinnoline rearranged to form oxindole with the same treatment. Similarly, 4-phenylcinnoline was reduced to 3-phenylindole by zinc and acetic acid. Cinnolines will form addition compounds with alkali metals and these can be converted to 1,2-dihydrocinnolines. This will be discussed in greater detail in a later section.

Schofield and Simpson[33] carried out the nitration of 4-hydroxycinnoline and obtained the 6-nitro derivative as the principal product. Later, Schofield and Swain[34] nitrated 4-methylcinnoline and obtained 4-methyl-8-nitrocinnoline as the sole product. Bromination and chlorination of 4-hydroxy and 6-substituted 4-hydroxycinnolines has been carried out in acetic acid to yield the corresponding 3-halogenated cinnoline[35]. No other nuclear substitutions have been carried out on the cinnoline molecule.

When treated with a mixture of phosphorus pentachloride and phosphorus oxychloride, 4-hydroxycinnolines are converted to 4-chlorocinnolines[3,11,15]. The reactions of 4-chlorocinnolines will be discussed in a later section.

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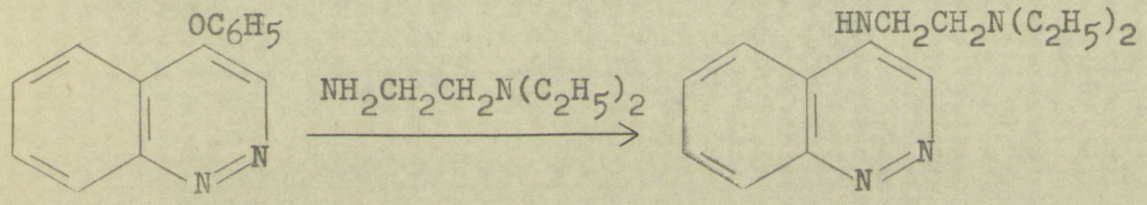
[33]Schofield and Simpson, J. Chem. Soc. 512 (1945)

[34]Schofield and Swain, ibid., 1367 (1949)

[35]Schofield and Swain, ibid., 384 (1950)

The reactivity of 4-phenoxycinnolines is demonstrated by refluxing them in dilute alcoholic potassium hydroxide to obtain corresponding 4-hydroxycinnolines. The 4-phenoxycinnolines on treatment with acetic anhydride produce the corresponding 4-acetoxycinnolines[36]. By addition of 4-phenoxycinnoline to molten ammonium acetate Keneford, Schofield and Simpson[36] have also prepared the corresponding 4-aminocinnoline in good yield. The 4-phenoxycinnolines can be converted to 4-dialkylaminoalkylaminocinnolines when condensed with the corresponding amine[37]:



Schofield and Theobald[38] have prepared 7-acetamido-4-hydroxylaminocinnoline by the action of hydroxylamine hydrochloride on 7-acetamido-4-phenoxycinnoline in ethanol and water.

In the synthesis of some cinnolines by the Borsche

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[36]Keneford, Schofield and Simpson, J. Chem. Soc. 358 (1948)

[37]Keneford and Simpson, ibid., 917 (1947)

[38]Schofield and Theobald, ibid., 2404 (1949)

reaction the replacement of a bromine by a chlorine atom has been observed in the diazonium salt stage[39,40,41]. Of even more interest is the exchange of chlorine for a bromine atom on the cinnoline nucleus, as observed by Leonard and Boyd[15] and further developed by Schofield and Swain[35]. Simpson also reports the replacement of a nitro group by a chlorine atom in the cinnoline nucleus[41].

The location of the basic center of a number of the cinnolines has been shown to be at N_1 by a study of the reactivity of 4-methylcinnoline[42] and the alkaline decomposition of 4-substituted alkyl cinnolinium salts[43].

Jacobs, et al.,[44] condensed 4-methylcinnoline with benzaldehyde to prepare 4-styrylcinnoline in good yield.

Schofield and Simpson[45] describe a complex reaction between pyridine, acetic anhydride and 4-hydroxycinnoline-3-carboxylic acid from which they obtained a compound postulated as 4-(2'-pyridyl)-cinnoline. This was recently proven

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[39] Schofield and Simpson, J. Chem. Soc. 1170 (1948)

[40] Atkinson and Simpson, ibid., 232 (1947)

[41] Keneford, Morley and Simpson, ibid., 1702 (1948)

[42] Atkinson and Simpson, ibid., 808 (1947)

[43] Simpson, ibid., 1653 (1947)

[44] Jacobs, et al., J. Am. Chem. Soc. 63, 1310 (1946)

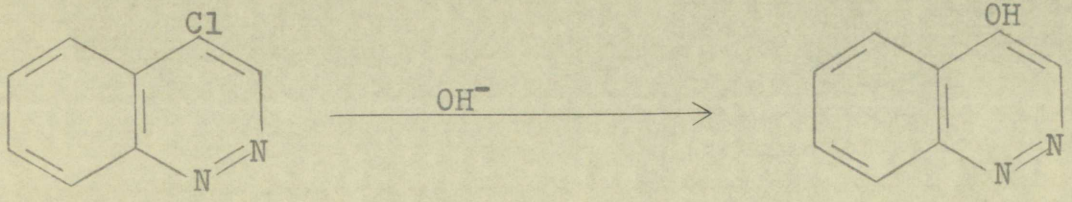
[45] Schofield and Simpson, J. Chem. Soc. 472 (1946)

less questionable method[46]. Other interesting pyridyl and quinolyl cinnolines are also described in the latter paper.

B. 4-Chlorocinnoline

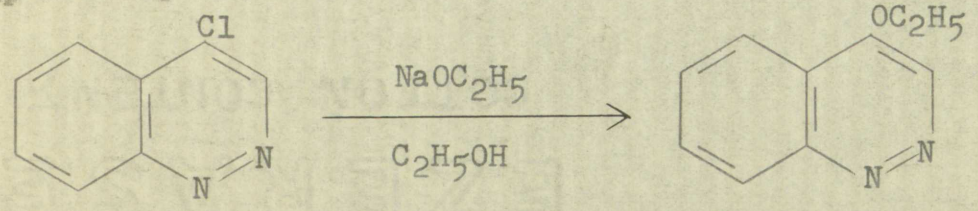
Since it was first prepared in 1897 by Busch and Rast[3], 4-chlorocinnoline has proven to be one of the more important cinnolines as an intermediate in the preparation of more complex compounds. Regardless of the nature of other groups on the ring, all 4-hydroxycinnolines have been converted to 4-chlorocinnolines on treatment with phosphorus pentachloride and phosphorus oxychloride. The reactivity of the chlorine in 4-chlorocinnoline is of the same order as the chlorine in 4-chloroquinoline, 4-chloropyridine, 4-chloroquinazoline and other aromatic nitrogen heterocycles. 4-Chlorocinnoline and some of the substituted 4-chlorocinnolines are unstable and decompose to a brown-black tar on standing. Recrystallized 4-chlorocinnolines can be employed in the following replacement reactions:

A. Replacement of Chlorine by the hydroxyl group[3].

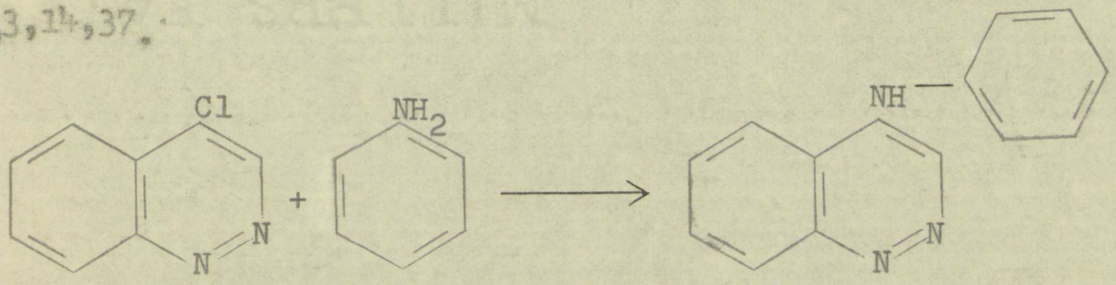


[46] Schofield, J. Chem. Soc. 2408 (1949)

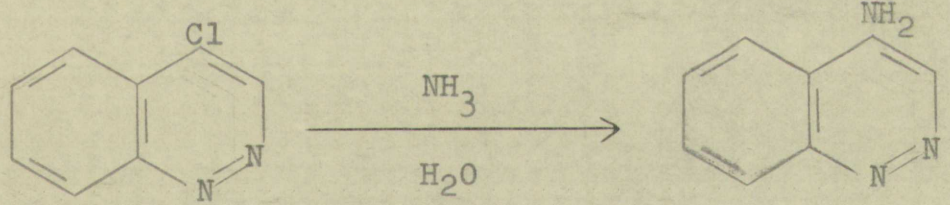
B. Replacement of the chlorine by an alkoxy group[3,33,40].



C. Replacement of chlorine by an alkyl or aryl amino group[3,14,37].



D. Replacement of chlorine by an amino group from aqueous ammonium hydroxide, under pressure[47].



E. Replacement of chlorine by the hydrazino group, using hydrazine hydrate[48].

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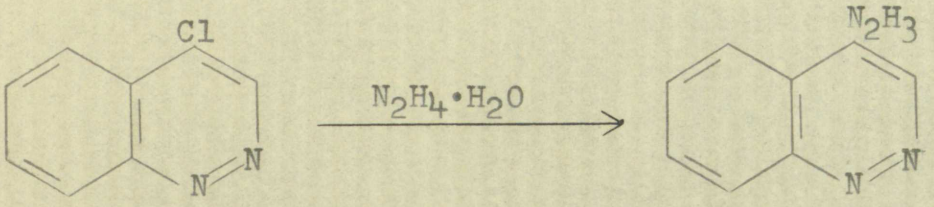
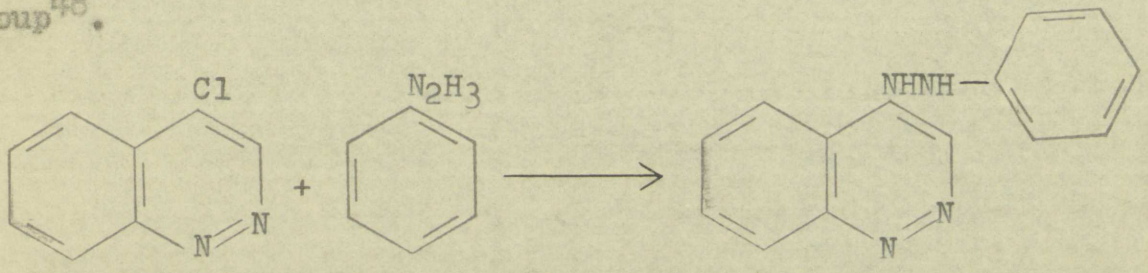
[47] R. N. Castle. Unpublished work on the reactions of the cinnolines.

[48] Schofield and Swain, J. Chem. Soc. 392 (1950)



F. Replacement of chlorine by a phenylhydrazino group[48].



C. Organo-metallic derivatives of aromatic N-heterocyclic compounds

1. Grignard Compounds

The preparation of Grignard reagents from nuclearly halogenated aromatic N-heterocyclic compounds is apparently difficult and usually unsuccessful. Mosher makes the following report on pyridyl Grignard compounds: "Proost and Wibaut[49] have been able to force a Grignard reaction with 2-bromopyridine by carrying out a concurrent reaction between ethyl bromide and magnesium. The resulting 2-pyridylmagnesium bromide successfully reacts with acetophenone,

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[49] Proost and Wibaut, Rec. trav. chim. 59, 971 (1940); C.A. 35, 4771[2] (1941)

benzophenone and ethyl benzoate to give methylphenyl-2-pyridyl-carbinol (12%), diphenyl-2-pyridyl carbinol (15%) and phenyl-di(2-pyridyl) carbinol (32%) respectively. 2,6-Dibromopyridine reacts with magnesium under the same conditions and, when coupled with benzaldehyde, gives the expected product, 2,6-di(phenylmethylol)pyridine as well as some of the reduction product, phenyl-2-pyridylcarbinol."[50]

Sachs and Sachs[51] reported that Grignard reagents could not be prepared from bromoquinolines. Their findings were later confirmed by Howitz and Kopke[52] who, however, reported the preparation of a Grignard compound from a lateral bromine derivative, 8-bromoethylquinoline.

2. Organo-lithium Compounds

In the field of heterocyclic organic chemistry organo-lithium compounds have proven more successful than Grignard compounds. Some organo-lithium compounds have been prepared by direct synthesis from the halide and lithium in poor yields[53]. The most satisfactory method for synthesis of organo-lithium derivatives of heterocyclic compounds

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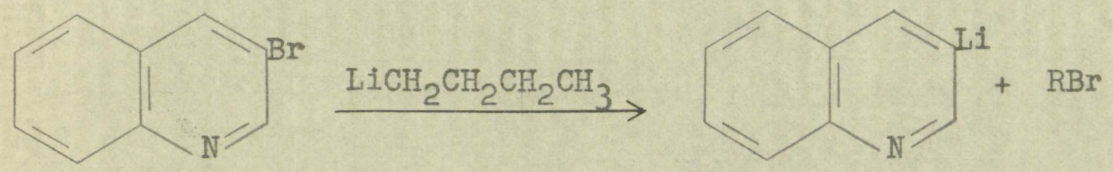
[50]Robert C. Elderfield, Heterocyclic Compounds, Vol. I (New York: J. Wiley and Sons, 1950), p. 520

[51]Sachs and Sachs, Ber. 37, 3088 (1904)

[52]Howitz and Kopke, Ann. 396, 38 (1913)

[53]Gilman and Kirby, J. Org. Chem. 1, 146 (1936)

is the halogen-metal interconversion reaction. The preparation of 3-quinolyl lithium was carried out by Gilman and Spatz[54]:



They suggest that the reactions be run at moderately low temperatures, (-45 to -35° for the above reaction) and with short reaction periods. Otherwise, secondary reactions predominate, particularly addition of the organo-lithium reagent to the azo-methine linkage, or in the case of the cinnolines, to the azo linkage. Organo-bromo compounds have produced the best results and n-butyl lithium is frequently used as the metalating agent. Gilman and Spatz[54] state that a chlorine-metal interconversion reaction has been observed only rarely.

Concerning the preparation and reactions of cinnolyl-lithium compounds, Wittig[55,56] found that 1,10-dimethylbenzo-(c)cinnoline formed addition products with two atoms of

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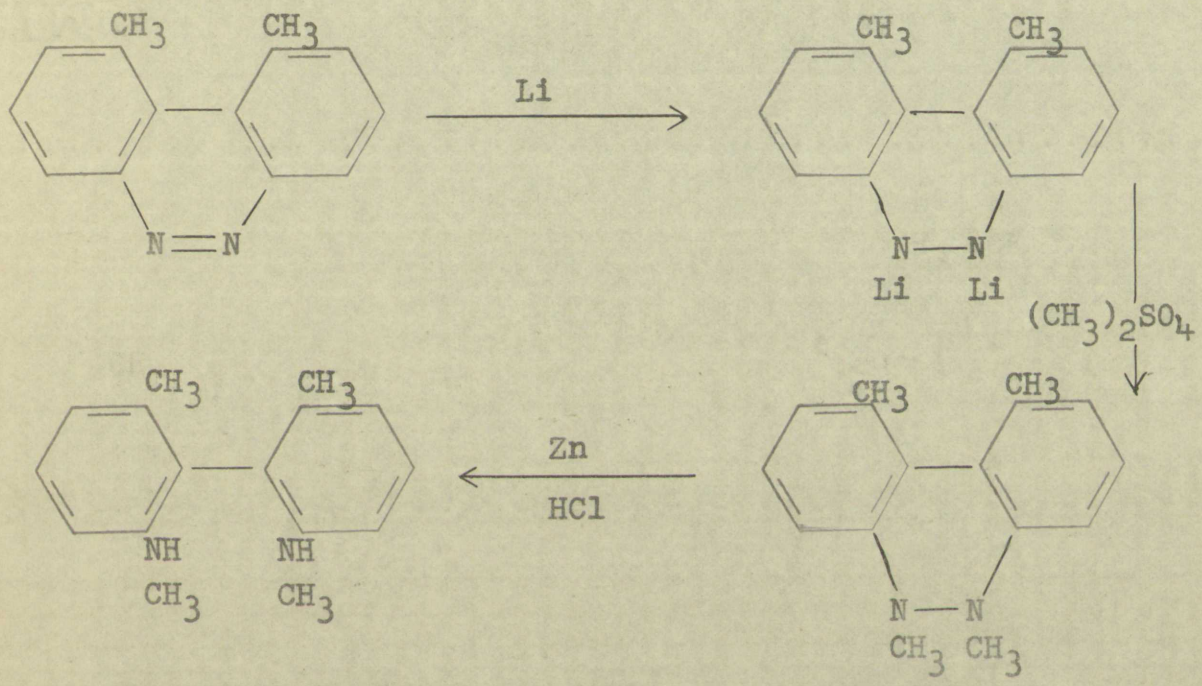
[54]Gilman and Spatz, J. Am. Chem. Soc. 63, 1553 (1941)

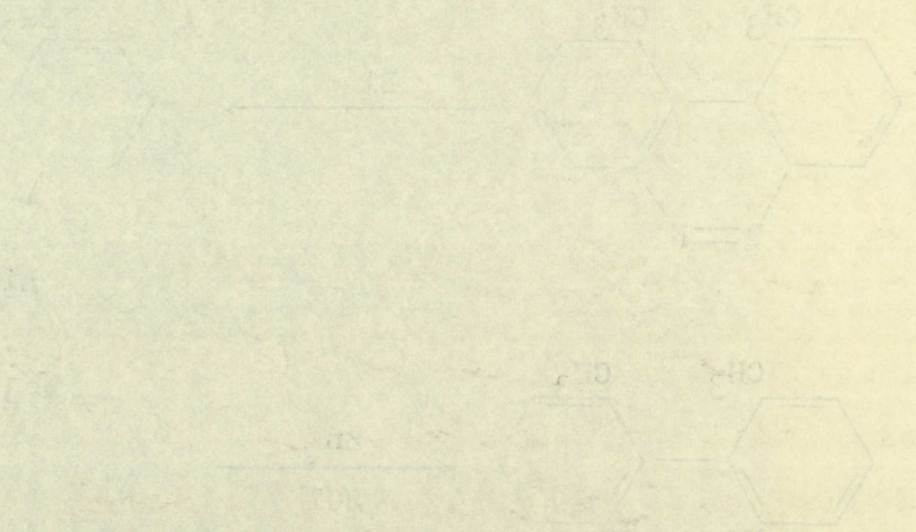
[55]Newer Methods of Preparative Organic Chemistry (New York: Interscience Publishers, Inc., 1948), p. 590

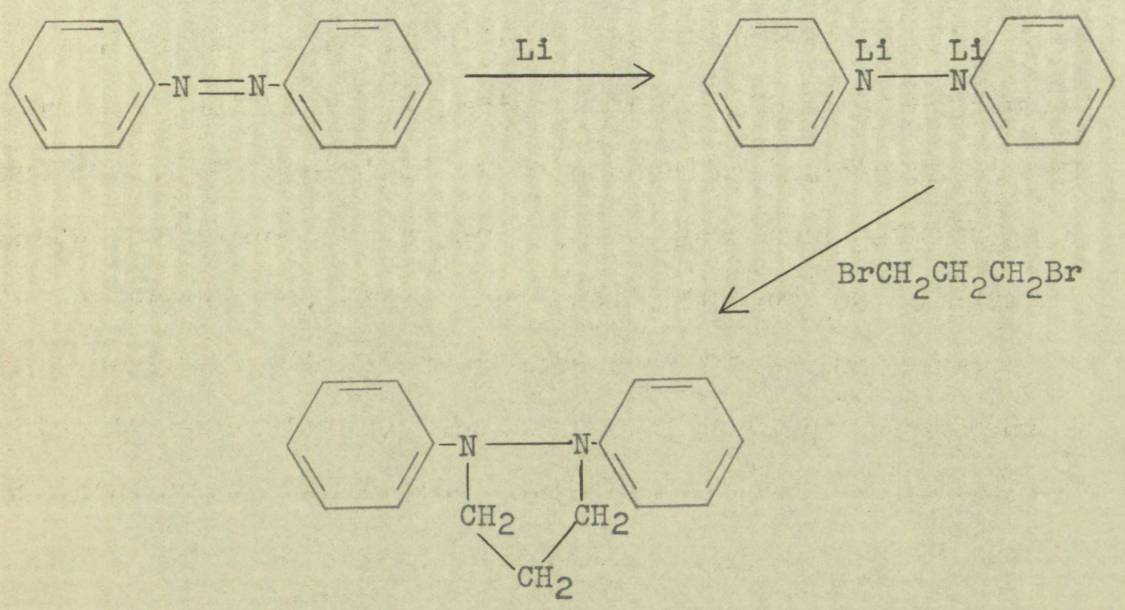
[56]Wittig and Stichnoth, Ber. 68B, 928 (1935)

either sodium, potassium or lithium. The dilithium adduct, by treatment with methyl sulfate, formed 5,6-dihydro-1,5,6,10-tetramethylbenzo(c)cinnoline, the structure of which was proven by further reduction with zinc and hydrochloric acid to the substituted biphenyl:

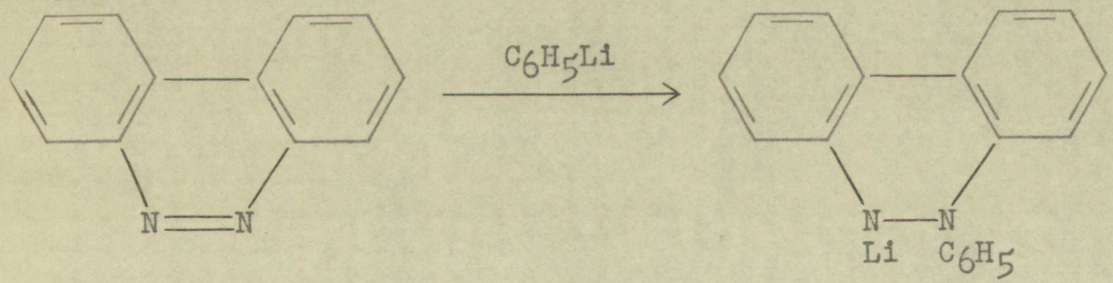


Similarly, alcoholysis of the dilithium adduct gives 9,10-dihydro-4,5-dimethylbenzo(c)cinnoline. According to Wittig[55] a similar dilithium adduct of azobenzene yields not only the N,N'-dimethyl compound on treatment with methyl sulfate, but on reaction with trimethylene bromide gives N,N'-diphenlypyrazolidine:





Gilman and Bailie[57] obtained hydrazobenzene and N,N'-diphenylhydrazobenzene from the reaction of azobenzene with phenyl lithium and subsequent hydrolysis. Wittig[55] also reported that the action of phenyl lithium on benzo(c)cinnoline produces 9,10-dihydro-N-lithium-N'-phenylbenzo(c)cinnoline:



There was no mention of the hydrolysis products of this

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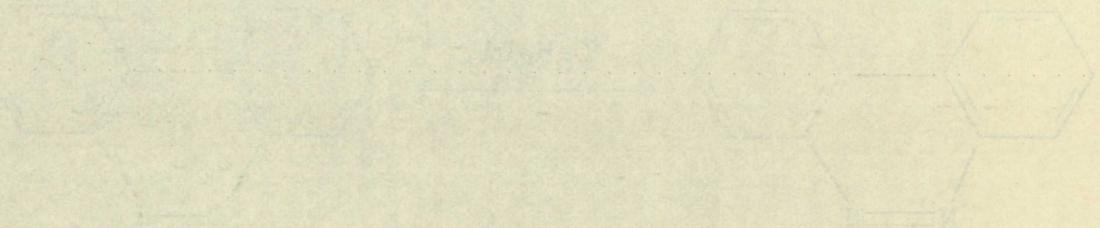
[57]Gilman and Bailie, J. Org. Chem. 2, 84 (1937)



compound. Ziegler and Zeiser[58,59] found that pyridine, quinoline, isoquinoline and acridone add alkyl and aryl lithium compounds at room temperature; and on hydrolysis or heating there are obtained compounds with the R group on the carbon of the nitrogen-carbon bond.

D. Some condensation reactions of halogenated aromatic N-heterocyclic compounds.

The condensation of sodio salts of compounds capable of enolization with nuclearly halogenated N-heterocycles will be considered first. This includes reactions of malonic ester, acetoacetic ester, benzoyl acetone, etc. There are apparently few halogenated aromatic heterocycles of sufficient reactivity to be condensed with acetoacetic or malonic ester. Koenigs and Jaeschke[60] condensed 4-chloro-2,6-dicarbethoxypyridine with sodio malonic ester and, on subsequent hydrolysis and decarboxylation, obtained 4-methyl-pyridine-2,6-dicarboxylic acid in an over-all yield of 35%. A similar reaction between 4-chloro-3-nitropyridine and malonic ester has been carried out to give 4-methyl-3-nitro

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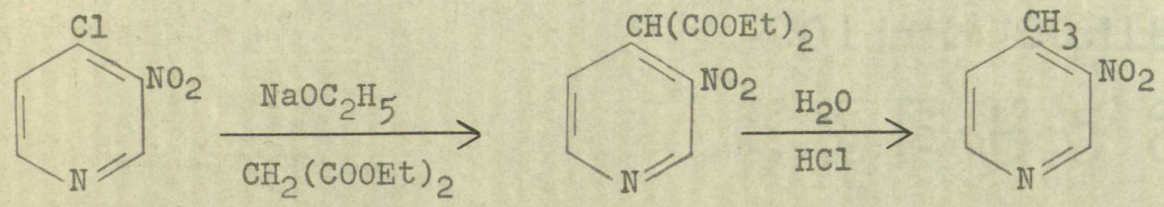
[58]Ziegler and Zeiser, Ber. 63, 1847 (1930)

[59]Ziegler and Zeiser, Ann. 485, 174 (1931)

[60]Koenigs and Jaeschke, Ber. 54, 1351 (1921)

pyridine:[61]



4-Propylpyridine-2,6-dicarboxylic acid has been prepared in the same manner.

Mosher[62] pointed out that the reactivity of the halogen in the 2,4 or 6 position of pyridine is further enhanced by the presence of a meta-directing group ortho or para to it. Thus it is seen that the ability of 4-chloro-3-nitropyridine to react with malonic ester is due in part to the resonance effect of the nitro group in the 3-position.

No condensation of other N-heterocycles of this type has been observed.

The methylenic hydrogens in phenylacetonitrile are known to be reactive. Migrdichian[63] describes many reactions of phenylacetonitrile throughout his book. Hancock

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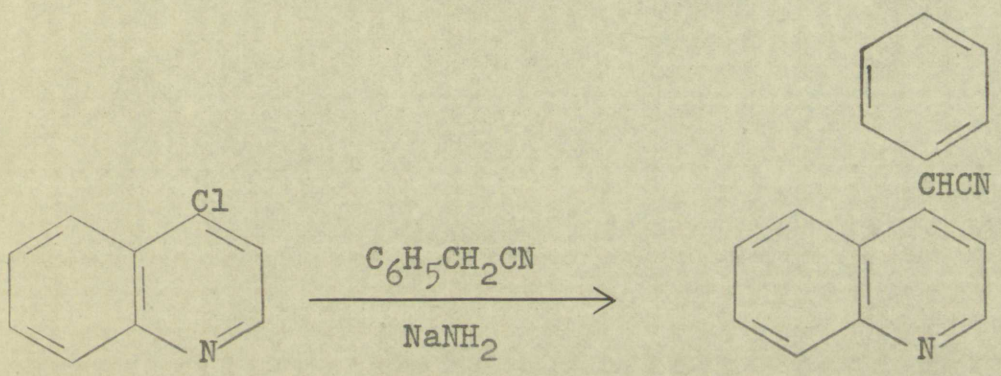
[61] Koenigs and Freter, Ber. 57, 1187 (1924)

[62] op. cit., pp. 623-625

[63] Vartkes Migrdichian, The Chemistry of Organic Cyanogen Compounds, (New York: Reinhold Publishing Corp., 1947)

and Cope[64] have prepared cyclohexylphenylacetonitrile by the method using sodium amide as the condensing agent. Cutler, Surrey and Cloke[65] report the successful condensation of 4-chloroquinolines with phenylacetonitrile, using the same condensing agent:



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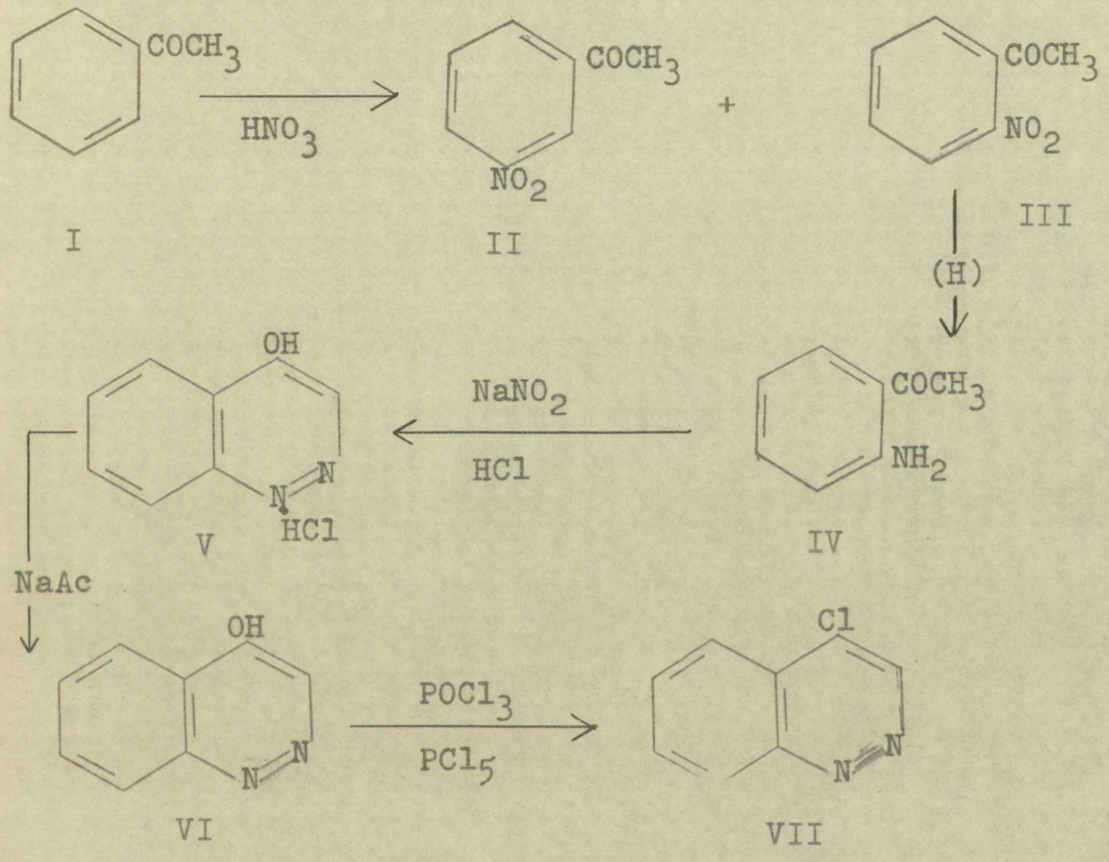
[64] Hancock and Cope, Org. Syntheses, 25, 25 (1945)

[65] Cutler, Surrey and Cloke, J. Am. Chem. Soc. 71, 3375 (1949)

III. A DISCUSSION OF THE SYNTHESIS OF 4-CHLOROCINNOLINE AND DERIVATIVES

A. Synthesis of 4-chlorocinnoline

Leonard and Boyd[15,66] describe the steps involved in the synthesis of 4-chlorocinnoline, beginning with the nitration of acetophenone, (I).



They report a yield of 33.6% of o-nitroacetophenone, (III). It was found that if one carried out the nitration in the

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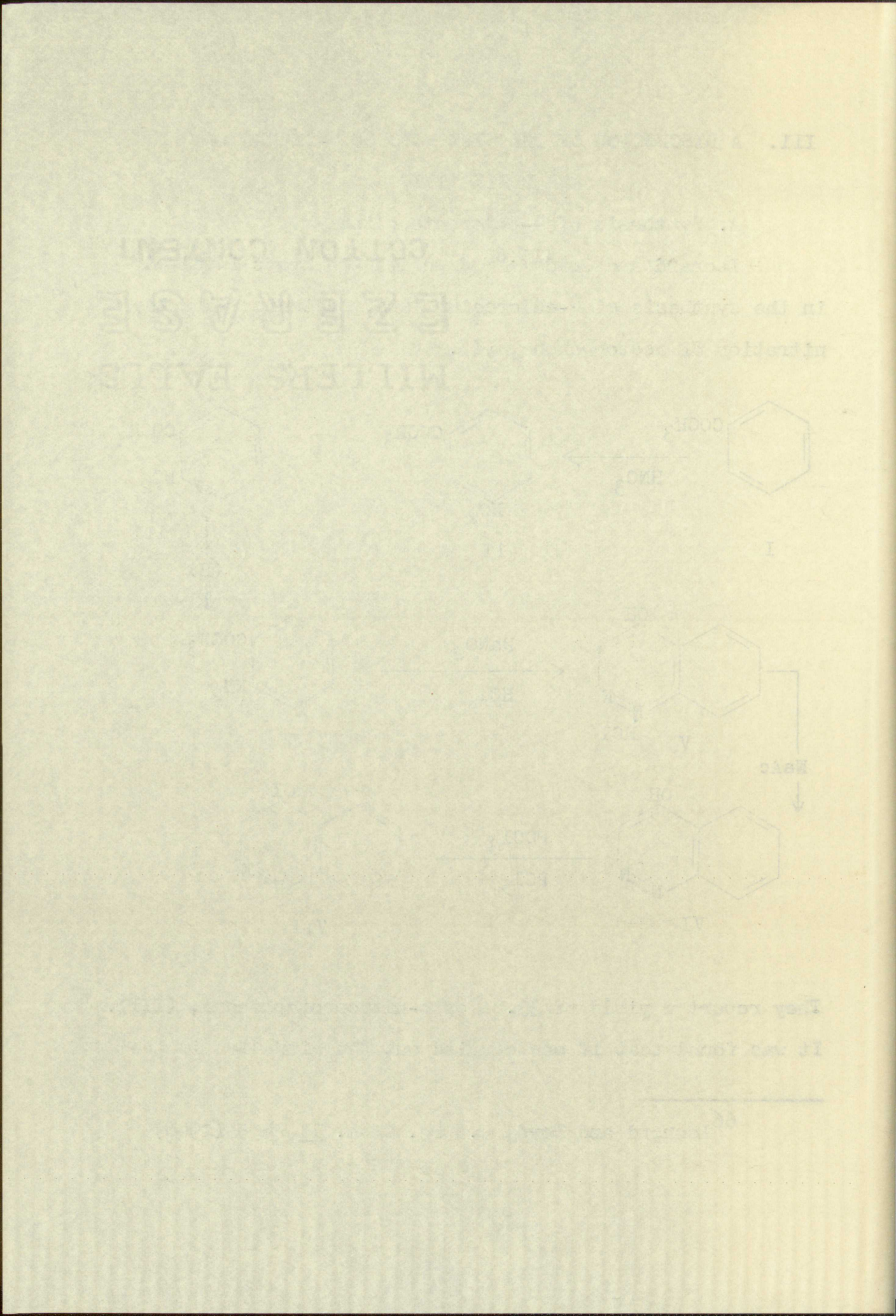
[66] Leonard and Boyd, J. Org. Chem. 11, 405 (1946)



temperature range -20 to -5°C. the best yield was obtained. Some glacial acetic acid was added to form acetyl nitrate to promote ortho substitution and reduce the amount of m-nitroacetophenone, (II), produced. The best yield obtained was 28%.

Reduction of (III) has been carried out by chemical means (tin and hydrochloric acid) and by catalytic hydrogenation. Leonard and Boyd, using Adam's catalyst, report 78% yield of the amine, (IV), by catalytic hydrogenation. This is in agreement with the 70% yield observed in these laboratories. Catalytic reduction could only be carried out on distilled (III), while chemical reduction with tin and hydrochloric acid did not require the purified nitro compound. The over-all yield by chemical reduction, followed by steam distillation and drying, was 36 to 40% of vacuum distilled amine.

Since the steps involved in the preparation of (IV) are lengthy, an attempt was made to prepare it in better yield by a new route. Two attempts were made to condense methyl anthranilate, (IX), with ethyl acetate, using sodium and sodium ethoxide as condensing agents, in the hope that ethyl o-aminobenzoylacetate, (X), might be obtained, from which (IV) should be available by hydrolysis and decarboxylation. The course of the reaction did not proceed as expected, but ring closure occurred to form 2,4-dihydroxy-

quinoline. Apparently the cyclization took place when the reaction mixture was treated with hydrochloric acid and ice in an attempt to isolate the ester. Other efforts to isolate the ester failed. This particular synthesis of 2,4-dihydroxyquinoline is essentially that described in the literature[67].

Diazotization of (IV) was carried out in concentrated hydrochloric acid and ring closure was effected by stirring and heating the diazonium salt at 60-75°C. Yields on this step ran 75% or better. The method of preparation of 4-chlorocinnoline was essentially that of Leonard and Boyd[15]. The black tar they describe was observed and (VII) slowly decomposed on standing, requiring a fresh batch be made up before each run. Due to the instability of (VII), yields often fall very low and care must be exercised in isolating and purifying it. The most favorable procedure was to prepare the cinnoline, (VII), weigh, dissolve in dry benzene or ether and store it in the cooler until needed. A light green residue formed in the step (V) to (VI). It was not characterized.

The other cinnoline studied was 6,7-dimethoxy-4-hydroxycinnoline, from which the corresponding 4-chloro

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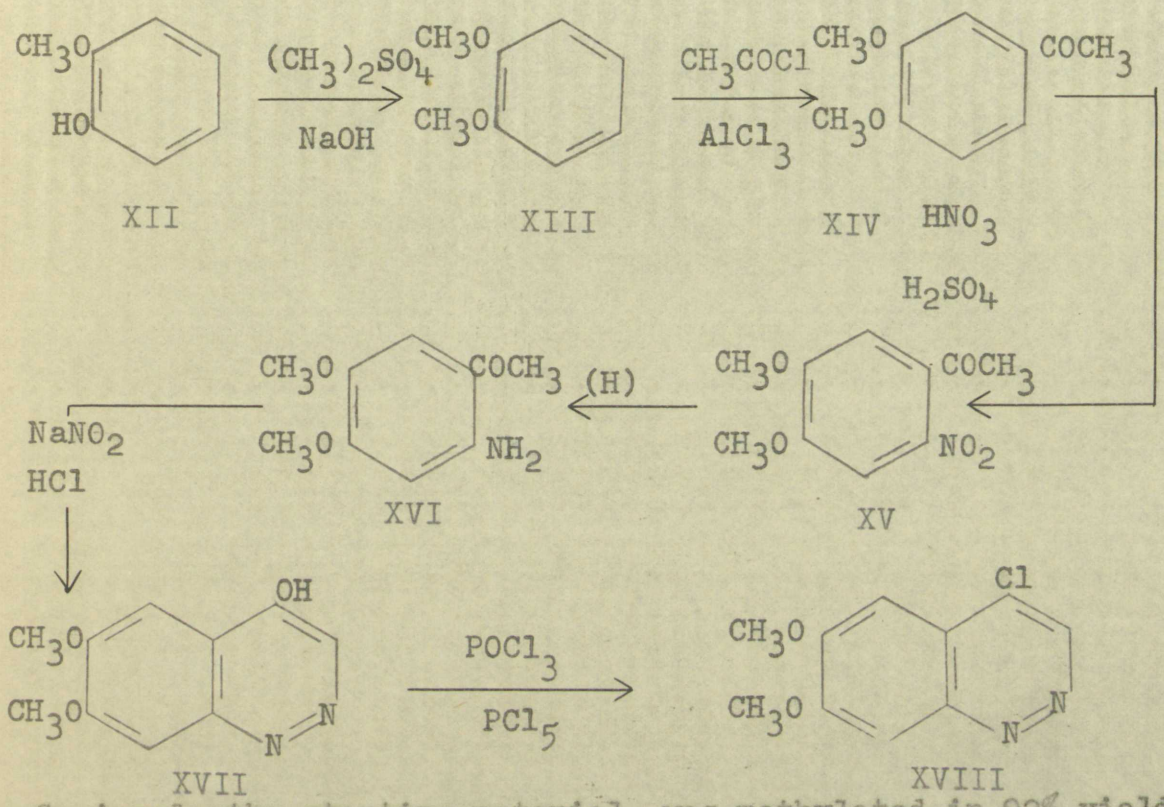
[67]Beilstein, 21, 171

compound was formed:



Guaiacol, the starting material, was methylated in 92% yield by the method of Buck[68] for veratraldehyde. The veratrole, (XII), was acetylated by the method of Koepfli[69] with 82% yield and this, (XIV), was nitrated and reduced as outlined by Simpson[70]. Chemical reduction with iron and hydrochloric

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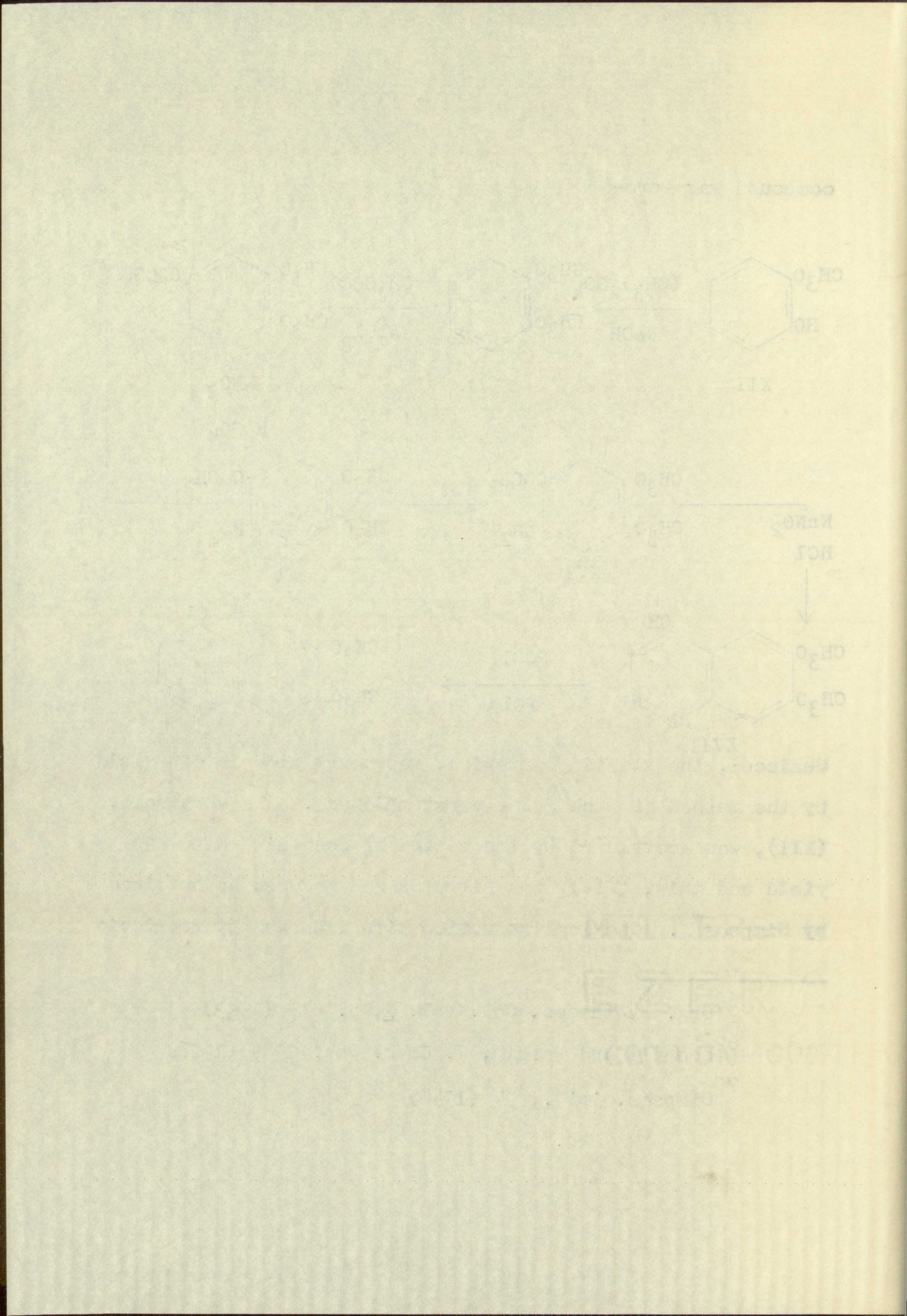
[68] Org. Syntheses, Col. vol. 2, p. 619 (1943)

[69] Koepfli and Perkin, J. Chem. Soc. 2989 (1928)

[70] Simpson, ibid., 94 (1946)



acid in ethanol was unsuccessful, as was reduction with tin and hydrochloric acid or with sodium hyposulfite. Reduction with iron and acetic acid gave yields of 26% to 36% in small batches. Catalytic reduction using Adam's catalyst in ethanol gave a 42% yield when carried out on 18 grams. A large scale, high yield, method of reduction is still lacking. One difficulty is the lack of solubility of the amine in most organic solvents, except chloroform. Simpson[12] was not able to obtain 6,7-dimethoxy-4-hydroxycinnoline from 2-amino-4,5-dimethoxyacetophenone, this probably being due to the low concentration of acid media used for ring closure. The cinnoline, (XVII), was prepared by diazotization and ring closure in 36% hydrochloric acid, with a yield of 60-70%. This 4-hydroxycinnoline reacts rapidly with phosphorus pentachloride and phosphorus oxychloride to produce the stable 4-chloro-6,7-dimethoxycinnoline, (XVIII), in 75% yield.

B. Reactions studied in an attempt to prepare 4-cinnolyl organo-metallic derivatives

The preparation of 4-cinnolyl magnesium chloride was attempted using a number of conditions. All runs were made using 4-chlorocinnoline.

In one attempt to form this Grignard reagent, Baeyer's catalyst (magnesium powder fused with iodine) was used in an

effort to start the reaction. In this experiment, most of the 4-chlorocinnoline was recovered. Another attempt was made using the method of Proost and Wibaut[50] for 2-bromocinnoline. They suggested that an equal molar quantity of ethyl bromide be mixed with the halide and that enough magnesium be used to accommodate both halides. The reaction did not start when magnesium, ethyl bromide, and 4-chlorocinnoline were mixed, until a few drops of ethyl magnesium bromide, formed separately, were added. Then a small amount of a red-curdy substance formed which, on isolation, separated as a dark red oil. This same substance was also formed in small yield when ethyl magnesium bromide was added to 4-chlorocinnoline in ether with subsequent treatment with carbon dioxide and then hydrolysis. This red oil was produced in such small quantity that it was not possible to identify it. A brown powder was also obtained. A number of different methods were attempted to purify this substance. However, tarry material was obtained from all solvents used.

It might be mentioned at this point that in all reactions in which some of the magnesium was apparently consumed, the solution was treated with solid carbon dioxide in the hope of obtaining the 4-cinnoline carboxylic acid which is on record and thus could serve as a guide to the course of the formation of the Grignard reagent.

Another attempt was made to form the Grignard reagent using usual conditions without success; i.e., an iodine crystal and freshly cut magnesium. In one run in which the ether was not distilled from sodium the reaction apparently started on the addition of iodine, but stopped shortly when the magnesium became coated with a black residue. Lastly, an attempt was made to form the Grignard reagent using n-butyl ether as the solvent at 50-75°C. This reaction was also unsuccessful.

During this research two runs were carried out in an effort to form the 4-cinnolyl lithium compound. One reaction was tried in dry ether, the other in dry dioxane. Lithium shot was used and was cut to expose fresh surfaces. In ether the fresh surfaces appeared to react but this did not continue when the lithium became covered with a black residue. In the dioxane solution higher temperatures (50-80°C.) were used but substantially the same phenomenon occurred.

It was desired to use the halogen-metal exchange reaction, but this required 4-bromocinnoline, which had not been previously prepared. Some attempts were made to prepare 4-bromocinnoline by the treatment of 4-hydroxycinnoline with phosphorus bromides. Tarry material was all that was produced. It appeared worthwhile to consider the preparation of 4-bromocinnoline from the 4-amino

compound via diazotization and the Sandmeyer reaction. In order to test the diazotization of 4-aminocinnoline, a coupling reaction with 2-naphthol was carried out. The 4-aminocinnoline, obtained by heating 4-chlorocinnoline with aqueous ammonia under pressure, was diazotized and then allowed to react with alkaline 2-naphthol. A yellow crystalline substance was obtained. This substance is insoluble in water, 10% sodium hydroxide and strong mineral acids, gives a positive nitrogen test, but does not give proper carbon and hydrogen analysis for the expected addition compound. The preparation of 4-bromocinnoline was not pursued further.

C. Condensation reactions with 4-chlorocinnoline

1. Keto-enol type compounds

As was indicated earlier, only activated 2,4 or 6-halogenated pyridines have been condensed with malonic ester. In order to determine the degree of reactivity of 4-chlorocinnoline it was decided to attempt condensation of (VII) with compounds such as malonic ester, acetoacetic ester, and benzoylacetone. The sodio salts of these compounds were formed from sodium hydride or sodium amide. A solution of 4-chlorocinnoline was added to the mixture and was heated and stirred for various periods of time.

Condensations were attempted with sodio salts of the following compounds with the condensing agent and solvent indicated: malonic ester using sodium in dry ether; ethyl

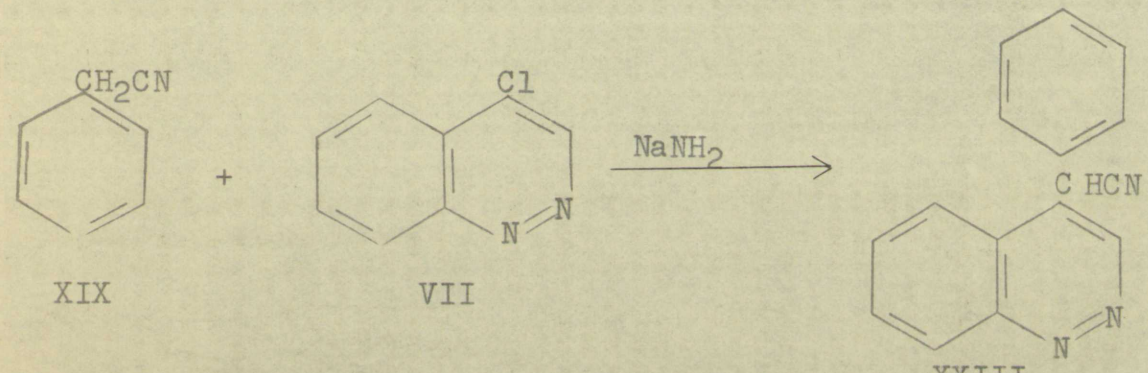
cyanoacetate, ethyl acetoacetate and benzoylacetone using sodium hydride in dry benzene; benzoylacetone using sodium amide in dry benzene; phenylacetone using sodium amide in dry benzene. None of these reactions were successful. In a few instances a reaction apparently took place, but no products were isolated.

This indicates that the chlorine in 4-chlorocinnoline is apparently not as reactive as the halogens in the 2,4 or 6-position in pyridine. The fact that no such condensation listed above is reported for 4-bromo- or 4-chloroquinoline in the literature can be taken as an indication that 4-chlorocinnoline has the same order of reactivity. The reactions in the next section substantiate this statement.

2. Phenylacetonitrile condensations

Cutler, Surrey and Cloke[65] have condensed phenylacetonitrile with 4-chloro-, 4,5-dichloro- and 4,7-dichloroquinoline in good yield. Since 4-chloroquinoline and 4-chlorocinnoline show similar reactivity, this condensation was investigated. Phenylacetonitrile, (XIX), and substituted phenylacetonitriles were treated with sodium amide in dry benzene to form the sodio salts. To this was added 4-chlorocinnoline in benzene. Phenylacetonitrile when condensed with 4-chlorocinnoline gave 94% yield of α-(4-cinnolyl)-phenylacetonitrile, (XXIII). The following substituted

phenylacetonitriles were also condensed: p-nitrophenylacetonitrile, p-methoxyphenylacetonitrile, and m-methoxyphenylacetonitrile. 3,4-Dimethoxyphenylacetonitrile would not form a sodio salt with sodium amide and therefore could not be condensed with (VII). Sodium hydride was used in the place of sodium amide in one synthesis, but the yield was very low.

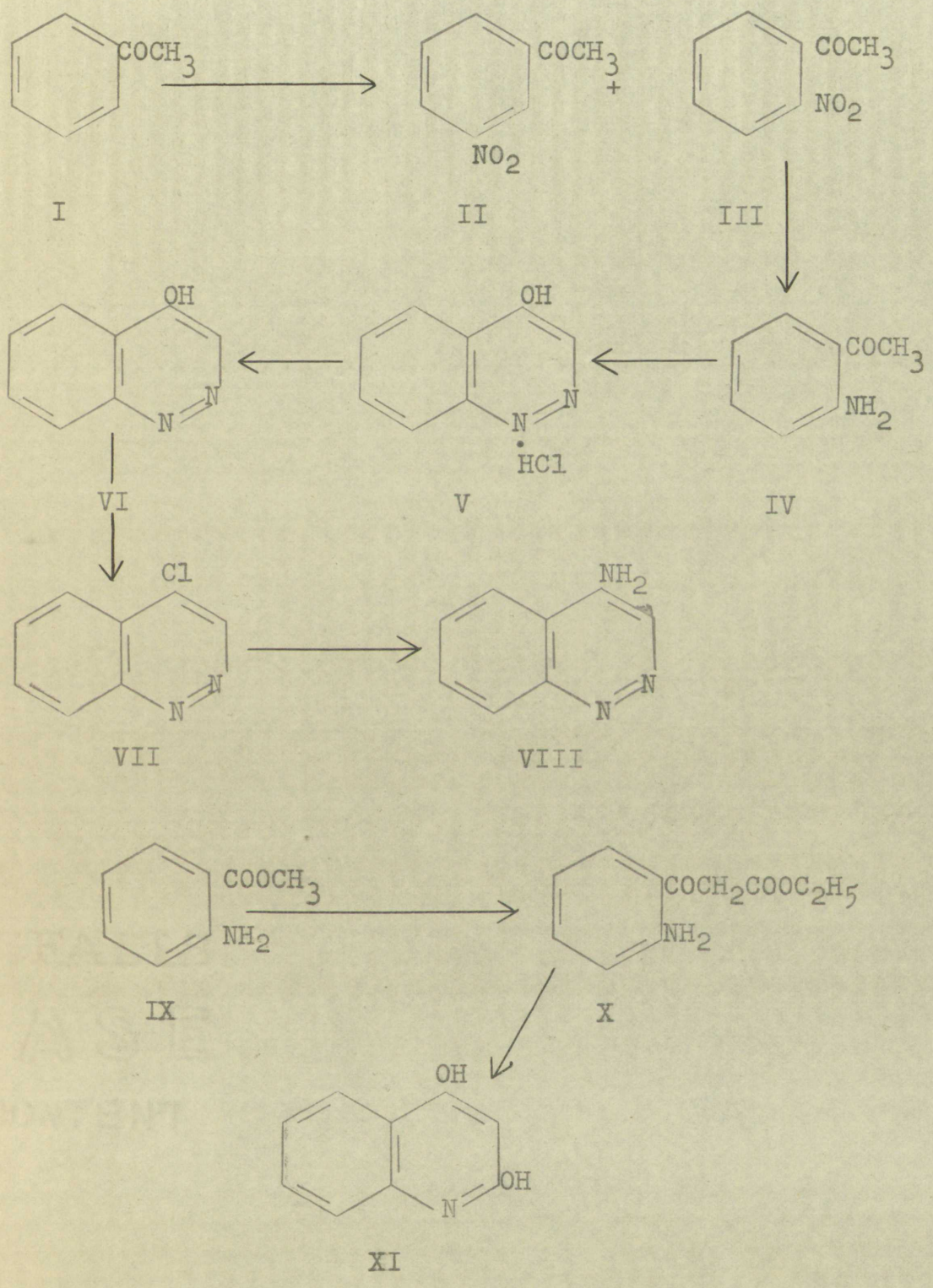


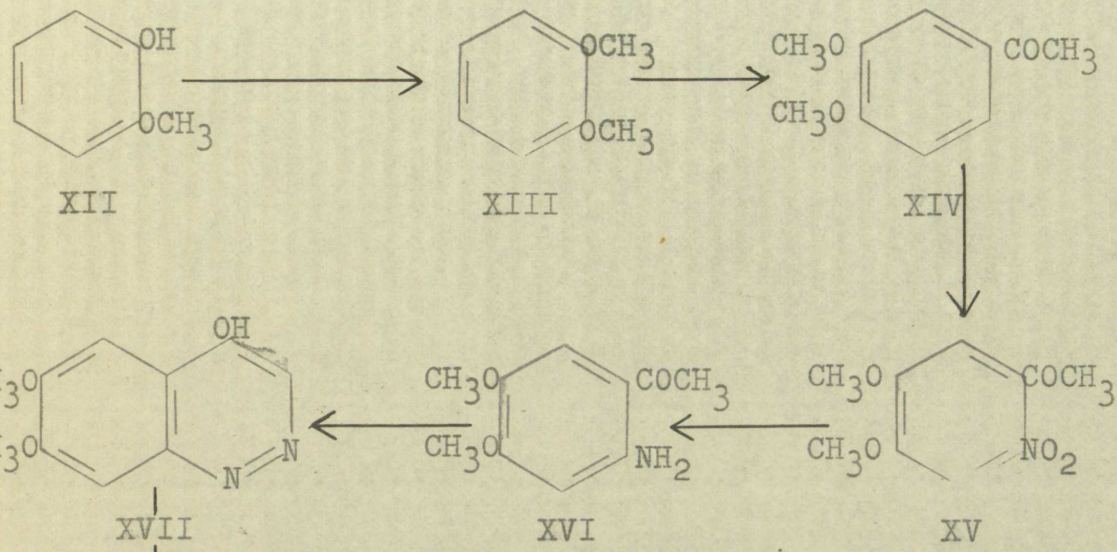
XIX VII XXIII

The p-nitrophenylacetonitrile reacted vigorously and the initial cinnolyl nitrile formed apparently changed composition on standing, as the carbon and hydrogen analysis did not agree with that expected for $C_{16}H_{10}N_4O_2$. The compound obtained is soluble in concentrated hydrochloric acid, insoluble in water and 10% sodium hydroxide, and partially soluble in dilute hydrochloric acid. It gives a positive nitrogen and negative halide test on sodium fusion. Rast cryoscopic molecular weight determination gives a value of 210-230, while $C_{16}H_{10}N_4O_2$ requires a value of 290. Preparation of two derivatives, to be described later, also gave compounds whose analyses did not agree with theory.

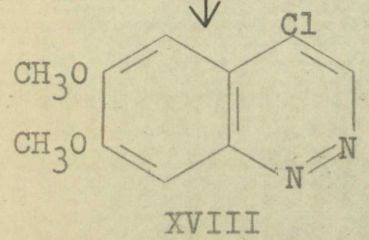
The 4-chloro-6,7-dimethoxycinnoline was also condensed with phenylacetonitrile to yield α-(6,7-dimethoxy-4-cinnolyl)-phenylacetonitrile.

Following the lead of Cutler, et al., α-(4-cinnolyl)-phenylacetamide, (XXVII), was prepared by allowing the nitrile, (XXIII), to stand overnight in concentrated sulfuric acid. By refluxing (XXIII) in 60% sulfuric acid 4-benzylcinnoline, (XXIX), was prepared. The corresponding derivatives of what was assumed to be α-(4-cinnolyl)-p-nitrophenylacetonitrile, (XXIV), were also prepared. Their carbon and hydrogen analyses did not check the theory. The acetamide of α-(6,7-dimethoxy-4-cinnolyl)-phenylacetonitrile was obtained in low yield.

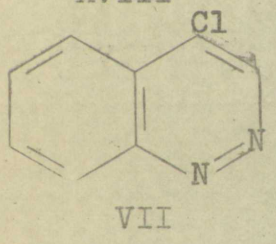

COCH3
NO2
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
OH
HCl
Cl
NH2
COOCH3
COCH2COOC2H5
N



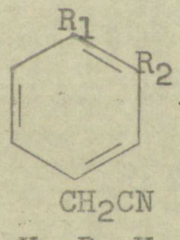
XII XIII XIV XV XVI XVII



XVIII

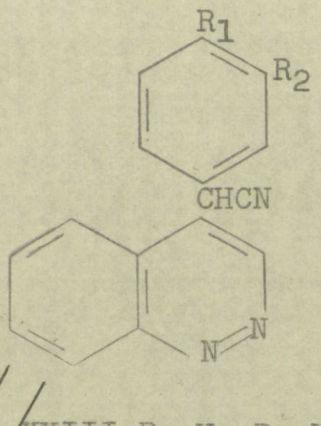


VII

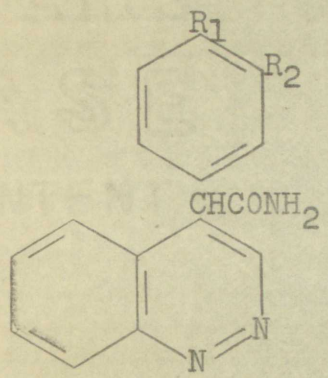


CH_2CN

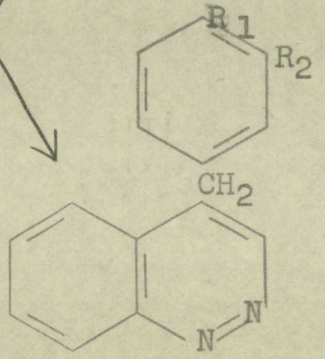
XIX R_1-H, R_2-H
XX R_1-NO_2, R_2-H
XXI R_1-H, R_2-OCH_3
XXII R_1-OCH_3, R_2-H



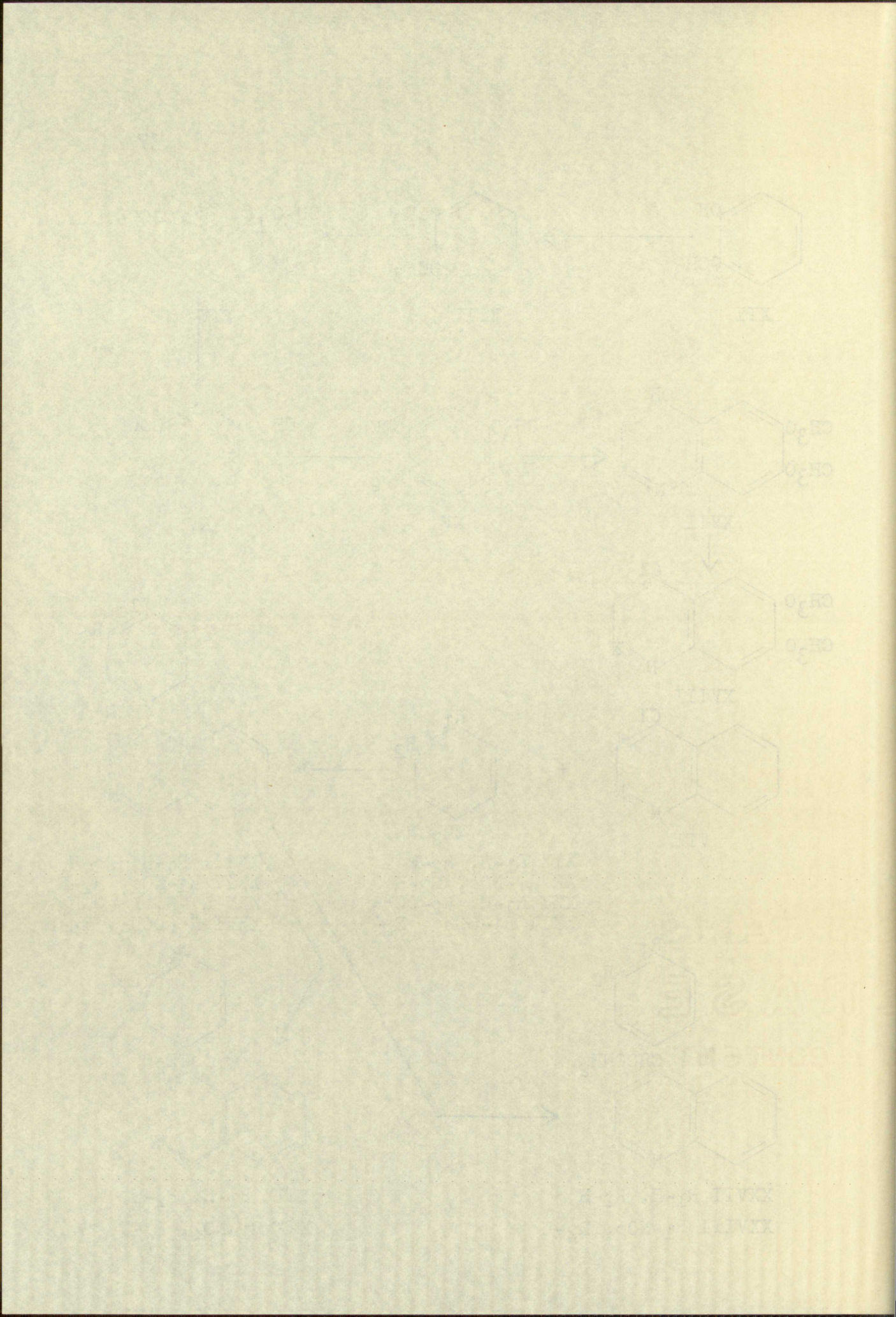
XXIII R_1-H, R_2-H
XXIV R_1-NO_2, R_2-H
XXV R_1-H, R_2-OCH_3
XXVI R_1-OCH_3, R_2-H

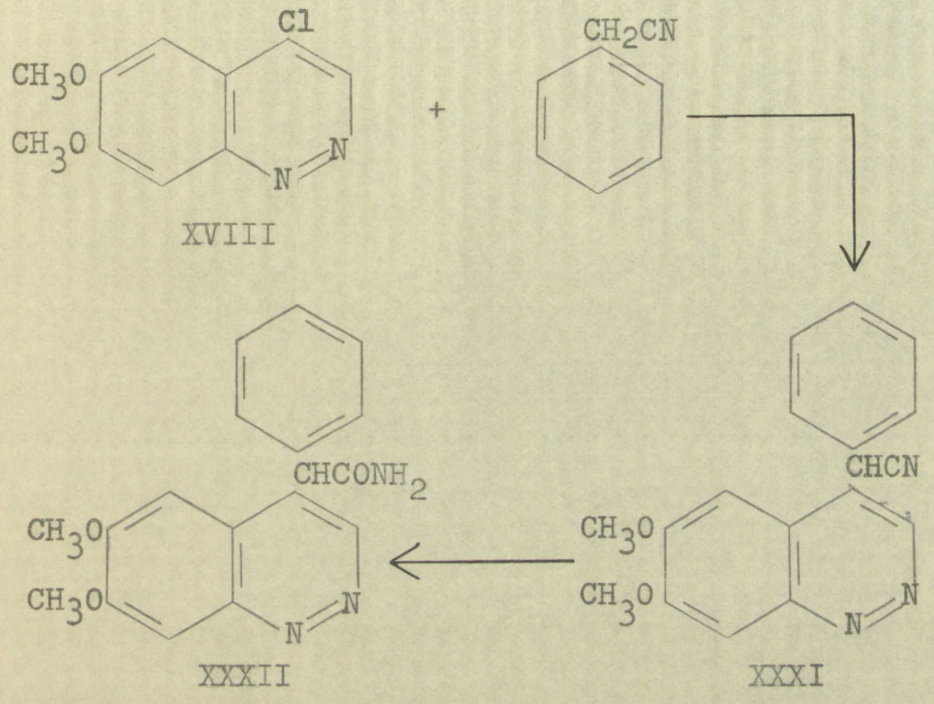


XXVII R_1-H, R_2-H
XXVIII R_1-NO_2, R_2-H



XXIX R_1-H, R_2-H
XXX R_1-NO_2, R_2-H




Cl
CH_3O
CH_3O
N
N
XVIII
+
CH_2CN
CHCN
XXXI
$CHCONH_2$
XXXII

IV. EXPERIMENTAL

All melting points designated (abs.) are absolute, taken at total immersion with certified Anschütz thermometers.

The nitrogen in the cinnoline ring is highly resistant to Kjeldahlization and therefore Dumas nitrogen analysis has been used.

A. Synthesis of 4-chlorocinnoline and 4-hydroxy-6,7-dimethoxycinnoline.

1. Synthesis of o-nitroacetophenone, (III).

A mixture of 277 g. of acetophenone, (I), and 25 ml. of glacial acetic acid was added slowly with stirring to 1,300 ml. of fuming nitric acid (sp. g. 1.47) which had been cooled to -25°C. in a methanol-dry ice bath. The addition took one hour during which time the temperature was maintained at -15 to -10°C. The mixture was stirred at -25°C. for an additional one and one half hours and was then poured over four liters of ice chips. The pale yellow solid (II) precipitated and was removed by filtration. The acid solution was then neutralized with sodium carbonate, which caused more (II) to precipitate. This was filtered and washed with ethanol to wash out any (III) retained by the solids. The filtrate was extracted with ether. The ether layer was washed with sodium bicarbonate solution, with

water and then dried over calcium sulfate. The ether was evaporated and the resultant oil was distilled under vacuum, b.p. 121-123° (2mm.). A source of dry nitrogen gas had to be attached to the bleeder for the distillation to prevent decomposition. There was obtained 94 g. of pale yellow oil for a 24.6% yield.

2. Synthesis of o-aminoacetophenone, (IV).

a. Chemical reduction. To 75 g. of (III) was added 400 ml. of concentrated hydrochloric acid and this mixture was vigorously stirred and heated in a three liter three-neck flask equipped with condenser and thermometer. The mixture was treated with 90 g. of mossy tin, added in small portions at a rate sufficient to maintain a gentle reflux without heating. This addition required forty five to seventy five minutes. The mixture was stirred and refluxed for an additional half hour.

The mixture was cooled and made alkaline with 20% sodium hydroxide solution while the stirring and cooling was continued to prevent excessive decomposition. The basic mixture was steam distilled, the distillate extracted with ether and the ether dried over calcium sulfate. The ether was evaporated and the amine, (IV), was distilled under vacuum, b.p. 95-98° (1½ mm.). There was obtained 22 g. of the pale yellow oil for a 35.8% yield.

b. Catalytic reduction. A mixture of 34 g. of (III),

150 ml. of absolute ethanol and 0.2 g. of platinum oxide was shaken in an Adam's hydrogenater over a period of six hours. During this time hydrogen was added under 45 lb. pressure in 'spurts'. The reaction tended to become rather warm and the shaking had to be stopped at times to keep the reaction under control.

The platinum oxide was collected on a sintered glass filter and the ethanol was removed by distillation. The amine was then distilled under vacuum, b.p. 93° (1mm.). There was obtained 18.5 g. for a 66% yield.

3. Synthesis of 4-hydroxycinnoline, (VI).

A mixture of 63 g. of the amine, (IV), 3700 ml. of concentrated hydrochloric acid and 650 ml. of distilled water was stirred in a 5 l. round bottom flask at a temperature of -7 to -3° maintained by an ice-brine bath. A solution of 32.5 g. sodium nitrite in 250 ml. water was added to the mixture over a period of forty five minutes and the stirring was continued for an additional hour, after which time 2-3 g. of urea was added to remove excess nitrous acid. The mixture was stirred and heated at 60 to 70° for four hours.

The solvent was removed at 60-70° by low pressure evaporation. On cooling, a crystalline mass of the hydrochloride, (V), was obtained and was removed by filtration. The evaporation was continued to near-dryness and a second

crop of (V) was obtained. The combined hydrochlorides were treated with a saturated potassium acetate solution to obtain crude 4-hydroxycinnoline, (VI). There was obtained 51.5 g. of tan crystals for a 76% yield. The cinnoline, (VI), could be recrystallized from ethanol-water to yield light tan crystals, m.p. 235° (uncorr.).

4. Synthesis of 4-chlorocinnoline, (VII).

To 10 g. of (VI) was added 20 ml. of phosphorus oxychloride and then 13 g. of phosphorus pentachloride (this order is important) and the mixture was gently refluxed for thirty minutes. Frequently the refluxing mixture turned dark toward the end of the reaction period. The liquid mixture was poured over cracked ice and was neutralized with solid sodium acetate to congo red. Usually the cinnoline, (VII), appeared at this point as a crystalline mush. Yields are improved if an excess of ice is maintained during the neutralization. The mixture was extracted with ether, the ether washed with dilute (5%) sodium carbonate solution and with water; and was dried over calcium sulfate. The bulk of the ether was evaporated and the last traces were removed by evaporation at reduced pressure. There was usually some dark residue present at this point. The compound, (VII), was immediately recrystallized from petroleum ether (b.p. 60-90°). Pale yellow needles were obtained, m.p. 75-76.5° (uncorr.). The yields varied, depending upon the degree of

decomposition, but the better yields ranged from 45 to 10%.

5. Attempted synthesis of o-aminoacetophenone, (IV), from methyl anthranilate.

Excess anhydrous ethanol (prepared by distilling from a sodium-toluene-ethanol mixture) and 12 g. of powdered sodium were allowed to react in a 500 ml. three-neck flask equipped with condenser, mercury-seal stirrer, dropping funnel and thermometer. Dry toluene was added from time to time to act as diluent as well as reaction media. To the mixture of sodium ethoxide and toluene was added 64 ml. of methyl anthranilate and this was stirred until homogenous. Then 50 ml. of anhydrous ethyl acetate was added over a period of two hours and the mixture was refluxed with stirring for three more hours at 80-85°.

The mixture was cooled and poured into concentrated hydrochloric acid. The toluene layer separated and a creamy-buff colored precipitate formed in the aqueous layer. The precipitate was removed by filtration. No further organic material could be isolated from the aqueous layer. The toluene layer was dried over calcium sulfate.

The buff colored precipitate was purified by sublimation. It had a melting point of 350-355° (uncorr.), contained nitrogen and proved to be 2,4-dihydroxyquinnoline, (XI).

The toluene was evaporated under reduced pressure and

the resultant oil was distilled, b.p. 136-137° (2mm.). The small amount of distillate obtained crystallized on cooling and was decolorized with charcoal and recrystallized from ethanol-water as fine white needles, m.p. 53-55° (uncorr.). This unknown compound is soluble in dilute hydrochloric acid, concentrated sulfuric acid and ether; is insoluble in 10% sodium hydroxide and water. The compound contains nitrogen. There was not sufficient quantity of this material for further characterization, but it is felt that it might be the desired ester protected from ring closure by the dilution with toluene.

6. Synthesis of veratrole, (XIII).

Guaiacol (300 g.) was added to 900 ml. water in a three liter three-neck flask equipped with mercury-seal stirrer, large dropping funnel, condenser, and thermometer. The mixture was heated to boiling and 720 ml. of a sodium hydroxide solution (300 g. in 1500 ml. water) was added. A clear, dark green solution resulted. Over a period of one hour 284 ml. of dimethyl sulfate was added to the refluxing solution, which was heated and stirred for an additional forty-five minutes. A clear oil began to separate. Then 60 ml. dimethyl sulfate was added and, after ten minutes refluxing, 120 ml. of the sodium hydroxide solution was added. The mixture was refluxed fifteen minutes. This procedure was repeated three times, 250 ml. of the sodium

hydroxide solution being added the last time.

The basic mixture was cooled and then was extracted with ether. The ether phase was washed with water, dried over calcium sulfate and warmed on the water bath to remove the ether. The oil was distilled under vacuum, b.p. 95° (6mm.). There was obtained 305 g. of (XIII) for a 93% yield. The aqueous layer was made acid with concentrated hydrochloric acid and was extracted with ether to recover the unchanged guaiacol. None was recovered in this instance.

7. Synthesis of 3,4-dimethoxyacetophenone, (XIV).

A mixture of 250 g. veratrole, (XIII), and 170 g. acetyl chloride was dissolved in 900 g. carbon disulfide and this mixture was cooled to 0°C. in an ice-brine bath. Over a twenty minute period 250 g. of anhydrous aluminum chloride was added to this well stirred mixture. The deep red mass was heated at reflux (52°) for a short while. The solvent was evaporated on a steam cone in a good hood, usually to near-dryness.

The dark red complex was hydrolyzed with crushed ice and water. The mixture was extracted with chloroform and the extract was washed with sodium bicarbonate solution and water, and then dried over calcium sulfate. The solvents were evaporated under reduced pressure and the resultant oil was vacuum distilled, b.p. 150-155° (7mm.). There was obtained 250 g. for a yield of 82% of theoretical.

8. Synthesis of 4,5-dimethoxy-2-nitroacetophenone, (XV).

To a mixture of 900 ml. concentrated nitric acid and 385 ml. concentrated sulfuric acid, cooled to -5° by an ice-brine bath, was added 250 g. (XIV) as rapidly as possible while still keeping the temperature below 5°C. The mixture was stirred for an additional hour and then poured over crushed ice. The yellow crystalline mass was removed by filtration and recrystallized from ethanol, m.p. 139° (uncorr.). There was obtained 295 g. for a 93% yield.

9. Synthesis of 2-amino-4,5-dimethoxyacetophenone, (XVI).

A mixture of 20 g. (XV) in 100 ml. glacial acetic acid was heated with stirring to reflux temperature. The mixture was diluted with 20 ml. water and 25 g. iron filings were added in small portions over a period of one hour. The slurry was heated and stirred for an additional hour, cooled, and filtered overnight. The filtrate was made just basic with 10% sodium hydroxide and the ferrous oxides removed by filtration. The filtrate and the ferrous oxide were separately extracted with large amounts of ether. The ether was combined, washed with water and dried over calcium sulfate. The ether was evaporated over a water-bath and the residue was recrystallized from ethanol-dilute ammonium hydroxide, tan crystals, m.p. 108-110° (uncorr.). There was obtained 6.4 g. of the amine for a 36% yield. Since the above method of Simpson did not give satisfactory yields when scaled up,

the following catalytic reduction was performed.

A mixture of 18 g. (XV) and 0.1 g. platinum oxide in 100 ml. absolute ethanol was treated with hydrogen under a pressure of 30 to 45 pounds while being vigorously agitated. This was continued for four hours or until the pressure gauge indicated no further uptake of hydrogen. Since the organic material was not all dissolved, 100 ml. additional ethanol was added. The platinum oxide was removed on a sintered glass filtering disk and the solution was reduced to one third volume by evaporation under reduced pressure. To this solution was added 10 ml. dilute ammonium hydroxide and on cooling there was obtained a mass of near-white plates, m.p. 109° (uncorr.). There was obtained 6.3 g. of the amine for a 41% yield.

A number of other reductions were attempted in an effort to find a method applicable to larger quantities. The use of iron filings and hydrochloric acid as suggested by West[71] proved unsuccessful. Two other methods, reduction by tin and hydrochloric acid and the use of sodium hyposulfite, produced only tars.

10. Synthesis of 6,7-dimethoxy-4-hydroxycinnoline, (XVII).

A mixture of 5.2 g. (XVI), 185 ml. concentrated hydrochloric acid and 28 ml. water was cooled in an ice-

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[71] West, J. Chem. Soc. 127, 494 (1925)

brine bath to -5°. This well stirred mixture was treated with 1.85 g. sodium nitrite in 8 ml. water, added over a period of forty five minutes. The mixture was stirred in the cold an additional hour and then stirred and heated at 60-75° for four hours. During this heating crystals appeared and more formed when cooled in the refrigerator. The grey-tan needles were removed by filtration and the filtrate yielded no more product on evaporation. The crystalline hydrochloride was treated with 10% sodium hydroxide causing the material to dissolve and then reprecipitate as the free cinnoline. The compound, (XVII), was taken up in 10% sodium hydroxide, boiled with decolorizing charcoal, filtered and precipitated by the careful addition of dilute hydrochloric acid. There was obtained 3.65 g. of the white powder for a 67% yield. The compound is high melting, m.p. 271-272° (abs.). This compound is soluble in strong hydrochloric acid and sodium hydroxide solution.

Analysis. Calculated for $C_{10}H_{10}O_3N_2$: C, 58.24, H, 4.89, N, 13.59; Found: C, 58.15, H, 4.95, N, 13.79.

11. Synthesis of 4-chloro-6,7-dimethoxycinnoline, (XVIII).

To 2.5 g. (XVII) was added 5 ml. phosphorus oxychloride and 3.5 g. phosphorus pentachloride. This mixture was warmed for fifteen minutes in a 50 ml. flask fitted with a

reflux condenser. It was poured on ice and neutralized with sodium acetate to congo red. The precipitate which formed was removed by filtration and recrystallized from ethanol. There was obtained 2.0 g. for 74% yield of soft cream needles, m.p. 195-196° (abs.).

Analysis. Calculated for $C_{10}H_9N_2O_2Cl$: C, 53.46, H, 4.04, N, 12.47, Cl, 15.92; Found: C, 54.37, H, 4.66, N, 12.53, Cl, 15.66.

B. Reactions of 4-chlorocinnoline.

1. Attempts to prepare 4-cinnolyl magnesium chloride.

In all runs of the next two sections the following apparatus was employed: a three-neck flask was fitted with a dropping funnel, mercury-seal stirrer, Hershberg type stirrer and Friedrichs condenser fitted with a drying tube and inlet for nitrogen gas. The reactions were conducted under an atmosphere of nitrogen which passed through ascarite and barium oxide before entering the flask. The solvent was stored over sodium ribbon and distilled from the container directly into the reaction flask which had been previously well dried. The magnesium and lithium were washed with anhydrous ether and cut to expose fresh surfaces before being placed in the reaction flask.

Magnesium ribbon, 0.5 g., was placed in the dry reaction flask and sufficient ether to cover the magnesium was distilled into the flask. A solution of 2.8 g. of

4-chlorocinnoline, (VII), in 30 ml. dry ether was placed in the dropping funnel and approximately twenty drops were added to the magnesium. The mixture was stirred and then heated. Some of the magnesium was crushed with a dry stirring rod. A crystal of iodine was added to the mixture. Finally 0.5 g. Baeyer's catalyst (magnesium and iodine fused in a dry test tube) was added. The mixture was stirred for two hours. No reaction occurred. The remainder of the cinnoline was added to the flask, but to no avail. In one run the magnesium appeared to react, but the metal was soon covered with a dark residue and the reaction ceased. Usually half or more of the cinnoline, (VII), was recovered.

Another run using the same portions of material was made with the following variation; an equivalent amount of ethyl bromide was mixed with the ether solution of (VII). Yet, no reaction occurred until a few drops of a suspension of ethyl magnesium bromide was added. A purple-red precipitate formed immediately and some of the magnesium appeared to react. The mixture was warmed, stirred two hours and allowed to stand at room temperature overnight. The red mixture was poured directly over 100 g. crushed solid carbon dioxide. Then 75 g. ice in 50 ml. water was added followed by 20 ml. concentrated hydrochloric acid. The acid mixture was extracted with ether which was washed with water and

and dried over sodium sulfate. Upon evaporation of the ether a deep red oil was obtained in too small quantity to be characterized.

Another variation tried was the substitution of n-butyl ether for ethyl ether as solvent. The mixture could then be heated to 70° or higher. No product was isolated.

2. Attempts to prepare 4-cinnolyl lithium.

Lithium shot (0.4 g.) was placed in the dry flask and dioxane was distilled into the flask. A solution of 3.6 g. (VII) was placed in the dropping funnel and fifteen drops were run into the flask. The mixture was warmed and stirred, more (VII) was added and the stirring was continued for seventeen hours. The mixture darkened and some residue appeared on the lithium. The mixture was poured over crushed dry ice, hydrolyzed, and worked up as usual. No organic material was recovered, other than tars and the bulk of the lithium was recovered unchanged.

3. Synthesis of 4-aminocinnoline, (VIII).

A mixture of 2.0 g. (VII) in 375 ml. concentrated (28%) ammonium hydroxide was placed in a pressure bottle which was capped, wrapped in towels and placed on the steam bath for seventeen hours. The bottle was then cooled in the refrigerator, opened and the solvent evaporated under reduced pressure. Pale cocoa-brown plates appeared and were removed from the last traces of solvent by filtration.

These plates were recrystallized from water to give pale tan plates, m.p. 213-214° (uncorr.). Simpson[31] reports m.p. 212-213° (uncorr.). There was obtained 1.02 g. of the amine for a 58% yield.

In an effort to obtain 4-bromocinnoline, diazotization of 4-aminocinnoline was attempted. A solution of 0.2 g. 4-aminocinnoline in 3 ml. 6N. hydrochloric acid was cooled in an ice bath to 0°C. Two chips of ice were added followed by small portions of a 1.5% sodium nitrite solution until an excess of nitrite was indicated by starch-potassium iodide paper. The clear solution was then poured into an alkaline solution containing excess 2-naphthol. A curdy precipitate formed. This yellow substance recrystallized from water as pale yellow plates, m.p. 128.0° (abs.) with softening at 101°. Mixed melting point with 2-naphthol, 111-115°; 2-naphthol m.p. 123-125°.

Analysis. Calculated for $C_{18}H_{12}N_4O$: C, 70.12; H, 3.92; Found: C, 77.84; H, 5.80. Calculated for 2-naphthol: C, 83.20 H, 5.55.

There was insufficient material for further investigations.

4. Attempts to prepare 4-bromocinnoline.

a. Treatment of (VI) with phosphorus pentabromide and phosphorus oxybromide. To a mixture of phosphorus

pentabromide and phosphorus oxybromide (1.5 g.) was added 2.0 g. of 4-hydroxycinnoline in a large test tube. The mixture was warmed gently over a micro flame after being mechanically mixed. A dark tar was produced from which nothing could be recovered.

b. Treatment of (VI) with a mixture of phosphorus and bromine. A mixture of 5.0 g. (VI) and 0.5 g. dry red phosphorus was placed in a 50 ml. round bottom flask. The mixture was cooled by an ice bath and 6.0 g. bromine was slowly added. The mixture was heated on a water bath, and then warmed to a dark melt over a free flame. The melt was poured over ice and water. This mixture was neutralized with sodium acetate to congo red, the neutralization inadvertantly being carried too far. The mixture was extracted with ether which was washed with dilute sodium carbonate and dried over calcium sulfate. Upon evaporation a yellow substance appeared. Recrystallization from petroleum ether gave a slight quantity of light yellow crystalline material, m.p. 175-177° (uncorr.), which was present in insufficient quantity to be characterized. This substance was apparently stable at room temperature.

c. Treatment of (VI) with phosphorus tribromide. To 1.5 g. (VI) was added 15 g. phosphorus tribromide and the mixture was refluxed for twenty minutes. The mixture was

poured over crushed ice, neutralized carefully to congo red, and immediately extracted with ether. The ether was washed with sodium carbonate solution and water, and dried over sodium sulfate. In order to maintain a dilute solution, 60 ml. dry petroleum ether was added to the ether solution before evaporation. The solution was evaporated to 50 ml. and cooled. Only tar was obtained, though as the mixture was evaporated to dryness in an open dish there appeared yellow crystals which decomposed rapidly.

5. Attempts to condense sodio malonic ester and other enolic compounds with 4-chlorocinnoline.

a. Malonic ester. To a solution of 5 g. diethyl malonate in 100 ml. dry ether was added 0.6 g. sodium ribbon. This was carried out in a three-neck flask equipped with a mercury-seal stirrer, dropping funnel, condenser and drying tube. The sodium was quickly consumed and the mixture was stirred four hours yielding a white homogenous paste of the sodio malonic ester. A solution of 4.3 g. (VII) in 50 ml. dry ether was added over a ten minute period. The vigorously stirred mixture was initially light yellow and in a short time some dark flecks appeared. Low heat from a mantle was applied for three hours and the color turned a pale olive-green. The mixture was allowed to stand for ten hours. It was carefully hydrolyzed with water. The ether layer which separated was washed once each with water,

dilute hydrochloric acid, dilute sodium bicarbonate and water. After being dried over calcium sulfate the solution was evaporated to a residue which appeared to be unchanged (VII), but turned to tar before any could be isolated.

b. Ethyl cyanoacetate. To a solution of 10 g. ethyl cyanoacetate in 30 ml. dry benzene in a flask as described above was added 2.0 g. sodium hydride. There was a rapid evolution of hydrogen and the temperature rose from 0° to 60°. The mixture was vigorously stirred until a homogenous paste was obtained. To this paste was added 6.6 g. (VII) over a period of twenty minutes. The mixture was stirred at room temperature overnight and was then hydrolyzed with a large amount of water. A goodly amount of yellow solid turned out to be unchanged (VII). No other compounds were obtained.

c. Ethyl acetoacetate. The sodio salt was prepared by the treatment of 5.5 g. ethyl aceoacetate in 35 ml. dry benzene with 1.0 g. sodium hydride. To the well stirred paste was added 5.7 g. (VII) in dry benzene. The mixture was alternately heated and stirred for sixteen hours. Water was added to hydrolyze the mixture and ether was added to aid separation of the layers. Only (VII) was recovered when the organic layer was washed, dried, and evaporated.

d. Benzoylacetone. The sodio salt was prepared by the treatment of 7.0 g. benzoylacetone with 1.0 g. sodium

hydride in 30 ml. dry benzene. To the well stirred sodio salt suspension was added 4.0 g. (VII) in dry benzene. After six hours stirring and heating the mixture was cooled and hydrolyzed with excess water. The organic phase was dried over calcium sulfate and upon evaporation most of the benzoylacetone was recovered. No (VII) was recovered in this instance. A similar run was made using sodium amide as the condensing agent, with essentially the same results.

e. Phenylacetone. To a solution of 1.0 g. phenylacetone in 15 ml. dry benzene was added 0.3 g. sodium amide. After stirring for one hour, 0.4 g. (VII) was added and the mixture was stirred an additional three hours. The mixture was hydrolyzed with water and extracted with ether which was washed with water and dried over calcium sulfate. Upon evaporation only a small amount of the phenylacetone was recovered.

6. Synthesis of α-(4-cinnolyl)-phenylacetonitrile, (XXIII).

The sodium amide used in the following syntheses was stored under dry toluene and was pressed between filter papers prior to weighing, an excess being used to allow for absorbed toluene.

Six grams of sodium amide was added to a solution of 13.0 g. phenylacetonitrile in 70 ml. dry benzene cooled in an ice-brine bath. The mixture was stirred for one hour and

at that time 8.23 g. (VII) in 75 ml. dry benzene was added over a period of fifteen minutes. The deep red-black color of the amide-nitrile mixture did not change on addition of (VII), though some orange residue appeared on the upper sides of the flask. The mixture was stirred for two hours at room temperature. It was then hydrolyzed with water, voluminous yellow curdy precipitate formed and remained suspended between the benzene and water layer. The mixture was filtered and ether was added to the benzene layer to facilitate separation of the layers. The solids obtained by filtration were recrystallized from ethanol-water as golden plates. The organic layer from above was washed with water, dried and evaporated on the steam cone. Some additional solid material was obtained and similarly recrystallized. A total of 11.45 g. of (XXIII) was obtained for a 93.5% yield. The compound has a melting point: 197.5-198.5° (abs.).

Analysis. Calculated for $C_{16}H_{11}N_3$: C, 78.34, H, 4.52, N, 17.13. Found: C, 78.09, H, 4.67, N, 16.77.

Z. Synthesis of α-(4-cinnolyl)-phenylacetamide, (XXVII).

One gram of the nitrile (XXIII), was allowed to stand overnight in 8.0 ml. concentrated sulfuric acid. The mixture was poured into 200 g. crushed ice and 25.0 ml. concentrated ammonium hydroxide. An orange-yellow precipitate appeared and was removed by filtration. The solids were washed with hot ethanol to remove unchanged (XXIII).

The product was not sufficiently soluble in any of the usual organic solvents, so it was purified by dissolving in concentrated hydrochloric acid and slowly reprecipitated from a hot solution with dilute base. There was obtained 1.0 g. for a 93% yield: pale yellow crystals, m.p. 248-249° (abs.).

Analysis. Calculated for $C_{16}H_{13}N_3O$: C, 72.98, H, 4.98. Found: C, 72.75, H, 5.18.

8. Synthesis of 4-benzylcinnoline, (XXIX).

A mixture of 4.0 g. (XXIII), 8.0 ml. concentrated sulfuric acid and 8.0 ml. water was refluxed for one hour. The cooled mixture was poured into cracked ice and 25 ml. concentrated ammonium hydroxide. The solid product was taken up in ether, which was washed, dried and evaporated. As the latter part of the solvent was evaporating, large pale yellow, lath-shaped crystals appeared. These were removed by filtration at two different stages of evaporation. There was also a crystalline residue of product which was recrystallized from ethanol-water. There was obtained a total of 1.55 g. for a 43% yield. The compound melted: 104.5° (abs.).

Analysis. Calculated for $C_{15}H_{12}N_2$: C, 81.79, H, 5.49, N, 12.72. Found: C, 81.77, H, 5.77, N, 12.53.

9. Synthesis of α-(4-cinnolyl)-m-methoxyphenylacetonitrile, (XXV).

To a solution of 4.0 g. m-methoxyphenylacetonitrile

in 20 ml. dry benzene was added 1.0 g. sodium amide. A vigorous reaction followed and the temperature rose from 25° to 55°. The mixture was stirred for one hour at room temperature and in that time turned dark red-black. A solution of 2.2 g. (VII) in 15 ml. dry benzene was then added to the flask in two portions and the temperature rose about 15°. The mixture was stirred at room temperature for three and one half hours and was then carefully hydrolyzed. A small amount of dilute hydrochloric acid was added to neutralize the basic solution. The mixture was extracted with ether and some of the solids were removed by filtration. These solids and those obtained from the ether after drying were combined and recrystallized from ethanol-water. There was obtained 2.1 g. deep orange-red plates for a 55% yield. The crystals melted: 194.5-195° (abs.), softening at 192°.

Analysis. Calculated for $C_{17}H_{13}N_3O$: C, 74.16, H, 4.76. Found: C, 74.14, H, 4.94.

10. Synthesis of α-(4-cinnolyl)-p-methoxyphenylacetonitrile, (XXVI).

A solution of 4.0 g. p-methoxyphenylacetonitrile in 25 ml. dry benzene was treated with 1.0 g. sodium amide and was stirred at room temperature for one half hour. Then 2.0 g. (VII) in 10 ml. dry benzene was added and the mixture was stirred an additional four hours. Water was carefully added. The red-orange mixture was decanted into a separatory

funnel and the solids left were recrystallized from ethanol-water. Likewise, the product obtained from the benzene-ether layer was recrystallized. There was obtained a total of 2.5 g. for a 66% yield. The nitrile was obtained as red-orange plates, m.p. 183-185° (abs.).

Analysis. Calculated for $C_{17}H_{13}N_3O$: C, 74.16, H, 4.76. Found: C, 74.36, H, 5.08.

11. Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-phenyl-acetonitrile, (XXXI).

To a solution of 2.5 g. phenylacetonitrile in 30 ml. dry benzene was added 1.0 g. sodium amide. The mixture was stirred at room temperature for one hour. Then a solution of 2.0 g. (XVIII) in 20 ml. dry benzene was slowly added and the mixture was extracted with ether. The bulk of the product remained in suspension between the two layers and had to be removed by filtration. The small amount of product obtained from the ether was combined with the initial solids and all was recrystallized from ethanol-water. There was obtained 1.16 g. of orange-red plates for a 40% yield. The compound melted: 220-221° (abs.).

Analysis. Calculated for $C_{18}H_{15}N_3O_2$: C, 70.80, H, 4.95. Found: C, 69.85, H, 5.10.

12. Condensation of 4-chlorocinnoline and p-nitrophenylacetonitrile.

To a solution of 7.0 g. p-nitrophenylacetonitrile in 30 ml. dry benzene was added 2.0 g. sodium amide and the mixture was stirred one hour at room temperature. A solution of 3.2 g. (VII) in 25 ml. dry benzene was added slowly to the deep red mixture. The mixture was stirred for an additional three hours at room temperature. By that time the mixture was a drab brown. It was carefully hydrolyzed, but the temperature rose somewhat and some dark material appeared. The mixture was extracted with ether which was dried over calcium sulfate and evaporated to yield 2.5 g. golden plates, m.p. 111.5-113° (uncorr.) which turned darker on standing. An additional batch of orange-red solid was obtained by filtering the material remaining in the reaction flask. This was initially darker than the product obtained by ether extraction. The products after standing two months all appeared the same and they could be recrystallized from ethanol-water to give red plates melting at 145° (uncorr.). The product was soluble in concentrated hydrochloric acid, insoluble in water or 10% sodium hydroxide. The analyses indicate it is not the expected α-(4-cinnolyl)-p-nitrophenylacetonitrile.

Analysis. Calculated for $C_{16}H_{10}N_4O_2$: C, 64.42, H, 3.38. Found: C, 50.28, H, 5.18.

The procedures indicated in B.7 and B.8 were followed with the intention of preparing α-(4-cinnolyl)-p-nitrophenylacetamide and 4-(p-nitrobenzyl)-cinnoline. The nitrile showed apparent high reactivity but the products obtained did not have the correct analysis. Some of the intended amide was heated for a number of hours at 100° over phosphorus pentoxide and under a vacuum of 1 mm. to investigate the possibility of water or ethanol of crystallization, but no change in the analysis occurred. The following analysis is reported for the amide and benzyl compound.

Calculated for the amide, $C_{16}H_{12}N_4O_3$: C, 62.33, H, 3.92. Found: C, 53.34, H, 4.69. M.p.: 193-194° (abs.).

Calculated for the benzyl, $C_{15}H_{11}N_3O_2$: C, 67.91, H, 4.18. Found: C, 53.40, H, 3.87. M.p.: 153-154° (abs.).

13. Attempted synthesis of α-(4-cinnolyl)-3,4-dimethoxyphenylacetonitrile.

A solution of 16.0 g. 3,4-dimethoxyphenylacetonitrile in 50 ml. dry benzene was stirred while 10 g. sodium amide was added. The mixture was stirred and warmed for one hour. Though no apparent reaction took place, a solution of 8.0 g. (VII) was added and the mixture was stirred overnight. There was only slight coloration and large quantities of ammonia were evolved when the mixture was hydrolyzed. The mixture was extracted with ether, the ether washed and dried over calcium sulfate. The bulk of the cinnoline, (VII), and

most of the 3,4-dimethoxyphenylacetonitrile was recovered.

In another run, 3,4-dimethoxyphenylacetonitrile was refluxed for twenty four hours in benzene with the evolution of practically no ammonia.

14. Synthesis of α-(6,7-dimethoxy-4-cinnolyl)-phenylacetamide, (XXXII)

A mixture of 0.35 g. of the nitrile, (XXXI), in 1.5 ml. concentrated sulfuric acid was allowed to stand twelve hours at room temperature. It was then poured over crushed ice and an excess of ammonium hydroxide. A creamy-white precipitate appeared. This was filtered and taken up in 95% ethanol. Water was added to the ethanol and when cooled to 10°, the solution yielded a small amount of opaque white crystals. The compound melted at 234.5-236.5° (abs.) with softening at 228-232°.

Analysis. Calculated for $C_{18}H_{17}N_3O_3$: C, 66.86, H, 5.30. Found: C, 66.83, H, 5.55.

SUMMARY

The reactivity of the chlorine in the 4-position of cinnoline has been further defined by the inability of 4-chlorocinnoline to form corresponding Grignard or organolithium compounds and by its lack of reactivity with sodio salts of malonic ester and other enolic-methylene compounds. It has been shown that 4-chlorocinnoline is sufficiently reactive to form 4-aminocinnoline when treated with ammonium hydroxide and will also condense with phenylacetonitriles to form α-(4-cinnolyl)-phenylacetonitriles from which the corresponding amides and 4-benzylcinnolines can be prepared.

The preparation of 6,7-dimethoxy-4-hydroxycinnoline and 4-chloro-6,7-dimethoxycinnoline is described.

The problem of a convenient method to prepare o-aminoacetophenone has not been solved, but an attempted new approach is described.

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The work of Simpson and Schofield constitutes the most important recent contribution to the field of cinnoline chemistry and, for convenience, their twenty six papers are listed as a unit.

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