

THE CHEMISTRY OF CINNOLINES

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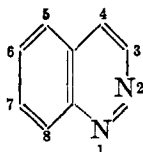
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I. INTRODUCTION

The discovery of cinnoline dates from 1883, but the compound and its derivatives have not received the attention accorded related heterocyclic nitrogen compounds. A number of substituted cinnolines have been described as useful dyes (22, 23, 24, 42, 43). No suggestion has yet appeared in the literature as to the possible utility of cinnoline compounds as medicinals or as reagents for analytical chemistry.

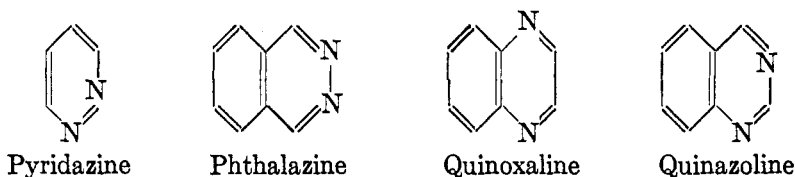
II. RELATION TO OTHER BINITROGEN HETEROCYCLES

Cinnoline is a heterocyclic binuclear base containing two vicinal nitrogen atoms. The numbering system follows that in quinoline. Cinnoline is related



Cinnoline

to pyridazine in that it is benzo[*c*]pyridazine or 3,4-benzopyridazine. It is the least well known of the family of condensed bicyclic aromatic compounds having



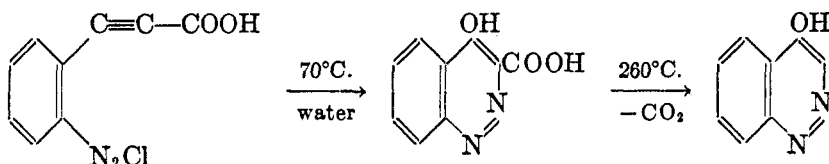
two nitrogen atoms in the same ring. The other members of the family are phthalazine, quinoxaline, and quinazoline.

III. SYNTHESIS OF CINNOLINES

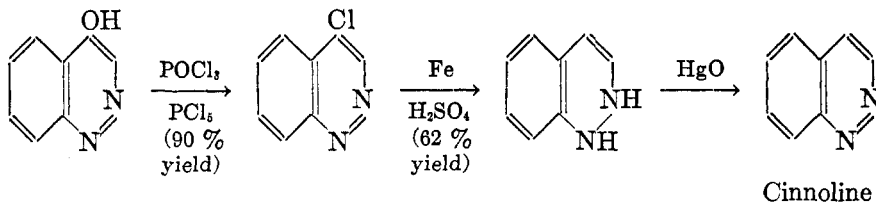
A. GENERAL METHODS

1. From *o*-aminophenylpropionic acids

The first synthesis of cinnoline was reported in 1883 by von Richter (32), who did not obtain the new compound in sufficiently pure condition for determination of its physical properties or for elementary analysis. The diazonium chloride obtained from *o*-aminophenylpropionic acid was heated in water solution at 70°C. Cooling caused the separation of 4-hydroxycinnoline-3-carboxylic acid in quantitative yield. When this acid was heated above its melting point, carbon dioxide was liberated and 4-hydroxycinnoline was formed in nearly theoretical yield. Distillation of 4-hydroxycinnoline with zinc dust furnished a small amount of a basic oil, which was assumed to be cinnoline.

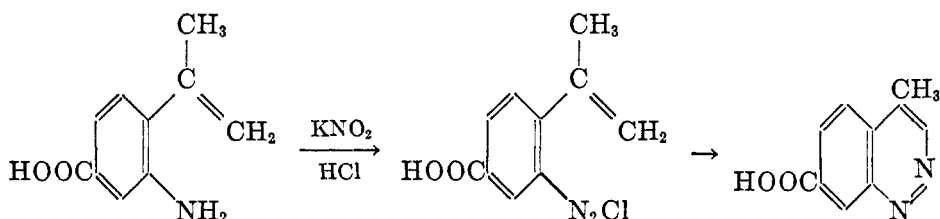


This preparation of 4-hydroxycinnoline was repeated by Busch and Klett (11), although in less satisfactory yield than that reported by von Richter. The 4-hydroxycinnoline was converted successfully to cinnoline *via* the 4-chloro compound by Busch and Rast (12).

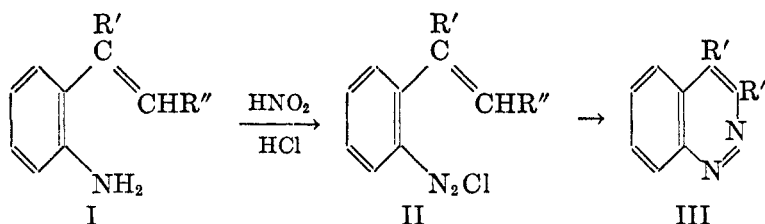


2. From *o*-aminophenylethylenes

When diazonium salts prepared from certain *o*-aminophenylethylenes are allowed to stand, cinnolines are formed. When diazotized 3-amino-4-isopropylbenzoic acid was allowed to stand at room temperature, it was found by Widman (53, 54) to undergo ring closure to 4-methylcinnoline-7-carboxylic acid.



This method was extended by Stoermer, Gaus, and Fincke (44, 45). Diazotization of the substituted *o*-aminophenylethylene was followed by cyclization, which usually occurred spontaneously at room temperature in nearly quantitative yield.



Stoermer obtained substituted cinnolines when R' was phenyl, *p*-tolyl, or *p*-anisyl and R'' was hydrogen, and when R' was phenyl and R'' was methyl.

TABLE 1

Influence of substituents R' and R'' in the formation of cinnolines from o-aminophenylethylenes

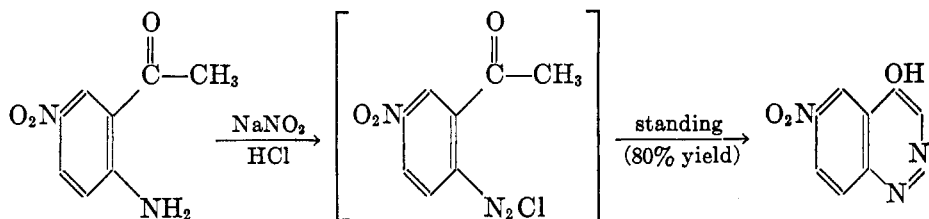
R'	R''	RESULT
COOH	C ₆ H ₅	(Pschorr reaction)
COOH	<i>m</i> -CH ₃ C ₆ H ₄	(Pschorr reaction)
H	C ₆ H ₅ (<i>cis</i>)	(Pschorr reaction)
H	COOH	(No cinnoline formation)
H	COOC ₂ H ₅	(No cinnoline formation)
H	CN	(No cinnoline formation)
C ₆ H ₅	H	4-Phenylcinnoline
C ₆ H ₅	CH ₃	3-Methyl-4-phenylcinnoline
C ₆ H ₅	C ₆ H ₅ (<i>cis</i>)	3,4-Diphenylcinnoline
C ₆ H ₅	C ₆ H ₅ (<i>trans</i>)	3,4-Diphenylcinnoline
C ₆ H ₅	C ₆ H ₅ CH ₂	3-Benzyl-4-phenylcinnoline
C ₆ H ₅	α -C ₁₀ H ₇	3-(1'-Naphthyl)-4-phenylcinnoline

When R' was phenyl and R'' was bromine, diazotization in hydrochloric acid solution produced 4-phenylcinnoline in 22 per cent yield rather than the expected bromophenylcinnoline. Stoermer deduced, from the fact that *o*-aminocinnamic acid did not yield a cinnoline, that a negative group (R'') on the β -ethylenic carbon atom of the *o*-aminophenylethylene inhibits the cyclization. In a recent report of original experiments, correlated with existing data on the synthesis of cinnolines by the Widman-Stoermer reaction, Simpson (40, 41) has indicated the limitations of this method of cyclization (I \rightarrow II \rightarrow III). It will be seen in table 1 that the nature of the substituents R' and R'' has a strong directing effect

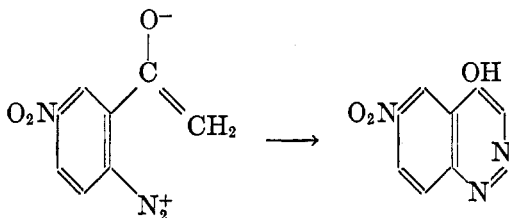
upon the course of the reaction. The available data lead to the conclusion that cinnoline formation does not occur when R'' is aryl or another negative group and R' is either hydrogen or carboxyl. When R' is a phenyl or a substituted phenyl group, cinnoline formation is favored in spite of the presence of an aryl group, R'' , on the β -carbon atom. 3,4-Diphenylcinnoline was obtained in quantitative yield from either *cis*- or *trans*- α -(*o*-aminophenyl)- α , β -diphenylethylene; therefore, in this case at least, the cyclization is independent of spatial configuration.

3. From *o*-aminoacetophenones

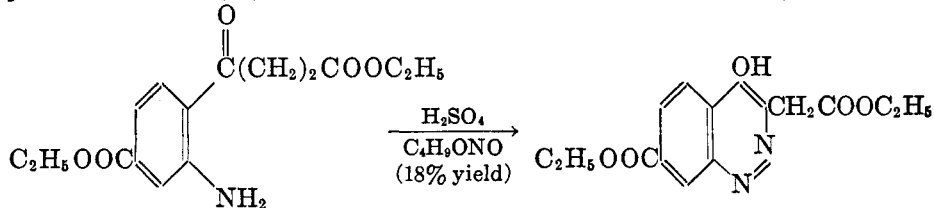
A related method, which would appear to be general for the synthesis of cinnolines, involves the diazotization of an *o*-aminoacetophenone. Borsche and Herbert (8) diazotized 2-amino-5-nitroacetophenone and allowed the diazonium salt solution to stand at room temperature. The product, 4-hydroxy-6-nitrocinnoline, separated in 80 per cent yield.



The reaction probably involves an intramolecular coupling of the diazonium



cation with the enolate anion. Such a mechanism would be similar to the coupling of an aryldiazonium ion with a phenoxide ion to form an azo compound. Koelsch (26) carried out a similar diazotization and ring closure:

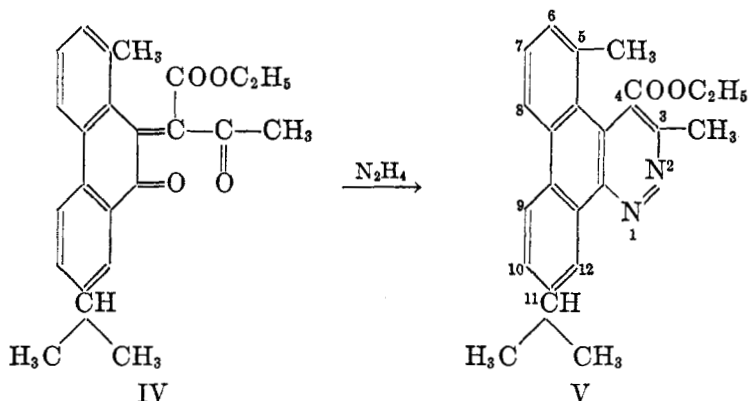


B. SPECIAL METHODS

1. From hydrazine and substituted hydrazines

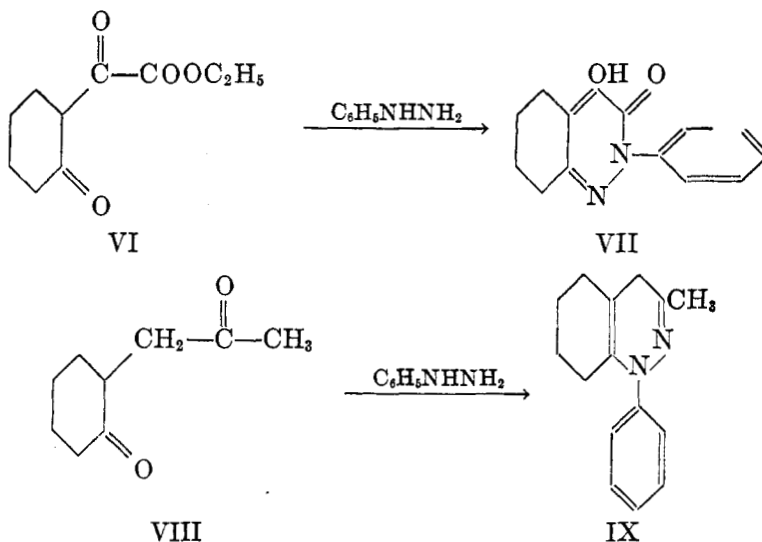
The reaction of a dicarbonyl compound with hydrazine to form an azine is well known. This reaction has been used to advantage by a number of workers

for the preparation of cinnolines from certain 1,4-dicarbonyl compounds. An example is provided by Heiduschka and Khudadad (21), who synthesized ethyl 3,5-dimethyl-11-isopropylidibenzof, h]cinnoline-4-carboxylate (V) by the condensation of "retoxyleneacetoacetic ester" (one possible formula, IV, is given) with hydrazine.



Further examples are found in table 2. Although some of the products are named on the basis of pyridazine or phthalazine, all may equally well be regarded as substituted cinnolines. Only highly substituted polynuclear cinnoline derivatives have been prepared in this manner.

Just as hydrazine has been used with certain 1,4-dicarbonyl compounds for cinnoline formation, so phenylhydrazine has been utilized (6, 18). Reaction of phenylhydrazine with ethyl cyclohexanonoxalate (VI) gave 5,6,7,8-tetrahydro-4-hydroxy-2-phenyl-3(2)-cinnolone (VII). Reaction of phenylhydrazine with acetoncyclohexanone (VIII) furnished 1,4,5,6,7,8-hexahydro-3-methyl-1-phenylcinnoline (IX).



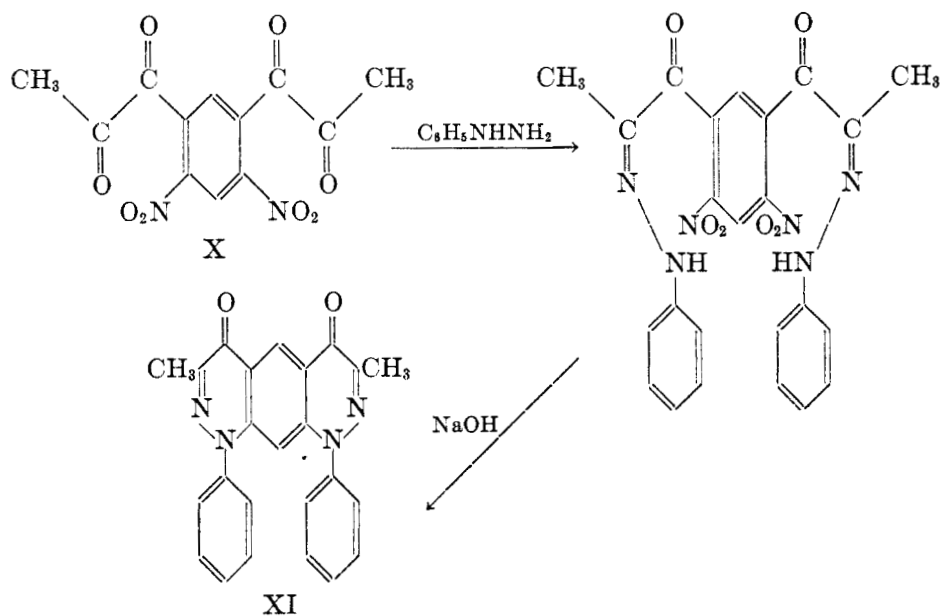
Closely related to these reactions with phenylhydrazine is the synthesis of 3,7-dimethyl-1,9-diphenylpyridazo[4,3-*g*]cinnoline-4,6(1,9)-dione (XI) by Ruggli and Straub (33).

TABLE 2

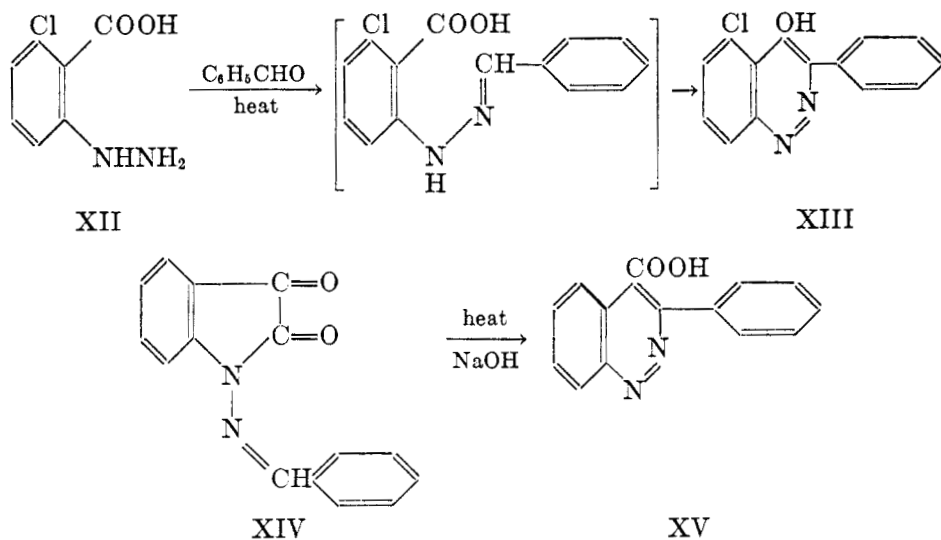
Formation of cinnolines and related compounds by condensation of diketones with hydrazine

DIKETONE	PRODUCT	REFER- ENCE
3,9-Dibenzoylperylene-4,10-quinone.	3,10-Diphenylperlylo[3,5- <i>cd</i> ,9,10- <i>c'd'</i>]di- pyridazine	(7)
Ethyl γ -phenyl- α -phenacylacetate	3-Phenylbenzo[<i>g</i>]cinnolin-5(10)-one	(9)
1,2,3,4 - Tetrahydro - 1 - keto - 3 - phenyl-2-naphthaleneacetic acid...	1,2,5,6 - Tetrahydro - 5-phenylbenzo [h] cin- nolin-3(4)-one	(10)
Dibenzo[<i>a,h</i>]phenanthrene - 5,6,7, 12-tetrone.....	Dinaphtho[1,2,3 - <i>de</i> ,1',2',3' - <i>ij</i>]phthala- zine-7,14-dione	(13)
Dibenzo[<i>c,m</i>]pentaphene - 5,8,15, 16-tetrone.....	Diphenanthro[1,2,3- <i>de</i> ,3',2',1'- <i>ij</i>] phthal- azine-5,8-dione	(14)
11-Methylbenzo [c] pentaphene-5,8, 13,14-tetrone.....	11-Methylnaphtho[1,2,3- <i>de</i>]phenanthro- [3',2',1'- <i>ij</i>]-phthalazine-5,8-dione	(14)
2,10-Dimethyldibenzo[<i>b,h</i>]phenan- threne-5,6,13,14-tetrone.....	2,10-Dimethyldinaphtho [1,2,3- <i>de</i> ,3',2',1'- <i>ij</i>]phthalazine-5,8-dione	(15)
Retroxyleneacetoacetic ester.....	Ethyl 3,5-dimethyl-11-isopropyldibenzo- [<i>f,h</i>]cinnoline-4-carboxylate	(21)
Triphthaloylbenzene.....	Trinaphthylene[5,6,11,12]dipyridazine- 17,18-dione	(30)
Dibenzo [b, h] phenanthrene-5,8,13, 14-tetrone-3-carboxylic acid.....	Dinaphtho[1,2,3- <i>de</i> ,3',2',1'- <i>ij</i>] phthala- zine-5,8-dione-3-carboxylic acid	(37)
Dibenzo [b, h] phenanthrene-5,8,13, 14-tetrone.....	Dinaphtho[1,2,3 - <i>de</i> ,3',2',1'- <i>ij</i>] phthala- zine-5,8-dione	(38)
1-Benzoyl-5-chloroanthraquinone....	8-Chloro-3-phenylnaphtho[1,2,3- <i>de</i>]phthal- azin-7-one	(42)
1-Amino-5-benzoylanthraquinone...	8-Amino-3-phenylnaphtho[1,2,3- <i>de</i>]phthal- azin-7-one	(43)
1-Propionylanthraquinone.....	3-Ethylnaphtho[1,2,3- <i>de</i>]phthalazin-7-one	(52)

There are two examples of the preparation of cinnolines from substituted phenylhydrazones of benzaldehyde. 5-Chloro-4-hydroxy-3-phenylcinnoline (XIII) was obtained in low yield by Pfannstiel and Janecke (29), and 3-phenyl-

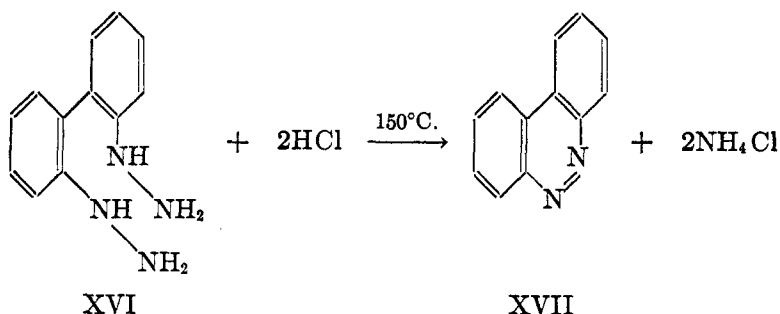


cinnoline-4-carboxylic acid (XV) was considered to be the product obtained by Stollé and Becker (46) in the following reactions:



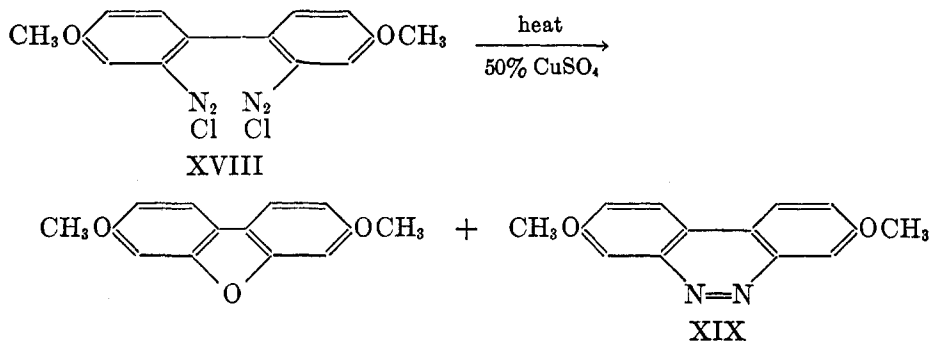
A dihydrazino compound has also been used for the preparation of a cinnoline. When 2,2'-dihydrazinobiphenyl (XVI) was heated with hydrochloric acid under pressure, Täuber (50) was able to obtain benzo[*c*]cinnoline (XVII) in quantitative yield. The reaction is parallel to the formation of carbazole by the

heating of 2,2'-diaminobiphenyl with acid. Täuber likewise obtained benzo[c]cinnoline by heating the diacetyl derivative of XVI.



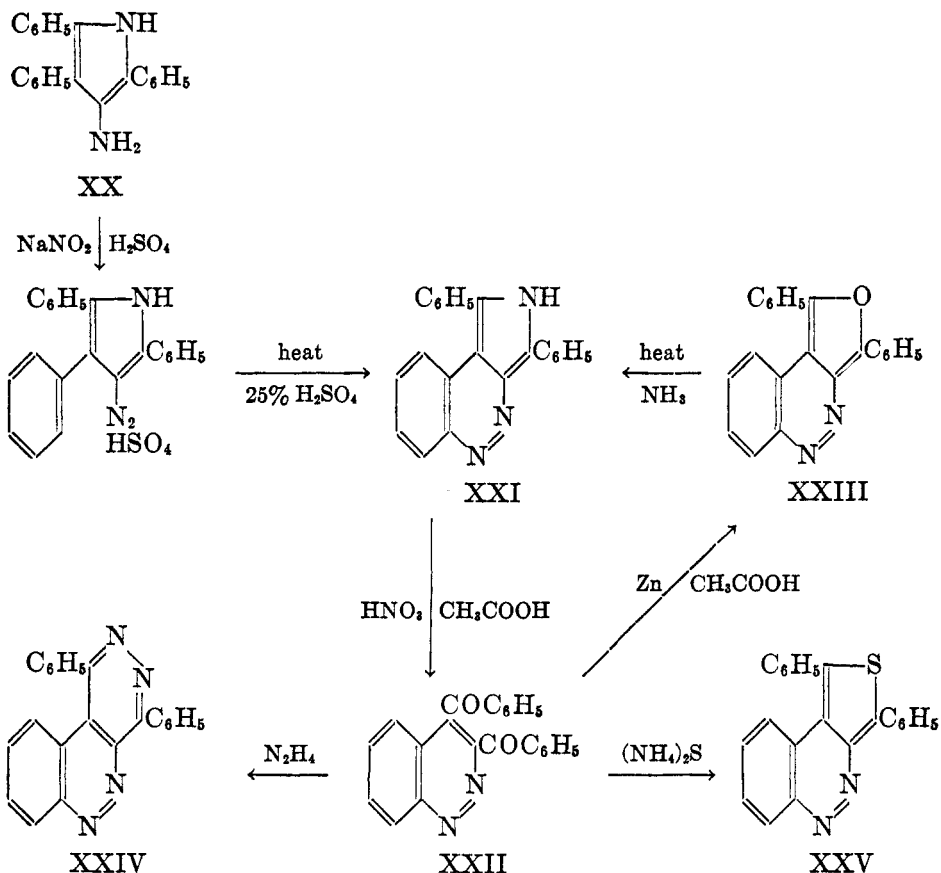
2. From diazo compounds .

Benzo[c]cinnolines have been prepared from tetrazonium salts. In 1935, Hata, Tatematsu, and Kubota (20) obtained 3,8-dimethoxybenzo[c]cinnoline (XIX) as a by-product in their synthesis of 2,7-dimethoxydiphenylene oxide by treatment of tetrazotized 2,2'-diamino-4,4'-dimethoxybiphenyl (XVIII) with copper sulfate.

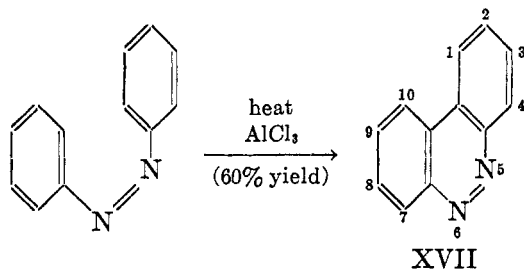


Later, Sandin and Cairns (35) obtained a 45 per cent yield of benzo[c]cinnoline by treatment of tetrazotized 2,2'-diaminobiphenyl with arsenious oxide in sodium carbonate solution. 3,8-Dimethylbenzo[c]cinnoline was prepared in a like manner from 2,2'-diamino-4,4'-dimethylbiphenyl.

When 4-amino-2,3,5-triphenylpyrrole (XX) was diazotized, it was found that the resulting diazonium salt could be converted to a cinnoline (XXI) by heating with dilute sulfuric acid. Angelico (1, 2, 3, 4, 5) used this diazonium salt for the preparation of several highly substituted cinnoline compounds: 1,3-diphenylpyrrolo[3,4-c]cinnoline (XXI), 3,4-dibenzoylcinnoline (XXII), 1,3-diphenylfuro[3,4-c]cinnoline (XXIII), 1,4-diphenylpyridazo[4,5-c]cinnoline (XXIV), and 1,3-diphenylthieno[3,4-c]cinnoline (XXV). Interconversion of these cinnolines was brought about by well-known reactions.



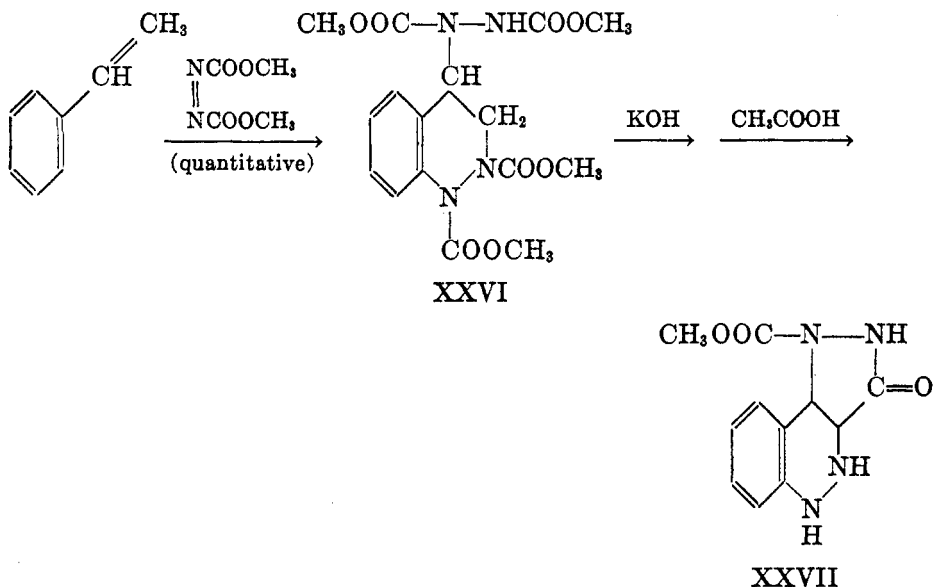
The conversion of a few azo compounds to cinnolines has been reported. The preparation of benzo[*c*]cinnoline (XVII) has been described in a patent (22) which calls for the fusion of azobenzene with aluminum chloride



and sodium chloride at 120°C . 3,8-Dimethylbenzo[*c*]cinnoline was similarly prepared from *m,m'*-azobistoluene at 100°C . in 25 per cent yield; 3,8-tetramethyldiaminobenzo[*c*]cinnoline, from *m,m'*-azobisdimethylaniline at 100°C . in 40 per cent yield.

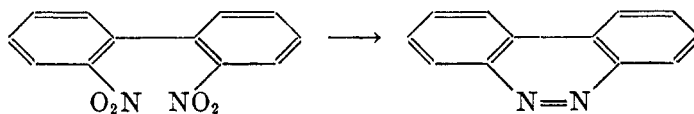
3. From styrene by a Diels-Alder condensation

The addition of dimethyl azodicarboxylate to styrene provides the only example of cinnoline (XXVI, XXVII) formation by means of a Diels-Alder reaction (16). α -Methylstyrene, propenylbenzene, and stilbene failed to give cinnoline-type compounds when treated with dimethyl azodicarboxylate.



4. By reduction of 2,2'-dinitrobiphenyls

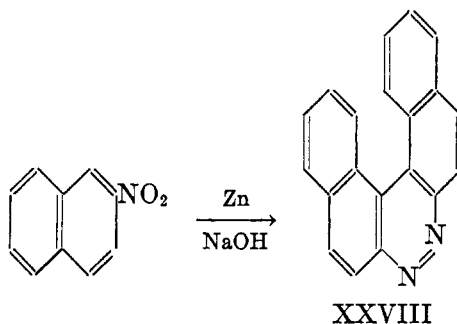
A number of workers have prepared substituted benzo[c]cinnolines by reduction of the correspondingly substituted 2,2'-dinitrobiphenyls. The reaction is parallel to the preparation of azobenzene by the reduction of nitrobenzene and is here illustrated for the production of benzo[c]cinnoline itself:



Examples of the production of substituted benzo[c]cinnolines by this method are found in table 3. Best yields are usually obtained by electrolytic reduction. Meisenheimer and Witte (27) prepared benzo[f]naphtho[2,1-c]cinnoline (XXVIII) by a somewhat similar reaction, the reduction of 2-nitronaphthalene with zinc and alcoholic sodium hydroxide. The cinnoline (XXVIII) was obtained in poor yield along with 2,2'-azonaphthalene and 2,2'-diamino-1,1'-binaphthyl.

TABLE 3
Preparation of benzo[c]cinnolines by reduction of 2,2'-dinitrobiphenyls

BIPHENYL	REDUCING AGENT	BENZO[c]CINNOLINE	YIELD	REFER- ENCE
			<i>per cent</i>	
2,2'-Dinitrobiphenyl.....	Na(Hg) + CH ₃ OH	Benzo[c]cinnoline	55	(47)
	Na ₂ S, then $\begin{cases} \text{SnCl}_2 \\ \text{HCl} \end{cases}$ Electrolytic	Benzo[c]cinnoline Benzo[c]cinnoline	95	(51, (17) (56)
4,4'-Diamino-2,2'-dinitro- biphenyl.....	Na(Hg) + CH ₃ OH	3,8-Diaminobenzo[c]- cinnoline		(47)
	Electrolytic	3,8-Diaminobenzo[c]- cinnoline	80	(51)
4,4'-Diamino-5,5'-dimeth- oxy-2,2'-dinitrobiphenyl....	Electrolytic	3,8-Diamino-2,9-di- methoxybenzo[c]- cinnoline	60	(51)
2,2'-Dinitro-4,4'-biphenyl- dicarboxylic acid.....	Zn + NH ₃	Benzo[c]cinnoline-3,8- dicarboxylic acid		(23)
4,4'-Difluoro-5,5'-dimethyl- 2,2'-dinitrobiphenyl.....	Na(Hg) + CH ₃ OH	3,8-Difluoro-2,9-di- methylbenzo[c]cin- noline	75	(36)
4,4'-Dimethyl-2,2'-dinitro- biphenyl.....	Electrolytic	3,8-Dimethylbenzo[c]- cinnoline		(51)
6,6'-Dimethyl-2,2'-dinitro- biphenyl.....	Na(Hg) + CH ₃ OH	1,10-Dimethylbenzo[c]- cinnoline		(25)
	Electrolytic	1,10-Dimethylbenzo[c]- cinnoline	62	(55)
	Na ₂ S, then $\begin{cases} \text{SnCl}_2 \\ \text{HCl} \end{cases}$	1,10-Dimethylbenzo[c]- cinnoline		(34)
2,2'-Dinitro-4,4'-tetraethyl- aminobiphenyl.....	Electrolytic	3,8-Tetraethylamino- benzo[c]cinnoline	50	(51)
2,2'-Dinitro-4,4'-tetra- methylaminobiphenyl.....	Electrolytic	3,8-Tetramethyl- aminobenzo[c]cin- noline	56	(51)
	Na ₂ S, then elec- trolysis	3,8-Tetramethyl- aminobenzo[c]cin- noline	54	(51)
	Na ₂ S, then $\begin{cases} \text{SnCl}_2 \\ \text{HCl} \end{cases}$	3,8-Tetramethyl- aminobenzo[c]cin- noline	68	(51)



IV. PROPERTIES OF CINNOLINES

A. PHYSICAL PROPERTIES

Cinnoline crystallizes from ether as a solvate of colorless needles, m.p. 24–25°C. (12). The compound separates from ligroin as yellow crystals, m.p. 39°C., free of solvent. Cinnoline has a quinoline-like odor and is soluble in the usual organic solvents. The cinnolines in general have been described as colored compounds.

The ultraviolet absorption spectrum of cinnoline itself has not been described in the literature, but spectra of two closely related compounds have been determined. Ramart-Lucas and Biquard (31) reported the ultraviolet absorption spectrum of benzo[*c*]cinnoline and compared it with that of azobenzene. Evans and Wiselogle (19) have recently described the ultraviolet spectrum of pyridazine in hexane and water solutions from 2400 to 3800 Å. It appears, from infrared absorption spectrum studies on pyridazine (26a), that the ring frequencies in pyridazine are closely analogous to those in *o*-benzene-*d*₂. This indicates that there must be resonance in pyridazine of roughly the same order of magnitude as there is in benzene. One concludes that the nitrogen–nitrogen bond is neither a single nor a double bond but something intermediate. On this basis, cinnoline, which is benzo[*c*]pyridazine, would be expected to be a molecule of high resonance energy with no “fixation” of double bonds. Chemical evidence now available supports this view.

B. CHEMICAL PROPERTIES

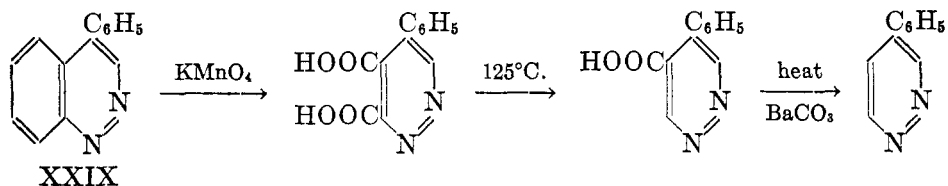
1. Salt formation

Cinnoline is a strong base and forms stable salts with hydrochloric and picric acids and an addition compound with methyl iodide (12). Most substituted cinnolines form neutral salts with acids and addition compounds with methyl iodide, ethyl iodide, and methyl sulfate (45, 56).

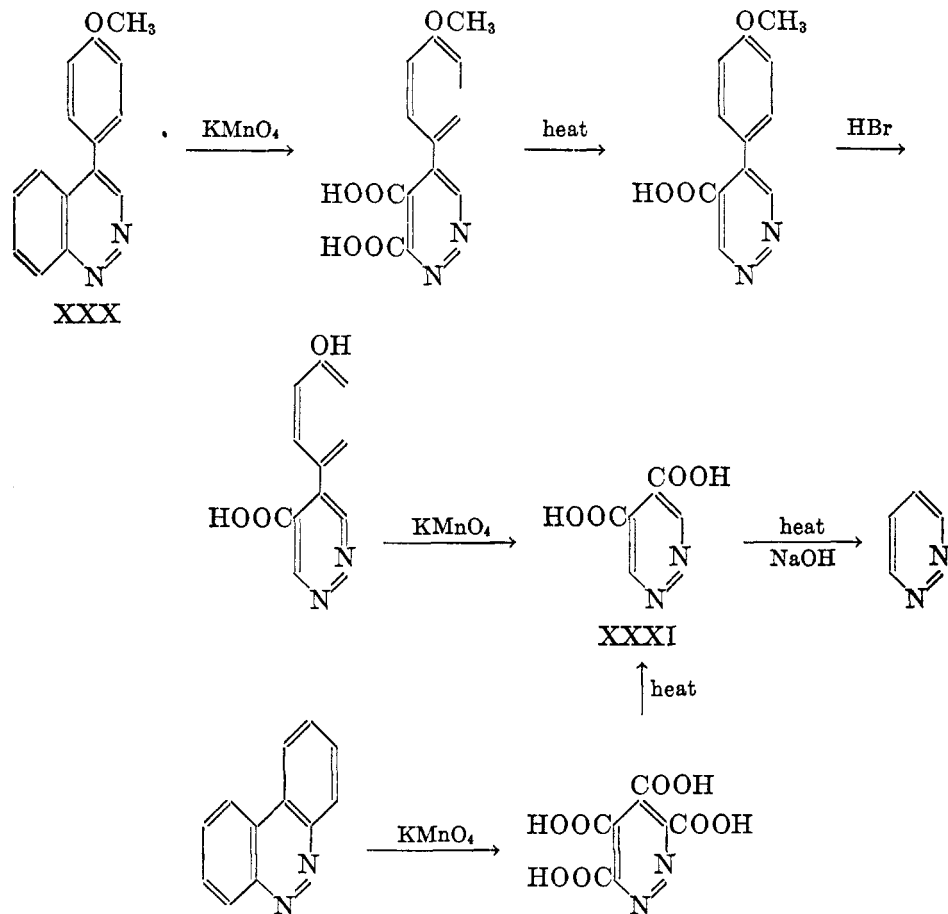
2. Oxidation

The nitrogen-containing ring in cinnoline is stable to oxidation. Potassium permanganate oxidation of 4-phenylcinnoline (XXIX) resulted in the formation

of 5-phenylpyridazine-3,4-dicarboxylic acid, which was subsequently decarboxylated in a stepwise manner to give 4-phenylpyridazine (45). Stoermer and Gaus (44) were able to show that with pyridazinedicarboxylic acids, as with pyridine-dicarboxylic acids, it is the carboxyl group nearer the nitrogen which is first

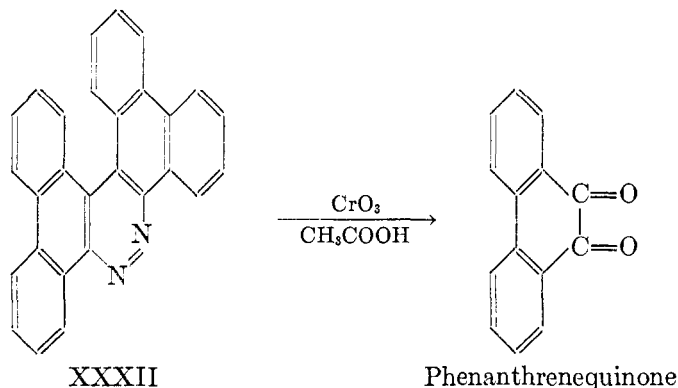


lost during decarboxylation. They oxidized 4-*p*-anisylcinnoline (XXX) and degraded the oxidation product to XXXI, which corresponded to the already known pyridazine-4,5-dicarboxylic acid.



Permanganate oxidation of benzo[*c*]cinnoline produced a pyridazinetetracarboxylic acid which was decarboxylated to the same acid, XXXI (49).

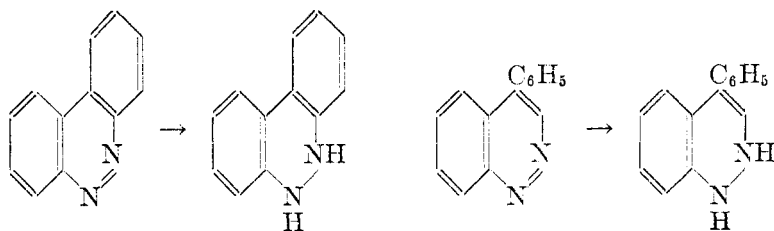
4-Phenylcinnoline (45) and benzo[*c*]cinnoline (48) resisted oxidation by chromic anhydride in acetic acid, but diphenanthro[9,10-*c*,9',10'-*e*]pyridazine (XXXII) was oxidized by chromic anhydride in acetic acid to phenanthrenequinone (39).



A few cinnolines are known to give *N*-oxides. The *N*-oxide of benzo[*c*]cinnoline was obtained by reduction of 2,2'-dinitrobiphenyl with sodium sulfide (17, 34, 51) or with the calculated amount of sodium amalgam in methanol (47), much as azoxybenzene is obtained from nitrobenzene. Excess sodium amalgam or stannous chloride in hydrochloric acid solution converted the *N*-oxide to benzo[*c*]cinnoline. The *N,N'*-dioxide of benzo[*c*]cinnoline was obtained in 25 per cent yield by reduction of 2,2'-dinitrobiphenyl with zinc and potassium hydroxide; this dioxide could be converted to the cinnoline with sodium amalgam in methanol (47).

3. Reduction

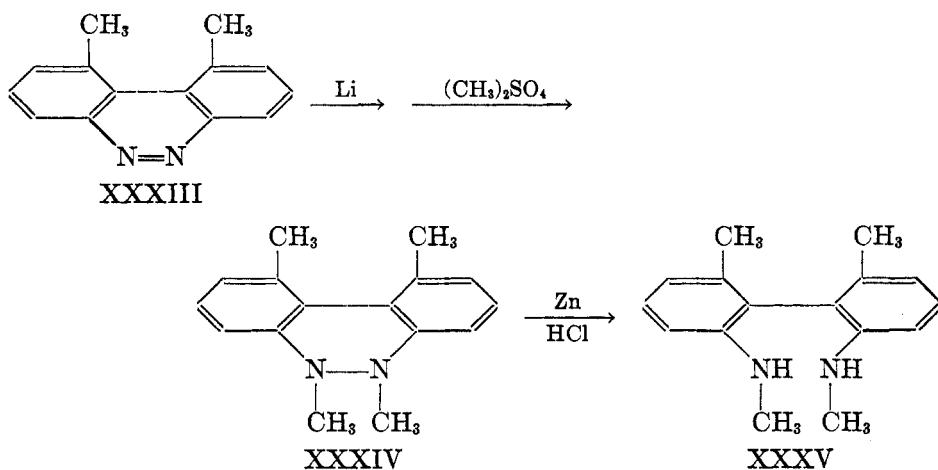
Benzo[*c*]cinnoline was reduced to 5,6-dihydrobenzo[*c*]cinnoline by means of zinc and potassium hydroxide (17), a parallel to the reduction of azobenzene to hydrazobenzene. Zinc and ethanolic ammonia brought about the reduction of 4-phenylcinnoline to 1,2-dihydro-4-phenylcinnoline (28). Iron and mineral



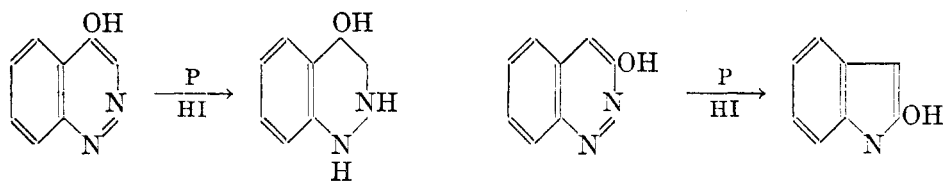
acid (12) and zinc and mineral acid (47, 55) have been used to form dihydrocinnolines, but the latter reagent when used in large excess caused the cleavage of the nitrogen-nitrogen bond. Zinc and acetic acid has likewise encouraged such cleavage in certain cinnolines (27, 39).

Cinnolines will form addition compounds with the alkali metals. Wittig

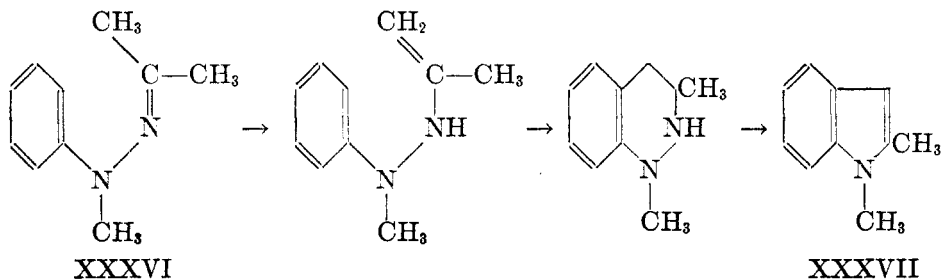
and Stichnoth (55) found that 1,10-dimethylbenzo[*c*]cinnoline (XXXIII) formed addition products with two atoms each of either sodium, potassium, or lithium. The dilithium adduct, by treatment with methyl sulfate, formed 5,6-dihydro-1,5,6,10-tetramethylbenzo[*c*]cinnoline (XXXIV), the structure of which was proved by further reduction with zinc and hydrochloric acid to the substituted biphenyl, XXXV.



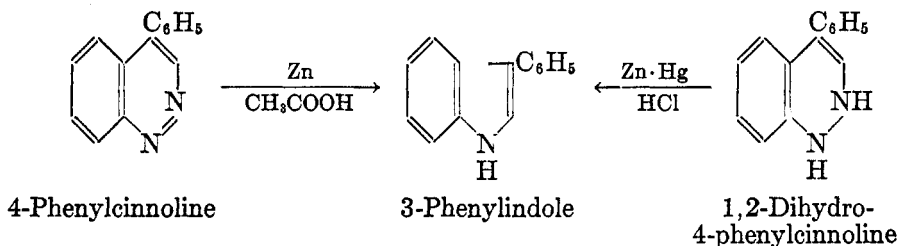
Reduction of two hydroxycinnolines with phosphorus and hydriodic acid was carried out by Neber (28), who found that 4-hydroxycinnoline was converted to the tetrahydro derivative and 3-hydroxycinnoline underwent rearrangement to oxindole.



He suggested at one time that tetrahydrocinnolines might be intermediates in the Fischer indole synthesis, as represented by XXXVI to XXXVII, but later carried out reduction studies in the cinnoline series which showed this view to



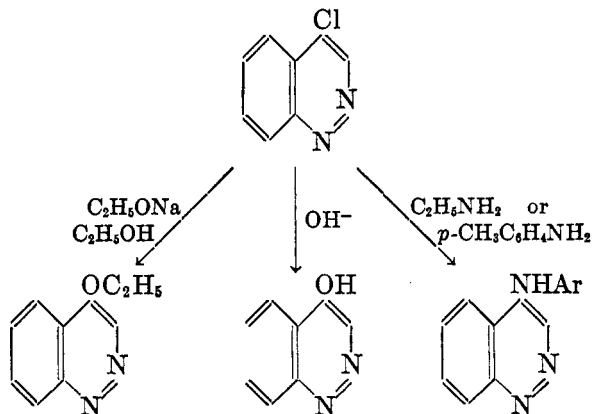
be untenable. 4-Phenylcinnoline and 1,2-dihydro-4-phenylcinnoline were converted to 3-phenylindole by treatment with zinc in acid solution.



If the reaction proceeded through the tetrahydrocinnoline, then 1,2,3,4-tetrahydro-4-phenylcinnoline (prepared from the dihydrocinnoline by catalytic hydrogenation over platinum oxide catalyst) should have given the same product, 3-phenylindole. However, 1,2,3,4-tetrahydro-4-phenylcinnoline remained unchanged when subjected to the same conditions. 1,2-Dihydro-4-phenylcinnoline, when heated at 100°C., underwent disproportionation to 4-phenylcinnoline and 1,2,3,4-tetrahydro-4-phenylcinnoline.

4. Replacement reactions

No nuclear substitution reaction has been carried out on the cinnoline molecule. Replacement reactions studied have been limited to those of 4-chlorocinnoline (11), prepared in 90 per cent yield from 4-hydroxycinnoline by phosphorus oxychloride and phosphorus pentachloride. The 4-chloro group was replaced readily with an ethoxyl group, an aromatic amino group, or again with a hydroxyl group.



The high reactivity of chlorine in the 4-position is similar to that of the chlorine in 4-chloroquinoline.

V. SUMMARY

The methods of synthesis and the physical and chemical properties of cinnolines have been reviewed.

Cinnolines have been made from diazotized *o*-aminophenylpropionic acids, *o*-aminophenylethylenes, and *o*-aminoacetophenones. The nature of the substituent groups in the *o*-aminophenylethylenes has a delimiting effect upon the applicability of this ring-closure method.

A special method for the preparation of polynuclear cinnoline derivatives depends upon the reaction of hydrazine with 1,4-diketones. Certain benzo[*c*]cinnolines have been formed from diazo compounds or substituted 2,2'-dinitro-biphenyls. Two cinnoline derivatives have been made by means of a Diels-Alder condensation.

The cinnolines are basic compounds which readily undergo reduction to dihydrocinnolines. The nitrogen-containing ring of cinnoline is stable to oxidation.

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