CONDENSED PYRIDAZINES INCLUDING CINNOLINES AND PHTHALAZINES

Edited by

Raymond N. Castle

DEPARTMENT OF CHEMISTRY
BRIGHAM YOUNG UNIVERSITY
PROVO, UTAH

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This is the twenty-seventh volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

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A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

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The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

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Preface

The subject matter in this book was originally intended for inclusion in a single volume on pyridazines, condensed pyridazines, and cinnolines and phthalazines. It became apparent, however, that the topics should be divided, simple pyridazines comprising one volume and condensed pyridazines, which are limited for the most part to two rings, making up a separate volume.

This volume is organized into three sections that deal with the two benzopyridazines, cinnolines and phthalazines, and condensed pyridazines in which the second ring contains one or more heteroatoms.

The literature on cinnolines and phthalazines covered here continues that reviewed by J. C. E. Simpsom in *Condensed Pyridazine and Pyrazine Rings* (*Cinnolines, Phthalazines and Quinoxalines*), Interscience Publishers, Inc., New York (1953), with only relatively small areas of overlap caused by an effort to provide continuity. The literature is discussed up to mid-1971 using *Chemical Abstracts* as the guide to the original literature.

The field of condensed pyridazines containing heteroatoms in both rings has in many instances experienced comparatively little research and, therefore, these rings provide many fruitful research areas. Furthermore, a number of possible condensed pyridazine rings have not appeared in the literature; they present opportunities for research in the synthesis of new condensed pyridazine rings.

I hope that this volume will stimulate research in heterocyclic chemistry by alerting chemists to the fascinating and challenging problems that await solution in these ring systems.

I am indebted to the four authors, Professor Tišler, Dr. Stanovnik, Dr. Patel, and Dr. Singerman, for their cooperation and understanding in the preparation of this volume.

RAYMOND N. CASTLE

Provo, Utah
April 1972

Contents

CHAPTER 1

Cinnolines

GARY M. SINGERMAN

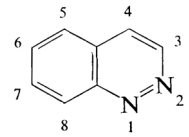
Gulf Research and Development Company, Pittsburgh, Pennsylvania

Part A. Cinnoline

I. Physical Properties

Cinnoline (1,2-diazanaphthalene) (**1**) is a pale yellow solid which is soluble in water and organic solvents. It rapidly liquifies and turns green on standing in air (1), apparently with little decomposition (2). It may be safely stored as the yellow solid under nitrogen at 0° C. When crystallized from ether, it forms a colorless etherate complex which melts at 24–25° C (3). The solvent-free base melts at 40–41° C (2) [37–38° C (1)] and has a boiling point

of 114° C at 0.35 mm Hg (2). The cinnoline ring system was first prepared in 1883 (4), and unsubstituted cinnoline was subsequently made in 1897 (3). Cinnoline itself is toxic and shows antibacterial action against *Escherichia coli* (3). Neither it nor its derivatives have been found in nature. It is numbered according to IUPAC nomenclature as indicated in structure **1**.



1

Cinnoline, with a pK_a equal to 2.51 in 50% aqueous ethanol at 21–22° C (5) [2.70 (6) or 2.29 (7) in water at 20° C], is a weak base compared to quinoline [pK_a 4.94 in water at 20° C (6)] and isoquinoline [pK_a 5.40 in water at 20° C (7)].

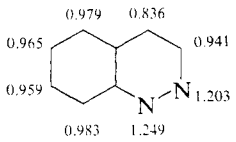
Cinnoline has a dipole moment of 4.14 D in benzene solution compared to values of 4.32 D for pyridazine (8), 2.18 D for quinoline, and 2.52 D for isoquinoline (9), all in benzene solution.

The first and second ionization potentials of cinnoline have been determined by photoelectron spectroscopy to be 8.51 and 9.03 eV (electron volts), respectively. The first ionization potential corresponds to loss of nonbonding electrons (the "lone pair" electrons) from nitrogen, and the second is a π ionization. For comparison, the first ionization potential of naphthalene (π ionization) is 8.11 eV, that of quinoline (π ionization) is 8.62 eV, that of quinazoline (possibly π ionization, but uncertain) is 9.02 eV, and that of phthalazine (lone pair, nonbonding electron ionization) is 8.68 eV (10). Additional information concerning the ionization potentials of the azabenzenes and azanaphthalenes is given in an excellent review of photoelectron spectroscopy by Worley (11).

The heat of atomization of cinnoline, although not determined experimentally, has been calculated by a self-consistent field molecular orbital treatment to be 79.167 eV. This is similar to the calculated heats of atomization of phthalazine (79.215 eV), quinazoline (80.306 eV), and quinoxaline (79.739 eV) (12).

Several molecular orbital calculations of the π-electron density distribution in cinnoline have been made by the Hückel method (13–16). The results of three of these calculations are given in structures **2**, **3**, and **4**. The π-electron distribution in structure **4a** was calculated by the complete neglect of differential overlap (CNDO) method (35). Although the electron density assignments for these structures are not in complete agreement with each other, all four locate the highest electron density for the ring carbon atoms at

positions 5 and 8, indicating that electrophilic substitution should occur preferentially at these sites. This is borne out experimentally, at least for



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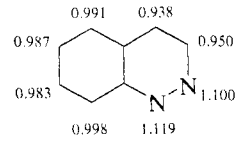

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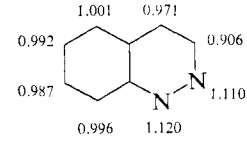

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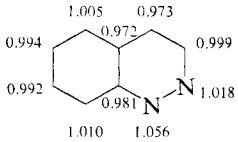
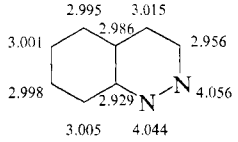


4a



4b

simple electrophilic substitution reactions such as nitration (2, 17, 18), and concurs with the results of calculations by Dewar (19, 24). A higher π-electron density is assigned to N-1 than to N-2 in structures **2**, **3**, **4**, and **4a**, whereas a higher σ-electron density is assigned to N-2 than to N-1 in structure **4b** (35). Experimentally it is known that cinnoline undergoes *N*-oxidation (20, 21), protonation (22), and alkylation (23) preferentially at N-2. The 2-cinnolinium ion is calculated to be slightly more stable than the 1-cinnolinium ion (22). Recent molecular orbital calculations by Palmer and co-workers (24a) indicate that the electron densities are essentially equal at *N*-1 and *N*-2 for cinnoline, 4-methylcinnoline, 3-methylcinnoline, and 3,4-dimethylcinnoline, leading Palmer to conclude that preferential *N*-2 protonation is simply a result of steric hindrance to *N*-1 protonation by the *peri* C-8 proton. This correlates with experimental work by Palmer and McIntyre (24b) where such a steric effect was claimed to be balanced by a substituent in the 3-position.

The IR (infrared) absorption spectrum of cinnoline (Table 1A-1) has been recorded and absorption modes have been assigned to the bands when possible (25, 26). The Raman spectrum of cinnoline also has been recorded (26).

The UV (ultraviolet) absorption spectrum of cinnoline has been recorded in several different solvents. The spectral parameters thus obtained are given in Table 1A-2. In addition, several theoretical calculations of transition energies and band intensities have been made (27–29). The spectrum of cinnoline is reported to display from three to six absorption maxima in various solvents in the range 200–380 mμ (millimicrons) which are attributable to π-π* transitions and an n-π* absorption of low intensity at 390 mμ (in ethanol) due to the nonbonding electrons of the ring nitrogen atoms.

This n-π^* band is observed to occur at shorter wavelengths in both diazabenzenes and diazanaphthalenes when the two nitrogen atoms are nonvicinal (30). Thus the n-π^* band of quinazoline (1,3-diazanaphthalene) is reported to occur as a shoulder at 330 mμ (31). The UV absorption spectrum of cinnoline has been compared to those of naphthalene and phthalazine (32), and a very fine discussion of the spectrum of cinnoline in the vapor state is given by Wait and Grogan (33), supplemented by Glass, Robertson, and Merritt (34).

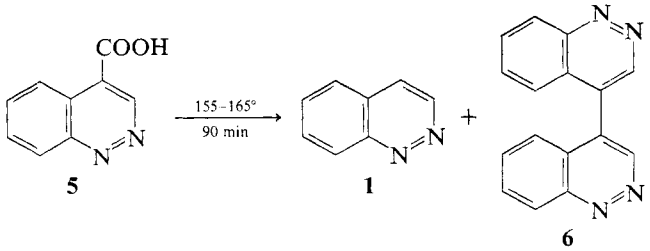
The pmr (proton magnetic resonance) spectrum of cinnoline is given in Table 1A-3. A study of the carbon-13 magnetic resonance spectrum of cinnoline has been published (35).

Mass spectral studies show that cinnoline fragments upon electron impact to lose first nitrogen and then acetylene (36, 37). The structure of the C_8H_6 cation resulting from initial loss of N_2 is unknown, even though 3- and 4-deuteriocinnoline and 3,4-dideuteriocinnoline were prepared and subjected to mass spectral analysis in an attempt to elucidate this cation's structure. Incorporation of deuterium in the acetylene arising by fragmentation of the C_8H_6 cation is completely random (37).

II. Methods of Preparation

A. Decarboxylation of Cinnoline-4-carboxylic Acid

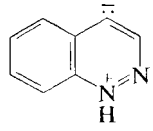
The best method now used to prepare cinnoline is the thermal decarboxylation of cinnoline-4-carboxylic acid (**5**) in benzophenone at 155–165°, which gives cinnoline (**1**) in 72% yield (1) and 4,4′-dicinnolinyl (**6**) in about 5.6% yield (2). The decarboxylation of **5** is regarded as proceeding through



5 **1** **6**

the protonated cinnolinyl anion (**7**) from which both cinnoline and 4,4′-dicinnolinyl are thought to be produced, the latter by attack of the anion **7**

on cinnoline (2). However, since 4,4′-dicinnolinyl is formed easily from cinnoline by action of the free radical initiator, *N*-nitrosoacetanilide, the possibility exists that decarboxylation may proceed at least in part via a free radical pathway (38) (see Section 1A-III-B).



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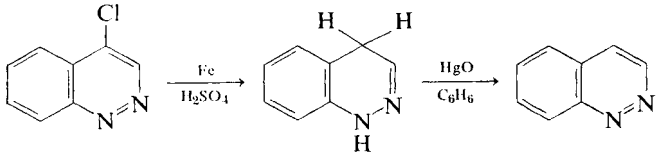
B. Removal of a 3- or 4-Halo Group

Cinnoline was first prepared by the chemical reduction of 4-chlorocinnoline (**8**) with iron and 15% sulfuric acid to give 1,4-dihydrocinnoline (**9**), which was then oxidized to cinnoline with mercuric oxide (3). The



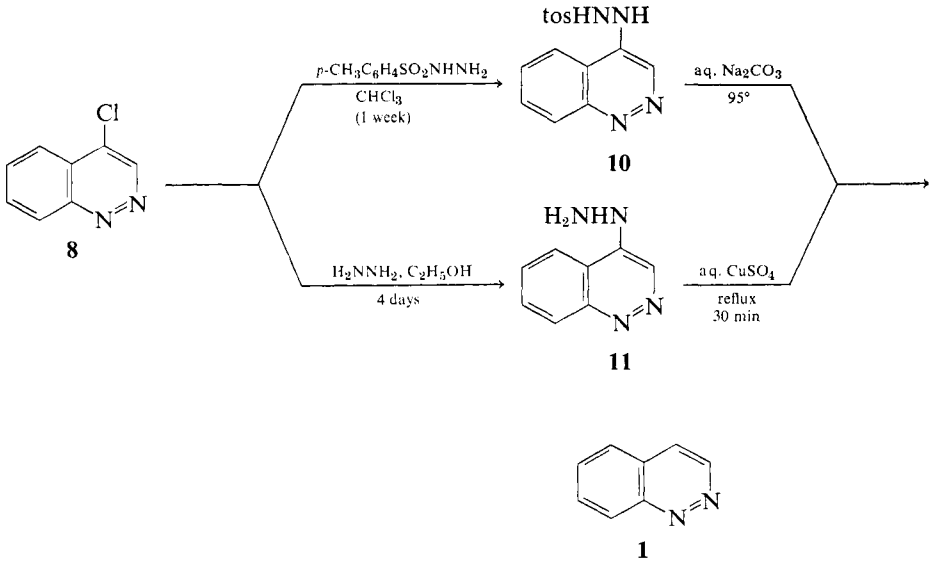
8 **9** **1**

reduced cinnoline **9** was originally assigned a 1,2-dihydro structure but has since been shown by pmr to have a 1,4-dihydro structure (39). Chemical reduction of 4-chlorocinnoline with lithium aluminum hydride in ether solution gives only 4,4′-dicinnolinyl (**6**) (40), whereas catalytic reduction of 4-chlorocinnoline in methanol with palladium on calcium carbonate gives only a trace of cinnoline, the main product also being 4,4′-dicinnolinyl (2).

Cinnoline also has been prepared by treating 4-chlorocinnoline with toluene-*p*-sulfonylhydrazide and decomposing the resulting 4-(toluene-*p*-sulfonylhydrazino)cinnoline (**10**) with aqueous sodium carbonate (17). The yield of cinnoline by this route is good.

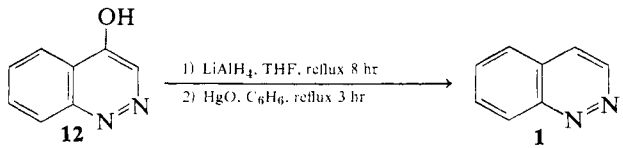
Treatment of 4-chlorocinnoline with hydrazine followed by oxidation of the resultant 4-hydrazinocinnoline (**11**) with aqueous copper sulfate gives cinnoline in a yield of about 56% (41).

Reduction of 3-bromocinnoline by hydrazine over palladium-charcoal in methanolic potassium hydroxide gives cinnoline in approximately 56% yield (42).



C. Reduction of 4-Hydroxy- and 4-Methoxycinnoline

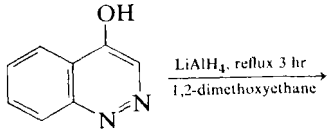
Direct reduction of 4-hydroxycinnoline (**12**) with lithium aluminum hydride in refluxing tetrahydrofuran for 8 hours followed by gentle oxidation of the resulting partially reduced cinnoline with mercuric oxide in refluxing benzene gives cinnoline in 74% yield (43). Reduction of **12** with lithium aluminum hydride in refluxing 1,2-dimethoxyethane for 3 hours without



subsequent treatment with mercuric oxide yields a mixture of cinnoline and 1,2,3,4-tetrahydrocinnoline (**13**), while a similar reduction of 4-methoxycinnoline (**14**) in a benzene-ether solution also gives **1** and **13**.

Cinnoline may be prepared from 4-hydroxycinnoline by polarographically reducing the hydroxycinnoline in acid solution, making the solution slightly alkaline, and then oxidizing the intermediate 1,4-dihydrocinnoline anodically. No isolation of the intermediate is necessary, and the overall yield of cinnoline is 70–80% (44).

Only 1,2,3,4-tetrahydrocinnoline is isolated when 3-hydroxycinnoline is reduced by lithium aluminum hydride in refluxing 1,2-dimethoxyethane for 3 hours (40).



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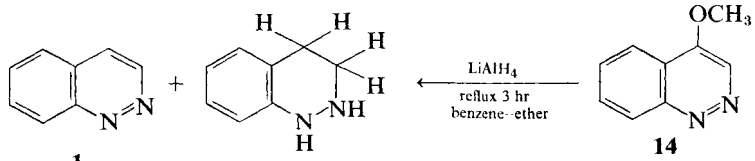
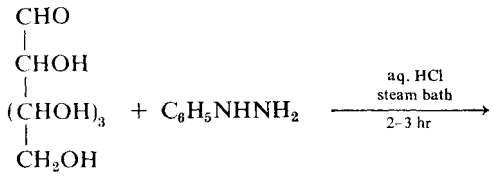


1 13 14

D. Cinnoline from Osazone Formation of Aldoses

When D-glucose (**15**) is heated with aqueous hydrochloric acid and an excess of phenylhydrazine, there is obtained a mixture of D-glucose phenylosazone (**16**) and 1-(3-cinnolinyl)-D-*arabino*tetritol (**17**) in yields of 35 and 20%, respectively. Treatment of **17** with UV light in aqueous sodium hydroxide for 8 hours then gives cinnoline (**1**). Under the same conditions D-mannose gives 25% of D-glucose phenylosazone (**16**) and 16% of the cinnoline derivative **17** (45).



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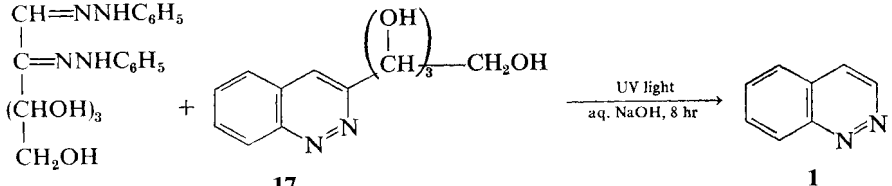
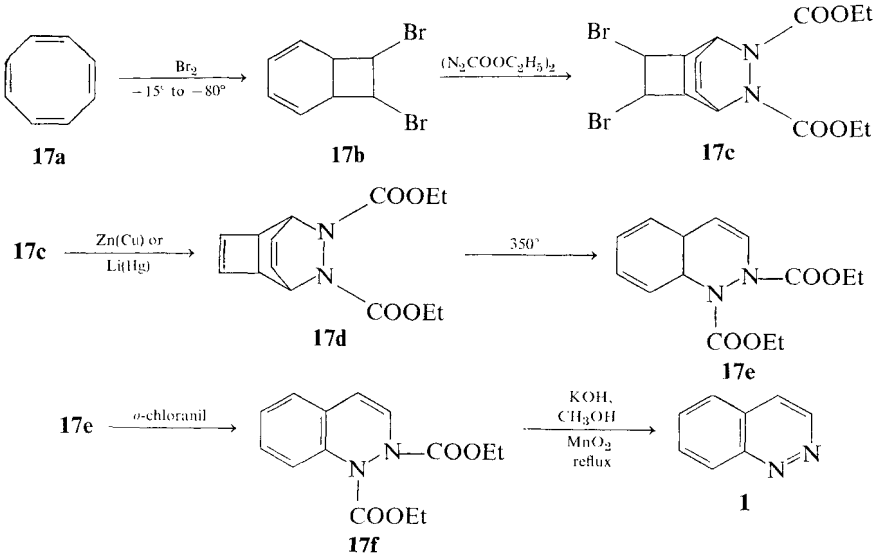


16 17 1

E. Miscellaneous

Desulfurization of 4-mercaptocinnoline with wet Raney nickel in ethanol gives cinnoline, isolated in 30% yield as its picrate (46).

Probably the most circuitous route ever taken to synthesize cinnoline is the one that begins with cycloöctatetraene (47, 48). In this method, cycloöctatetrene (**17a**) is brominated to give cycloöctatetrene dibromide (**17b**). The dibromide and ethyl azodicarboxylate give the adduct **17c**, which is then debrominated to produce adduct **17d** (47). Adduct **17d** when heated to 350° C rearranges to 1,2-diethoxycarbonyl-1,2,4*a*,8*a*-tetrahydrocinnoline (**17e**). The tetrahydrocinnoline **17e** is dehydrogenated by *o*-chloranil to 1,2-diethoxycarbonyl-1,2-dihydrocinnoline (**17f**), which is converted into cinnoline (**1**) by alkaline hydrolysis in the presence of activated manganese dioxide (48).

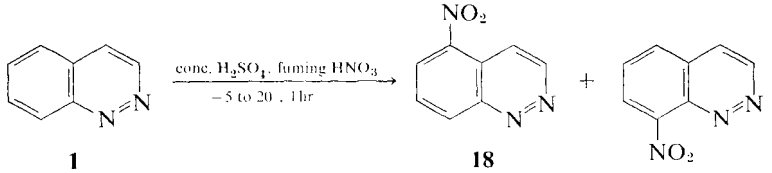


III. Reactions

A. Electrophilic Substitution

Very little experimental work has been done on electrophilic substitution reactions of cinnoline. Dewar (19) determined on the basis of molecular orbital calculations that the relative order of reactivities at different positions of the cinnoline ring system toward simple electrophilic substitution is $5 = 8 > 6 = 7 > 3 \gg 4$. That is, the 5- and 8-positions should be most reactive, and the 4-position should be least reactive toward electrophilic substitution. This is confirmed experimentally in the case of nitration in sulfuric acid, which results in 33% of 5-nitrocinnoline (**18**) and 28% of

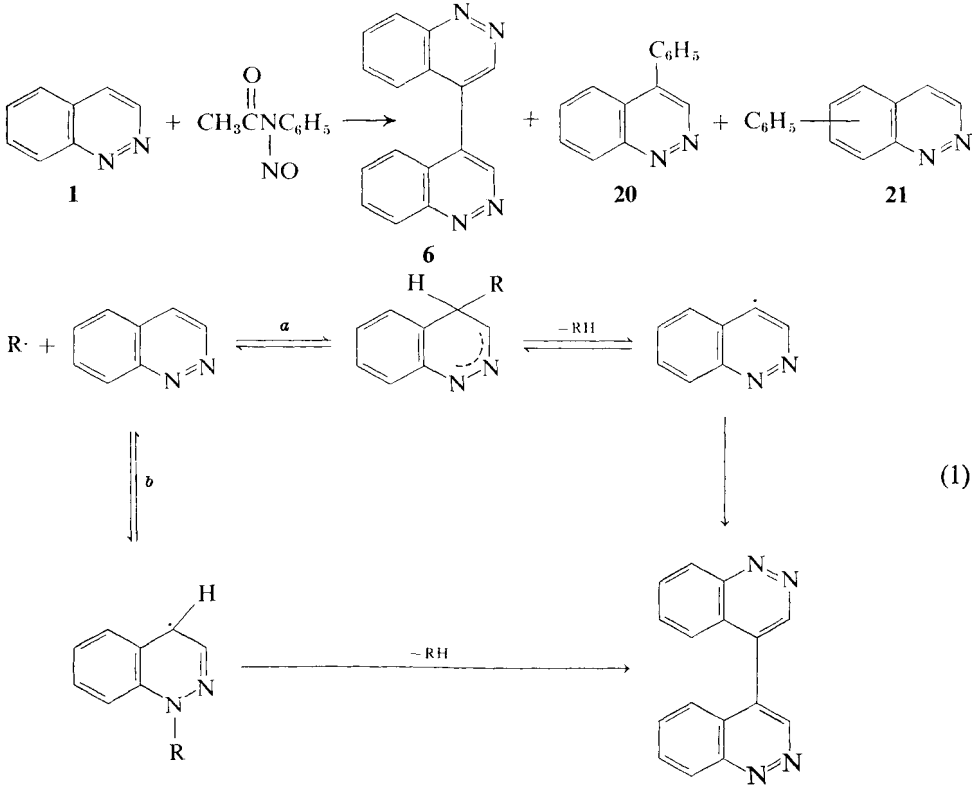
8-nitrocinnoline (**19**) as the sole nitration products (2, 17). The species nitrated is not cinnoline itself but the protonated 2-cinnolinium cation. At 80°, in the acidity range 76–83% sulfuric acid, this cation is nitrated 287 times more slowly than the isoquinolinium cation. This gives some measure of the deactivating power of the unprotonated N-1 atom on the nitration of the 2-cinnolinium ion (18).



1 **18** **19**

B. Free Radical Phenylation

Interaction of cinnoline with *N*-nitrosoacetanilide at 55–60° for 3 hours yields a complex mixture of products, 4,4′-dicinnolinyl (**6**) being the principal



1 **6** **20** **21**

(1)

product with a concentration in the product mixture 10 times that of all other products combined. Equal amounts of 4-phenylcinnoline (**20**) and 5 (or 8)-phenylcinnoline (**21**) (mp 131°; picrate, mp 208°) together with lesser amounts of four unidentified products are also obtained (38). Formation of 4,4′-dicinnolinyl is thought to arise by one of two routes, path *a* or path *b* shown in Eq. 1 (38).

C. Salt Formation

Cinnoline forms a number of stable salts, including a hydrochloride, mp 156–160° C (3), a picrate, mp 196–196.5° (1), a chloroplatinate, mp 280° (dec.) (3), an aurichloride, mp 146° (3), and many *N*-alkylcinnolinium halides from the interaction of cinnoline with an alkyl halide. It has been believed for many years that quaternization of cinnoline takes place at N-1, but recently Ames (22, 23, 49) showed on the basis of chemical and spectroscopic evidence that protonation and alkylation of cinnoline both occur at N-2.

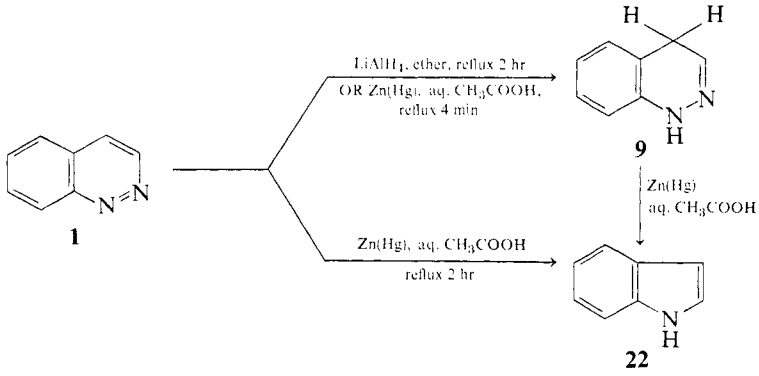
D. *N*-Oxide Formation

When cinnoline is treated with hydrogen peroxide in acetic acid or with a percarboxylic acid, there is obtained a mixture of cinnoline 1-oxide, cinnoline 2-oxide, and a small amount of cinnoline 1,2-dioxide. The predominant isomer is the 2-oxide. This reaction is discussed in Section 1J.

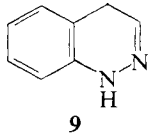
E. Reduction

Reduction of cinnoline with lithium aluminum hydride in refluxing ether solution gives 1,4-dihydrocinnoline (**9**) in 51% yield (39), whereas treatment of cinnoline with amalgamated zinc in refluxing 33% aqueous acetic acid for 2 hr yields indole (**22**) in approximately 57% yield. When this reduction is stopped as soon as the yellow color of the reaction mixture is discharged (4 min), then 1,4-dihydrocinnoline (**9**) is isolated and can be further reduced with amalgamated zinc in acetic acid to give indole (50).

A study of the catalytic hydrogenation of cinnoline in ethanol or in ethanolic hydrochloric acid at both low and high pressure has been performed using five different catalysts (51). Low-pressure hydrogenations were carried out at 27° C and 60 psi, while high-pressure hydrogenations were performed at 122–195° and 2230–2950 psi. Catalysts used were 5% rhodium on alumina, 5% rhodium on carbon, 5% palladium on carbon, ruthenium oxide, and



platinum oxide. Seven compounds were isolated from these reductions. Six were positively identified as 1,4-dihydrocinnoline (**9**), 1,2,3,4-tetrahydrocinnoline (**13**), indole (**22**), 2,3-dihydroindole (**23**), *cis*-octahydroindole (**24**), and *o*-aminophenethylamine (**25**). The seventh compound was not identified, but is proposed to be 1,1′,4,4′-tetrahydro-4,4′-dicinnolinyl (**26**). Each individual hydrogenation gives from one to five of the foregoing products, depending upon the reaction conditions and time. Specific results are summarized in Table 1A-4.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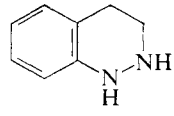
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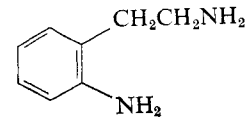
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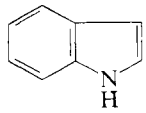
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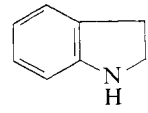
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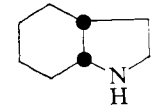
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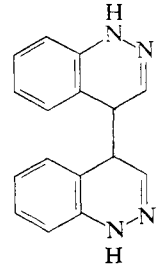
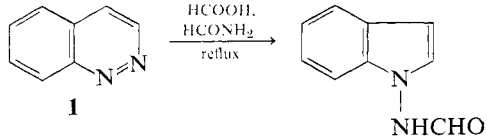

26

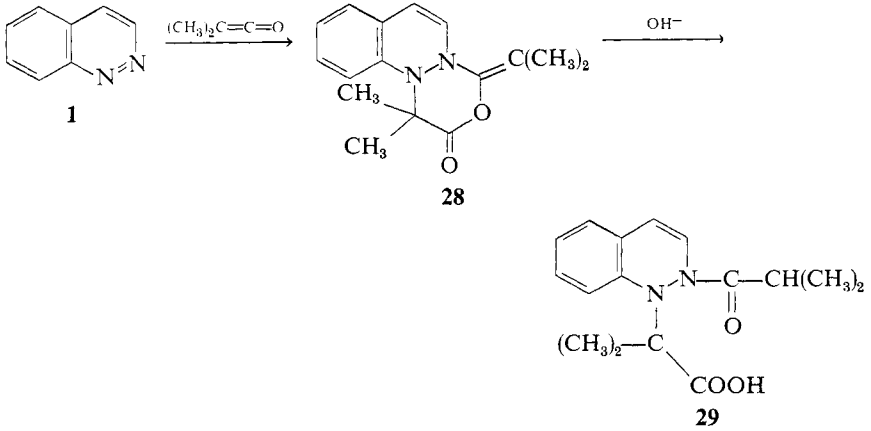
Cinnoline undergoes a reductive formylation when heated with formic acid and formamide to give 1-formamidoindole (**27**) in 55% yield. Under the same conditions 4-cinnolinecarboxylic acid also gives **27**, being decarboxylated during the reaction, while 4-methylcinnoline gives 1-formamido-3-methylindole (52).



1 **27**

F. Reaction with Dimethylketene

Cinnoline reacts with two equivalents of dimethylketene in ether solution to give 4-isopropylidene-1,1-dimethyl-4*H*[1,3,4]oxadiazino[4,3-a]cinnolin-2(1*H*)one (**28**). While this adduct is thermally stable and can be sublimed *in vacuo*, it is easily hydrolyzed in alkaline solution to the amido acid **29** (53).



1 **28** **29**

IV. Tables

TABLE 1A-1. Infrared Spectral Data for Cinnoline[a]

Absorption[b] (cm^{-1})	Intensity[c]	Absorption mode[d]
3,054	—	—
3,016 sh.	—	CH stretching
2,990 sh.	—	CH stretching
2,966 sh.	—	—
2,925	—	—

TABLE 1A-I. (*continued*)

Absorption[b] (cm^{-1})	Intensity[c]	Absorption mode[d]
1,663 sh.	vw	—
1,638 sh.	w	—
1,620 (1,623)	m	Skeletal stretching
1,593	w	Skeletal stretching
1,580 (1,581)	vs	Skeletal stretching
1,550 (1,553)	w-m	Skeletal stretching
1,538	w-m	—
1,491 (1,494)	s	Skeletal stretching
— (1,477)	w	Skeletal stretching
1,461	vw	—
1,440 (1,441)	m-s	Skeletal stretching
1,416 (1,417)	m-s	CH bending
1,410 sh.	vw	Skeletal stretching
1,392 (1,393)	s	Skeletal stretching
1,334	vw	—
1,291 (1,293)	m-s	Skeletal stretching (CH bending?)
1,258 (1,259)	m	CH bending
1,251	m	CH bending
1,221	vw	—
1,179 (1,182)	m-s	CH bending
1,170 sh.	w	—
1,158 (1,160)	w-m	CH bending
1,138 (1,139)	m-s	(Skeletal bending?)
1,117	vw	—
1,090 (1,091)	vs	Skeletal distortion
1,070	vw	—
— (1,041)	w	—
1,030 (1,029)	w	—
1,007 (1,008)	w-m	Skeletal distortion (skeletal stretching)
962 (964)	m	CH bending
875 (875)	m	CH bending
844 (843)	vs	CH bending
821 (823)	m	Skeletal breathing (CH bending)
794 (794)	m	CH bending
774 (775)	m	Skeletal distortion (CH bending)
748 (748)	vs	Skeletal distortion
716	vw	CH bending
650 (650)	m-s	Skeletal distortion
633	m-s	Skeletal distortion
530	m	Skeletal distortion
512	m	Skeletal distortion
470	s	Skeletal bending
373	s	Skeletal distortion

[a] Data taken from reference 26 except those in parentheses, which are from reference 25; the spectral data are those of cinnoline as a liquid.

[b] Abbreviation "sh." means that the absorption is a shoulder on another peak.

[c] Symbols used to designate intensity are vs = very strong, s = strong, m = medium, w = weak, and vw = very weak.

[d] A question mark indicates uncertainty of assignment; a dash indicates no assignment was made.

TABLE 1A-2. Ultraviolet Absorption Spectrum of Cinnoline

Solvent	$\lambda_{max}(m\mu)$	log E_{max}	Ref.
Ethanol	276	3.45	54
	286	3.42	
	308.5	3.29	
	317	3.25	
	322.5	3.32	
	390	2.42	
Cyclohexane	222	4.66	27
	276	3.52	
	287	3.48	
	310	3.35	
	318	3.30	
	322	3.40	
	392.5	2.45	
Methanol	225	4.60	27
	280	3.40	
	320	3.41	
H_2O pH = 7	226 (225)	4.64 (4.63)	7, 55
	283 (285)	3.38 (3.37)	
	290 (—)	3.38 (—)	
	321 (320)	3.44 (3.43)	
H_2O pH = 0.3	237	4.59	7
	294	3.31	
	305	3.32	
	353	3.40	
n-hexane	199	4.48	56
	219.5	4.72	
	275	3.49	
	322	3.40	

TABLE 1A-3. Proton Magnetic Resonance Spectrum of Cinnoline[a]

Parameter[b]	Solvent	
	Acetone	CCl_4[c]
τ_3	0.678	0.783
τ_4	1.917	
τ_5	1.988	2.24 ± 0.05
τ_6	2.163	
τ_7	2.068	
τ_8	1.510	1.523
$J_{3,4}$	5.75	5.80
$J_{4,8}$	0.83	—
$J_{5,6}$	7.87	—
$J_{5,7}$	1.57	—
$J_{5,8}$	0.85	—
$J_{6,7}$	6.94	—
$J_{6,8}$	1.34	—
$J_{7,8}$	8.64	—

[a] Data taken from reference 57; Spectra are recorded relative to tetramethylsilane as an internal reference.

[b] Chemical shift value is given in τ (tau) units in ppm; coupling constants are given as J in cps.

[c] Spectrum in carbon tetrachloride is not analyzed fully because of the near coincidence of the chemical shifts of protons 4, 5, 6, and 7. Besford, Allen, and Bruce (39) report the spectrum of cinnoline in carbon tetrachloride as a doublet at 0.78τ (J = 6.0 cps), a multiplet at 1.5–1.7τ, and a multiplet at 2.1–2.4τ using tetramethylsilane as an internal reference.

TABLE 1A-4. Catalytic Hydrogenation of Cinnoline[a]

Catalyst	Solvent	Temp. (°C)	Pressure (psi)	Time (hr)	Products[b]	Yield (%)
5% Rh/Al_2O_3	Ethanol	27	60	9	**9**	70
					26	30
		125	2,610	5	**22**	38
					13	5
					23	10
					25	48
		195	2,950	2	**24**	100
	Ethanol-HCl	27	60	12	**9**	100
		122	2,450	8	**22**	21
					24	79
5% Rh/C	Ethanol	27	60	12	**9**	52
					26	48
		122	2,230	3	**22**	25
					23	16
					24	59
RuO_2	Ethanol	27	60	25	**9**	56
					26	44
		123	2,500	5	**24**	100
	Ethanol-HCl	27	60	2	NR	—
5% Pd/C	Ethanol	27	60	3	**9**	37
					26	63
		124	2,530	5	**22**	14
					13	19
					23	21
					24	3
					25	43
	Ethanol-HCl	27	60.5	1	**9**	100
		125	2,400	6	**24**	86
					25	14
PtO_2	Ethanol	27	60	0.5	**26**	—
		122	2,500	8	**22**	1
					13	81
					25	18
	Ethanol-HCl	27	61.5	0.5	**22**	4
					13	65
					23	7
					24	2
					25	23
		27	60	3	**13**	100
		125	2,350	6	**22**	16
					13	36
					23	21
					25	27

[a] Data taken from reference 51.

[b] Products are assigned numbers within this column according to their assignments within the text of this chapter (Section 1A-III-E).

References

1. T. L. Jacobs, S. Winstein, R. E. Henderson, and E. C. Spaeth, *J. Am. Chem. Soc.*, **68,** 1310 (1946).
2. J. S. Morley, *J. Chem. Soc.*, **1951,** 1971.
3. M. Busch and A. Rast, *Ber.*, **30,** 521 (1897).
4. V. von Richter, *Ber.*, **16,** 677 (1883).
5. J. R. Keneford, J. S. Morley, J. C. E. Simpson, and P. H. Wright, *J. Chem. Soc.*, **1949,** 1356.
6. A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, **1948,** 2240.
7. A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, **1956,** 4191.
8. M. T. Rogers and T. W. Campbell, *J. Am. Chem. Soc.*, **75,** 1209 (1953).
9. R. J. W. LeFevre and J. W. Smith, *J. Chem. Soc.*, **1932,** 2810.
10. M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.*, **51,** 263 (1969).
11. S. D. Worley, *Chem. Revs.*, **71,** 295 (1971).
12. M. J. S. Dewar and T. Morita, *J. Am. Chem. Soc.*, **91,** 769 (1969).
13. A. Pullman, *Rev. Sci.*, **86,** 219 (1948); *Chem. Abstr.*, **43,** 2095 (1949).
14. H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.*, **1949,** 971.
15. S. C. Wait, Jr. and J. W. Wesley, *J. Mol. Spectrosc.*, **19,** 25 (1966).
16. O. W. Adams and P. C. Lykos, quoted by A. H. Gawer and B. P. Dailey, *J. Chem. Phys.*, **42,** 2658 (1965).
17. E. J. Alford and K. Schofield, *J. Chem. Soc.*, **1953,** 609.
18. R. B. Moodie, E. A. Qureshi, K. Schofield, and J. T. Gleghorn, *J. Chem. Soc. (B)*, **1968,** 312.
19. M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, **1957,** 2521.
20. M. Ogata, H. Kano, and K. Tori, *Chem. Pharm. Bull. (Tokyo)*, **11,** 1527 (1963).
21. I. Suzuki, M. Nakadate, T. Nakashima, and N. Nagasawa, *Tetrahedron Lett.*, **1966,** 2899.
22. D. E. Ames, G. V. Boyd, A. W. Ellis, and A. C. Lovesey, *Chem. Ind. (London)*, **1966,** 458.
23. D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, **1964,** 283.
24. M. J. S. Dewar and C. C. Thompson, Jr., *J. Am. Chem. Soc.*, **87,** 4414 (1965).

24a. M. H. Palmer, A. J. Gaskell, P. S. McIntyre, and D. W. W. Anderson, *Tetrahedron*, **27,** 2921 (1971).

24b. M. H. Palmer and P. S. McIntyre, *Tetrahedron*, **27,** 2913 (1971).

25. W. F. L. Armarego, G. B. Barlin, and E. Spinner, *Spectrochim. Acta*, **22,** 117 (1966).
26. R. W. Mitchell, R. W. Glass, and J. A. Merritt, *J. Mol. Spectrosc.*, **36,** 310 (1970).
27. G. Favini, S. Carra, V. Pierpaoli, S. Polezzo, and M. Simonetta, *Il Nuovo Cimento*, **8,** 60 (1958).
28. G. Favini, I. Vandoni, and M. Simonetta, *Theor. Chim. Acta (Berlin)*, **3,** 45, 418 (1965).
29. L. Goodman and R. W. Harrell, *J. Chem. Phys.*, **30,** 1131 (1959).
30. R. C. Hirt, F. T. King, and J. C. Cavagnol, *J. Chem. Phys.*, **25,** 574 (1956).
31. S. F. Mason, *J. Chem. Soc.*, **1962,** 493.
32. E. D. Amstutz, *J. Org. Chem.*, **17,** 1508 (1952).
33. S. C. Wait, Jr., and F. M. Grogan, *J. Mol. Spectrosc.*, **24,** 383 (1967).
34. R. W. Glass, L. C. Robertson, and J. A. Merritt, *J. Chem. Phys.*, **53,** 3857 (1970).
35. R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *J. Am. Chem. Soc.*, **91,** 6381 (1969).

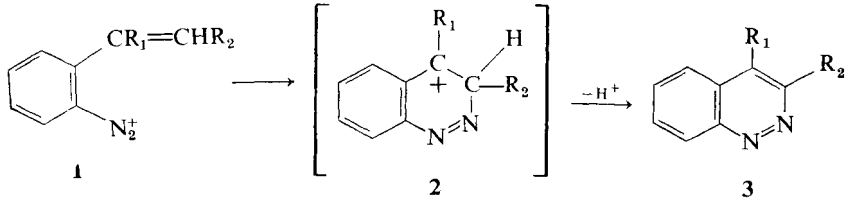
36. J. R. Elkins and E. V. Brown, *J. Heterocyclic Chem.*, **5,** 639 (1968).
37. M. H. Palmer, E. R. R. Russell, and W. A. Wolstenholme, *Org. Mass Spectrom.*, **2,** 1265 (1969).
38. C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, **1959,** 3040.
39. L. S. Besford, G. Allen, and J. M. Bruce, *J. Chem. Soc.*, **1963,** 2867.
40. D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, **1962,** 1509.
41. K. Schofield and T. Swain, *J. Chem. Soc.*, **1950,** 392.
42. E. J. Alford and K. Schofield, *J. Chem. Soc.*, **1953,** 1811.
43. C. M. Atkinson and C. J. Sharpe, *J. Chem. Soc.*, **1959,** 2858.
44. H. Lund, *Acta Chem. Scand.*, **21,** 2525 (1967).
45. H. J. Haas and A. Seeliger, *Ber.*, **96,** 2427 (1963).
46. H. J. Barber and E. Lunt, *J. Chem. Soc. (C)*, **1968,** 1156.
47. R. Askani, *Chem. Ber.*, **102,** 3304 (1969).
48. G. Maier, *Chem. Ber.*, **102,** 3310 (1969).
49. D. E. Ames, G. V. Boyd, R. F. Chapman, A. W. Ellis, A. C. Lovesey, and D. Waite, *J. Chem. Soc. (B)*, **1967,** 748.
50. L. S. Besford and J. M. Bruce, *J. Chem. Soc.*, **1964,** 4037.
51. J. D. Westover, Ph.D. Dissertation (Brigham Young University, Provo, Utah), August, 1965; University Microfilms (Ann Arbor, Mich.), Order No. 66-2137.
52. D. E. Ames and B. Novitt, *J. Chem. Soc. (C)*, **1970,** 1700.
53. M. A. Shah and G. A. Taylor, *J. Chem. Soc. (C)*, **1970,** 1642.
54. J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, **1951,** 3318.
55. G. Favini, *Rend. Ist. Lombardo Sci., pt. I, Classe Sci. Mat. e Nat.*, **94A,** 331 (1960).
56. G. Favini and I. R. Bellobono, *Rend. Ist. Lombardo Sci. Lett.*, **A99,** 380 (1965).
57. P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18,** 707 (1965).

Part B. Alkyl- and Arylcinnolines

I. Methods of Preparation

A. Widman-Stoermer Synthesis

The most widely used method to prepare cinnolines which have an alkyl, aryl, or heteroaryl group at the 4-position or at both the 3- and 4-positions is the Widman-Stoermer synthesis. By this method, a diazotized *o*-aminoarylethylene (**1**, R_1 = alkyl, aryl, or heteroaryl; R_2 = hydrogen, alkyl, aryl, or heteroaryl) cyclizes upon standing to give the cinnoline (**3**). Table 1B-1 lists most of the *o*-aminoarylethylenes that have been successfully diazotized



1 **2** **3**

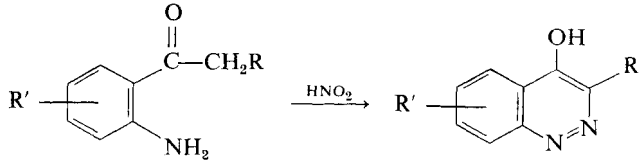
and cyclized to cinnolines. Inspection of this table shows that the α-carbon of the ethylene moiety is always substituted with an alkyl, aryl, or heteroaryl group (designated as R_1 in the table and in structures **1**, **2**, and **3**). This appears to be necessary because all attempts to prepare unsubstituted cinnoline or cinnolines substituted only in the benzenoid ring or only at the 3-position have failed. That is, all cinnolines prepared by the Widman-Stoermer method are substituted at the 4-position, or at both the 3- and 4-positions with alkyl, aryl, or heteroaryl groups. Attempts to prepare cinnoline-4-carboxylic acids by diazotization of *o*-aminoarylethylenes in which R_1 is the electron-attracting carboxyl group have met with failure.

These results are explicable when one considers that the success of the reaction depends upon the stability of the intermediate benzylic carbonium ion **2**, or, to be more precise, it depends upon the energy difference between the diazonium ion **1** and the transition state that leads to **2**. In the most successful reactions, R_1 is an electron-donating group such as the *p*-methoxyphenyl group which can stabilize **2** by charge delocalization, hence lowering the energy of the transition state between **1** and **2** and increasing the rate of the reaction. Even when R_1 is a heteroaryl group such as 2-pyridinyl, charge

delocalization in **2** by the pyridinyl ring can occur and the reaction is successful. Apparently, when R_1 is hydrogen or carboxyl, the energy difference between **1** and the transition state leading to **2** is high enough to be essentially insurmountable.

B. Borsche Synthesis

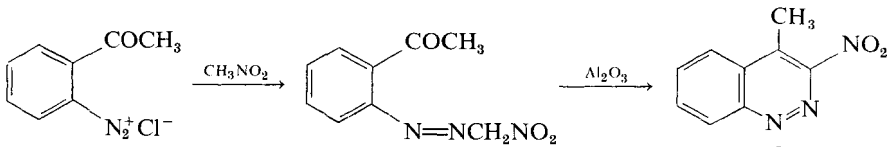
The Borsche synthesis is described in Section 1C-I-A-3, as a method to prepare 4-hydroxycinnolines (**5**) by the diazotization and cyclization of 2-aminoacetophenones (**4**). Little more need be added here except that at least 30 4-hydroxycinnolines substituted at the 3-, 6-, 7-, or 8-position with an alkyl or aryl group (**5**, R = alkyl, aryl; R′ = 3-, 6-, 7-, or 8-alkyl or aryl) have been prepared by this method.



4 **5**

Table 1B-2 lists some 2-aminoacetophenones that have been successfully diazotized and cyclized to the corresponding alkyl- or aryl-substituted 4-hydroxycinnolines. It is interesting that apparently no 5-alkyl- or 5-aryl-4-hydroxycinnolines have yet been prepared by the Borsche synthesis.

An ingenious modification of the Borsche synthesis was devised by Baumgarten (1), who coupled diazotized 2-aminoacetophenone (**6**) with nitromethane in a dilute, basic solution to give nitroformaldehyde 2-acetylphenylhydrazone (**7**) in yields up to 98%. Cyclization of **7** in the presence of aluminum oxide then gives 4-methyl-3-nitrocinnoline (**8**) in a yield of 59%.

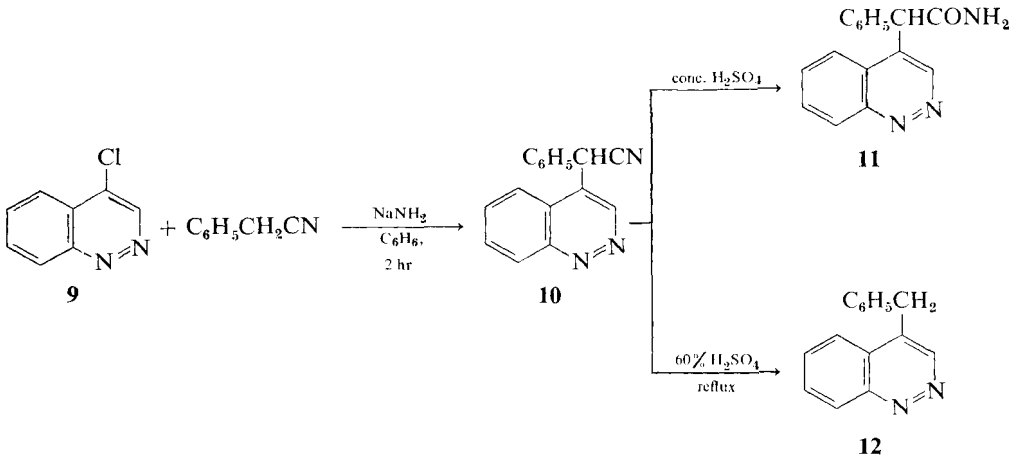


6 **7** **8**

C. 4-Alkylcinnolines from 4-Chloro- and 4-Methylsulfonylcinnolines

Several 4-alkylcinnolines have been prepared by the nucleophilic displacement of chloride ion from 4-chlorocinnoline (see Table 1B-5). For example,

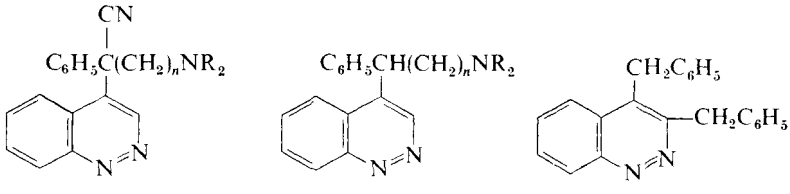
the condensation of 4-chlorocinnoline (**9**) with the sodio derivative of phenylacetonitrile in benzene solution yields α-(4-cinnolinyl)phenylacetonitrile (**10**) in 94% yield (2). This is easily converted to α-(4-cinnolinyl)-



9 10 11 12

phenylacetamide (**11**) by allowing it to stand overnight in concentrated sulfuric acid at room temperature. Alternatively, **10** is readily converted to 4-benzylcinnoline (**12**) by refluxing it for 1 hr in 60% sulfuric acid (2).

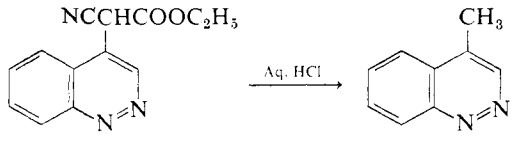
A number of α-(ω-dialkylaminoalkyl)-α-phenyl-α-(4-cinnolinyl)acetonitriles (**13**) have been prepared similarly from α-(ω-dialkylaminoalkyl)-phenylacetonitriles and 4-chlorocinnoline. These may be hydrolyzed and decarboxylated in refluxing 60% sulfuric acid to the corresponding 4-[(1-phenyl-ω-dialkylamino)alkyl]cinnolines (**14**) (3). Specific examples are listed in Table 1B-5. Likewise the condensation of 3-benzyl-4-chlorocinnoline with phenylacetonitrile in benzene solution, using sodium amide as the condensing agent, followed by treatment of the product with refluxing aqueous sulfuric acid yields 3,4-dibenzylcinnoline (**15**) (4).



13 14 15

An indirect preparation of 4-methylcinnoline (**17**) from 4-chlorocinnoline

has been executed by condensation of 4-chlorocinnoline with ethyl cyanoacetate, followed by hydrolysis of the resulting ethyl 4-cinnolinylcyanoacetate (**16**) in hot aqueous hydrochloric acid (5).



16 **17**

Ethyl acetoacetate does not give the expected product when condensed with 4-chlorocinnoline in benzene solution under the influence of sodium amide. Instead, ethyl 4-cinnolinylacetate is obtained, derived from ethyl α-(4-cinnolinyl)acetoacetate by loss of the acetyl group (5).

Generally, sodium amide in benzene solution is a good condensing agent to convert 4-chlorocinnolines to 4-alkylcinnolines of the types just described, but when this reagent gives poor results, as in the case of 3,4-dimethoxyphenylacetonitrile or *p*-aminophenylacetonitrile, potassium amide in liquid ammonia is found to be an effective condensing agent (6).

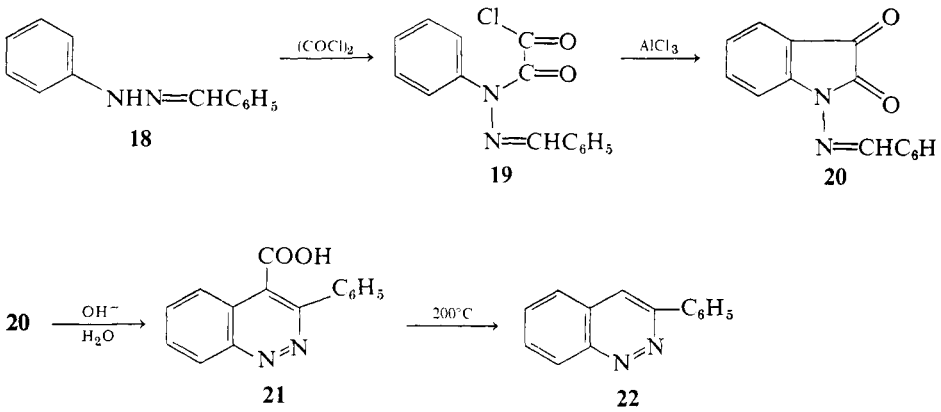
Hayashi and Watanabe (6a–6d) have studied the reaction of 4-methylsulfonylcinnoline with ketones under the influence of basic condensing agents to give 4-alkylcinnolines. This reaction is discussed in Section 1F-III, and the 4-alkylcinnolines prepared by this method are listed in Table 1B-5. Like 4-chlorocinnoline, 4-methylsulfonylcinnoline also reacts under basic conditions with esters and nitriles having labile α-hydrogen atoms to give 4-alkylcinnolines (6e).

D. Cyclization of Phenylhydrazone Derivatives

1. *Benzaldehyde Phenylhydrazones (Stolle-Becker Synthesis)*

Benzaldehyde phenylhydrazone (**18**), when allowed to react with excess oxalyl chloride, yields *N*-benzylideneamino-*N*-phenyloxamyl chloride (**19**), which can be cyclized by aluminum chloride in chloroform solution (7) or in methylene chloride (8) to give *N*-benzylideneaminoisatin (**20**). Treatment of the isatin **20** with hot aqueous sodium or potassium hydroxide gives 3-phenylcinnoline-4-carboxylic acid (**21**) in 75–85% yields (7, 8). Rearrangement of the isatin to the cinnoline almost certainly proceeds first by alkaline hydrolysis of the amide linkage in the isatin to open the ring. This would be followed by a recyclization and aromatization to give the cinnoline. The

carboxyl group of **21** can be removed thermally to give 3-phenylcinnoline (**22**) in 51–74% yields (7).

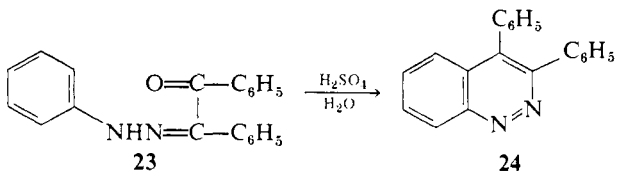


Similarly, 6-methyl-3-phenylcinnoline-4-carboxylic acid was prepared in 53% overall yield from benzaldehyde *p*-tolylhydrazone. Thermal decarboxylation then gave 6-methyl-3-phenylcinnoline. This same sequence, however, failed with benzaldehyde *p*-chlorophenyl-, *p*-anisyl-, and 1-naphthylhydrazone, so that the reaction does not appear to represent a general synthesis of 3-arylcinnolines (7). In addition, substituents attached to the benzene ring of the phenylhydrazine portion of the benzaldehyde phenylhydrazone may be limited to those allowing mild conditions for the Friedel-Crafts cyclization step (8).

Several attempts to use acetaldehyde phenylhydrazone (to give 3-methylcinnoline-4-carboxylic acid), phenylacetaldehyde phenylhydrazone (to give 3-benzylcinnoline-4-carboxylic acid), or isonicotinaldehyde phenylhydrazone [to give 3-(4-picolinyl)cinnoline-4-carboxylic acid] have been unsuccessful (8).

2. *Benzil Monophenylhydrazone*

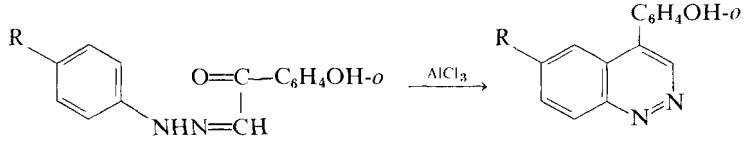
Benzil monophenylhydrazone (**23**) may be cyclized in 75–80% sulfuric acid solution to 3,4-diphenylcinnoline (**24**) in 75% yield (9). The use of concentrated sulfuric acid lowers the yield of **24** and produces sulfonated benzil monophenylhydrazones (10).



The use of substituted benzil monophenylhydrazones in this reaction has not been reported.

3. *Phenylglyoxal Monophenylhydrazones*

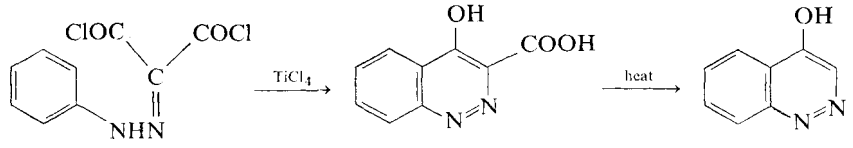
Cyclization of the *o*-hydroxyphenylglyoxal monophenylhydrazones (**25**, R = hydrogen, methyl, or chlorine) to the corresponding 6-substituted 4-(*o*-hydroxyphenyl)cinnolines (**26**) has been effected by the action of fused aluminum chloride at 180–190° C for 5 min in the absence of a solvent. Cyclization could not be effected in the presence of inert solvents. Anhydrous zinc chloride, polyphosphoric acid, phosphorus oxychloride, and boron trifluoride did not cause cyclization to the cinnoline (11). A single attempt to prepare 4-phenylcinnoline from unsubstituted phenylglyoxal monophenylhydrazone by cyclization in concentrated sulfuric acid solution gave only sulfonic acid derivatives of the hydrazone, but no 4-phenylcinnoline (10).



25 **26**

4. *Mesoxalyl Chloride Phenylhydrazones*

The titanium tetrachloride-catalyzed cyclization of mesoxalyl chloride phenylhydrazone (**27**) or one of its substituted derivatives is especially useful for the preparation of 4-hydroxycinnoline-3-carboxylic acid (**28**) or 4-hydroxycinnoline (**29**) or their derivatives which are substituted in the benzenoid ring. This reaction is discussed in detail in Section 1C-I-A-4.



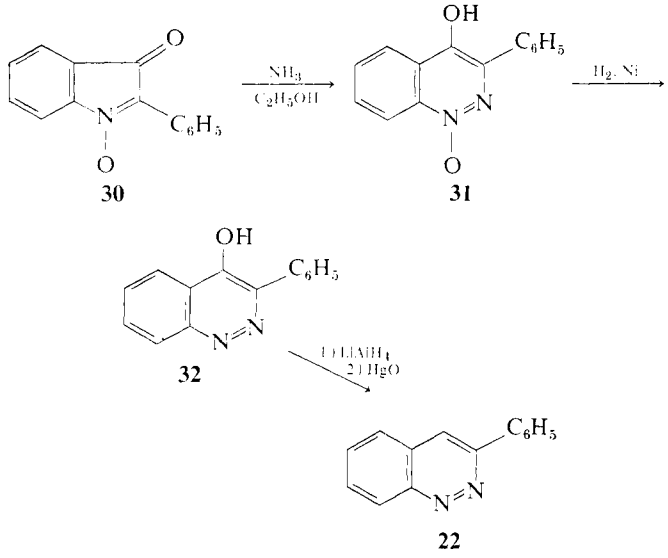
27 **28** **29**

Both 6-methyl- and 8-methyl-4-hydroxycinnoline have been prepared in this manner in good yield (12). Since the 4-hydroxy group can be removed from the cinnoline ring, the reaction provides a method to synthesize alkylcinnolines having the alkyl groups in the benzenoid ring only. The 4-hydroxy group may be removed by first refluxing it in a mixture of phosphorus

pentachloride and phosphorus oxychloride to convert it to the 4-chlorocinnoline. This is then converted to the 4-toluene-*p*-sulfonylhydrazone derivative, which will decompose in hot aqueous sodium carbonate solution to give a cinnoline with a hydrogen atom at the 4-position (13–15).

E. 2-Phenylisatogen to 3-Phenylcinnoline

The reaction of 2-phenylisatogen (**30**) with ethanolic ammonia at 140–145° C in an autoclave for 6 hr gives 26% of 4-hydroxy-3-phenylcinnoline 1-oxide (**31**). A possible mechanism for this rearrangement is discussed in Section 1J-I-B. Catalytic hydrogenation of **31** over Raney nickel then gives 4-hydroxy-3-phenylcinnoline (**32**) in 45% yield (16). Reduction of **32** with lithium aluminum hydride followed by gentle oxidation of the product with mercuric oxide then gives 3-phenylcinnoline (**22**) (17).



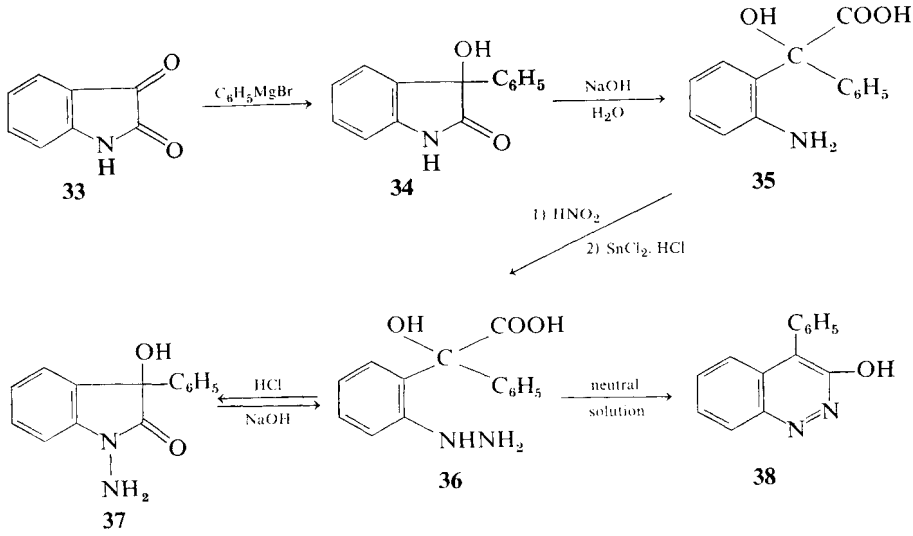
30 **31** **32** **22**

No other cinnolines have been prepared by this route.

F. Isatin to 4-Alkyl- and 4-Aryl-3-hydroxycinnolines

The reaction of isatin (**33**) with Grignard reagents yields 3-alkyl- or 3-aryldioxindoles. In the example shown, phenylmagnesium bromide and isatin give 3-phenyldioxindole (**34**) in 55% yield (18). The dioxindole can be cleaved in aqueous alkaline solution to give 2-aminomandelic acid (**35**),

which upon diazotization and reduction is converted to 1-amino-3-phenyldioxindole (**37**) by spontaneous cyclization of the hydrazine **36**. If **37** is hydrolyzed back to the hydrazine **36**, and the reaction mixture is then carefully neutralized, 3-hydroxy-4-phenylcinnoline (**38**) is obtained in 46% yield (18).



33 34 35 36 37 38

By this same route, 4-benzyl-3-hydroxycinnoline has been synthesized from isatin and benzylmagnesium chloride (18), but apparently no other alkyl- or arylcinnolines have been prepared in this way.

II. Physical Properties

Generally, the alkyl- and arylcinnolines are solid materials, ranging in color from colorless to orange-red. Most are yellow. They are basic materials that form a number of salts, including picrates, hydrochlorides, and methiodides. Very little has been recorded about their actual basic strengths, but the alkylcinnolines are expected to be somewhat more basic than cinnoline itself, in accordance with the usual slight base-strengthening effect of alkyl groups in heterocyclic bases. Like cinnoline itself (and unlike 4-aminocinnoline), the basic center of 3-, 4-, and 8-methylcinnoline is at N-2. This is known by molecular orbital calculations (19) and by experimentation (19). The experimental proof was obtained by showing that the UV spectra of protonated 3-, 4-, and 8-methylcinnoline are very similar to the spectra of the corresponding 2,3-, 2,4- and 2,8-dimethylcinnolinium perchlorates. The