

**CONDENSED PYRIDAZINES
INCLUDING CINNOLINES
AND PHTHALAZINES**

Edited by
Raymond N. Castle

CONDENSED PYRIDAZINES INCLUDING CINNOLINES AND PHTHALAZINES

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DEPARTMENT OF CHEMISTRY
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AND PHTHALAZINES**

This is the twenty-seventh volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors



Contributors

Natu R. Patel, *Gulf Research and Development Company, Merriam, Kansas*

Gary M. Singerman, *Gulf Research and Development Company, Pittsburgh, Pennsylvania*

B. Stanovnik, *Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia*

M. Tisler, *Department of Chemistry, University of Ljubljana, Ljubljana, Yugoslavia*

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.

ARNOLD WEISSBERGER

*Research Laboratories
Eastman Kodak Company
Rochester, New York*

EDWARD C. TAYLOR

*Princeton University
Princeton, New Jersey*

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 benzo-pyridazines, 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

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CHAPTER 1

Cinnolines

GARY M. SINGERMAN

Gulf Research and Development Company, Pittsburgh, Pennsylvania

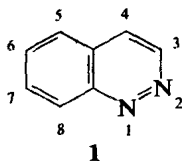
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I. Physical Properties

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.



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)].

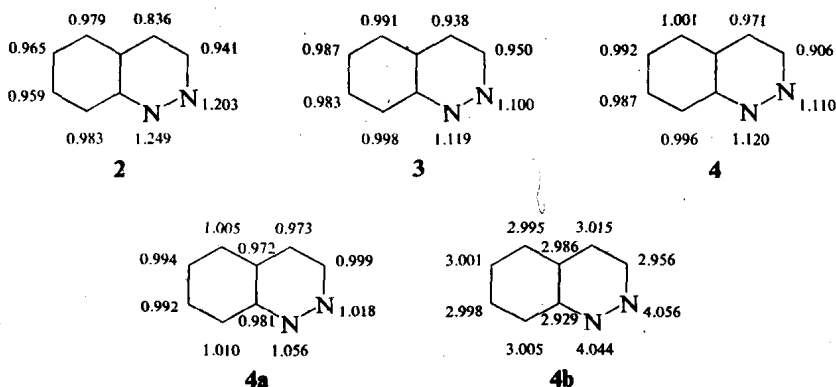
Cinnoline has a dipole moment of 4.14 D in benzene solution compared to values of 4.32 D for pyridazine (8), 2.18 D for quinoline, and 2.52 D for isoquinoline (9), all in benzene solution.

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



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 $m\mu$ (millimicrons) which are attributable to π - π^* transitions and an n - π^* absorption of low intensity at 390 $m\mu$ (in ethanol) due to the nonbonding electrons of the ring nitrogen atoms.

This $n-\pi^*$ band is observed to occur at shorter wavelengths in both diaza-benzenes and diazanaphthalenes when the two nitrogen atoms are non-vicinal (30). Thus the $n-\pi^*$ band of quinazoline (1,3-diazanaphthalene) is reported to occur as a shoulder at $330\text{ m}\mu$ (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).

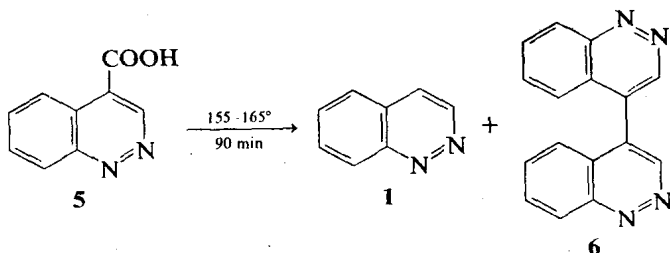
The pmr (proton magnetic resonance) spectrum of cinnoline is given in Table 1A-3. A study of the carbon-13 magnetic resonance spectrum of cinnoline has been published (35).

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

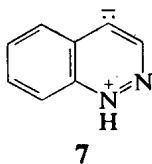
A. Decarboxylation of Cinnoline-4-carboxylic Acid

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



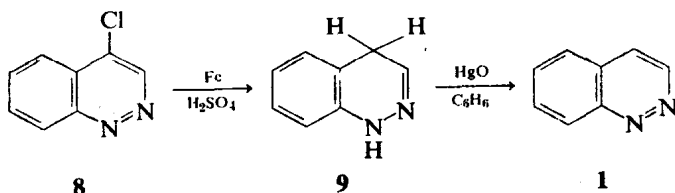
the protonated cinnoliny anion (**7**) from which both cinnoline and 4,4'-dicinnoliny are thought to be produced, the latter by attack of the anion **7**

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).



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

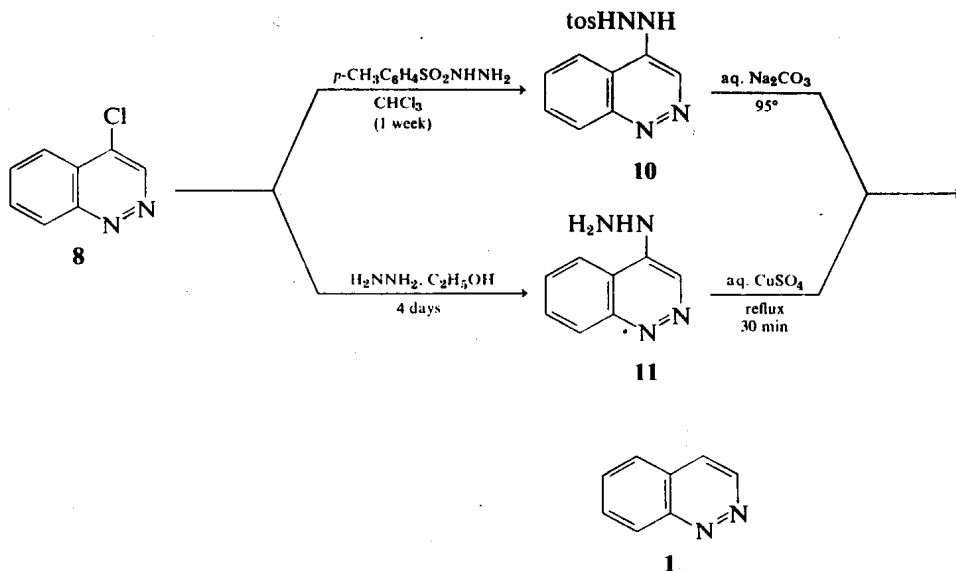


reduced cinnoline 9 was originally assigned a 1,2-dihydro structure but has since been shown by pmr to have a 1,4-dihydro structure (39). Chemical reduction of 4-chlorocinnoline with lithium aluminum hydride in ether solution gives only 4,4'-dicinnolinyl (6) (40), whereas catalytic reduction of 4-chlorocinnoline 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.

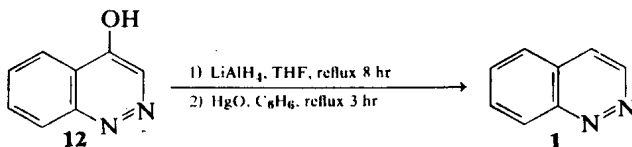
Treatment of 4-chlorocinnoline with hydrazine followed by oxidation of the resultant 4-hydrazinocinnoline (11) with aqueous copper sulfate gives cinnoline in a yield of about 56% (41).

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

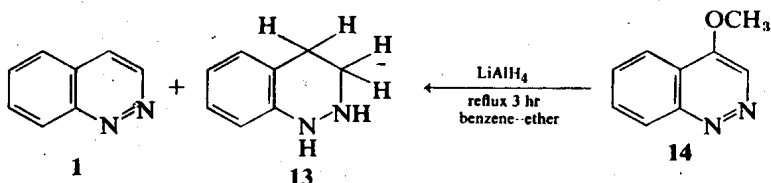
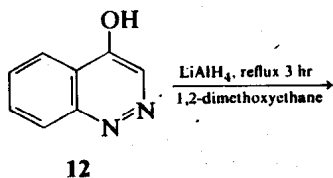
Direct reduction of 4-hydroxycinnoline (**12**) with lithium aluminum hydride in refluxing tetrahydrofuran for 8 hours followed by gentle oxidation of the resulting partially reduced cinnoline with mercuric oxide in refluxing benzene gives cinnoline in 74% yield (43). Reduction of **12** with lithium 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**.

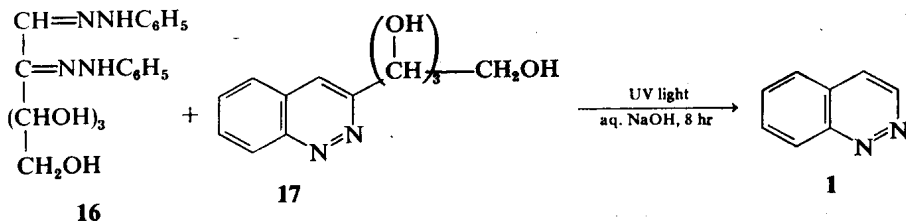
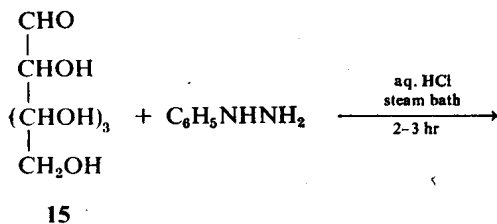
Cinnoline may be prepared from 4-hydroxycinnoline by polarographically reducing the hydroxycinnoline in acid solution, making the solution slightly alkaline, and then oxidizing the intermediate 1,4-dihydrocinnoline anodically. No isolation of the intermediate is necessary, and the overall yield of cinnoline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



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-arabinotetritol (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).



E. Miscellaneous

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