CONDENSED PYRIDAZINE
AND PYRAZINE RINGS
(Cinnolines, Phthalazines,
and Quinoxalines)

This is the fifth volume published in the series
THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
CONDENSED PYRIDAZINE AND PYRAZINE RINGS
(Cinnolines, Phthalazines, and Quinoxalines)

J. C. E. SIMPSON
Late Member of Scientific Staff
Medical Research Council
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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.

I am deeply sorry that the author of this volume will not see the completed book. Dr. Simpson died on February 7, 1952, while his manuscript was being set in print.

Dr. Simpson’s friend and colleague, Dr. C. M. Atkinson, volunteered to take over the author’s burden in the production of the book, and I want to thank him most sincerely for his generous help. He has also supplied the obituary of Dr. Simpson, printed on the following pages, which we hope will help to make the book a lasting memorial to its author.

Research Laboratories
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Rochester, New York

ARNOLD WEISSBERGER
J. C. E. SIMPSON
1908—1952

James Charles Edward Simpson was born on August 14, 1908, in Cheshire, where his father was Vicar of Liscard and later Residentiary Canon of Chester Cathedral. He received his education at St. Edward's School, Oxford, and proceeded to the University of Liverpool, where he was graduated in 1929 and was awarded the Leverhulme Chemistry Prize and the Campbell Brown Fellowship.

Under the direction of Professor (now Sir Ian) Heilbron, Simpson's first researches provided a number of contributions to the elucidation of the structure of ergosterol. After two years' work he obtained the Ph. D. degree, and in 1933 he went as a Commonwealth Fund Fellow to the Rockefeller Institute, New York, where he collaborated with Dr. W. A. Jacobs in proving the presence of the steroid skeleton in the digitalis sapogenins.

In 1935, Simpson became an assistant lecturer at King's College, London, and published from there a series of contributions on the isolation and chemistry of various triterpenes; in this field he was one of the first workers to apply the chromatographic technique to the separation of mixtures. Four years later he took up a temporary lectureship in the Durham Division of the University of Durham, where his interest in heterocyclic chemistry first found expression in studies on cinnoline derivatives. This work, which was linked initially to a wartime program on potential antimalarials, but contained much fundamental work on the scope and mechanism of cinnoline syntheses, established Simpson as the authority on this ring system and led to his recognition in the wider field of related nitrogenous heterocyclic compounds. In 1945 he was awarded the D. Sc. degree of the University of Liverpool and moved as I. C. I. Fellow to the Chemotherapy Department of the Liverpool School of Tropical Medicine. Collaboration with the director, at that time Dr. E. M. Lourie, on the application of cinnolines and related heterocyclic types to the chemotherapy of trypanosomiasis was most successful, and this happy partnership continued after 1949 when Simpson joined the Department of Chemistry at Manchester.
University as director of a Medical Research Council Group for Research on Chemotherapy. The chemical work during this period consisted of the synthesis of compounds which might be regarded as simple analogs of the trypanocidal phenanthridinium salts, and afforded an opportunity to study the properties of a group of related heterocyclic compounds. This program was being extended to test further a derived hypothesis, of proven usefulness, on the structural features required by trypanocidal compounds in this group, at the time of Simpson's death.

Apart from his research communications, Simpson contributed to reviews of heterocyclic chemistry and carried out editorial work for the Bureau of Abstracts. He was concerned always at the multiplication of labor involved in the separate literature surveys of research workers and he agreed readily to write this volume. As a memorial to him it cannot, of course, show his contributions to the field of natural products and it does not reflect his wider chemical horizon, but it represents well his insistence on the accurate classification of data.

He was well known for his energetic devotion to research and for his zealous approach as a teacher. A similar enthusiasm characterized his pastimes, which included fell-walking and playing tennis or badminton. He was an active member of choral societies and the early interest in campanology which he formed at Liscard developed during his life to such an extent that his intellectual and physical prowess were recognized throughout England.

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PREFACE

Although the chapters of this volume are numbered continuously, the subject matter falls naturally into three distinct sections: (1) cinnolines and (2) phthalazines—both formed by condensation of a pyridazine nucleus with an aromatic ring, and (3) quinoxalines, which represent the fusion of a pyrazine with an aromatic ring.

This book has been written with the objective of ensuring continuity with, and expansion from, Meyer-Jacobson's *Lehrbuch der organischen Chemie*, Volume II, 3, and in order to avoid the creation of possible gaps the literature has been fully covered from 1917 up to the end of 1948. Adequate reference is also made to the 1949 literature, and in many instances details of compounds there described have been included in the tables. Throughout the book the emphasis is on a critical presentation, so far as is reasonably possible, of the facts, rather than on a mere compilation of data. However, the treatment given to cinnolines and phthalazines differs slightly from that given to quinoxalines by reason of the fact that, twenty-five years ago, the chemistry of cinnoline and, to some extent, of phthalszine derivatives also, was very largely undeveloped, whereas that of quinoxaline compounds rested on a much broader basis of established fact and has already been reviewed, so far as the early literature is concerned, in Meyer-Jacobson's *Lehrbuch*. In this volume, therefore, references to the quinoxaline literature earlier than 1917, though numerous, are incidental; the accounts of cinnoline and phthalazine chemistry, on the other hand, are intended to be exhaustive. This selective treatment of quinoxaline chemistry applies particularly to those chapters dealing with compounds containing three or more fused rings.

Mention should be made of one or two conventions that have been adopted. Heterocyclic rings for which alternative formulations are possible by reason of tautomerism (for example, rings substituted in appropriate positions by amino and hydroxyl groups) are written in the form which approximates most closely the aromatic state; this procedure has been followed purely for reasons of simplicity of classification, and no indication is thereby implied that a given compound exists in the form
shown rather than in the alternative imino- or keto-dihydro modification. Where substituents in the tables have been represented by cyclic formulas no effort has been made to show fully bonded (aromatic) structures but this can be assumed where representation is not clearly a reduced form (alicyclic). Colors of bases are not mentioned unless deeper than "almost colorless" or "very pale yellow"; and by the same token no mention is made of the colors of picrates which are merely "yellow." The keys to the various tables are not intended to furnish full experimental detail, but are usually so worded as to indicate in outline the conditions required to prepare a given compound. Standard British nomenclature has been used throughout this volume.

The following condensed mixed heterocyclics are included in the present volume: For condensed cinnolines and phthalazines, the choice has been based essentially on the Ring Index, and includes all compounds in which the cinnoline or phthalazine nucleus is intact and also those in which one CH group in the benzene ring of these nuclei is replaced by N. Compounds in which a CH group of these nuclei is replaced by other hetero elements are excluded. The same principles govern the selection of condensed quinoxalines, with the further exclusion of phenazines, condensed phenazines, and their aza analogs. In all these compounds, the intact quinoxaline nucleus is preserved.

Much of the work entailed in the preparation of this book was carried out at the Liverpool School of Tropical Medicine, and the author is greatly indebted to Dr. E. M. Lourie, then Director of the Warrington Yorke Department of Chemotherapy, for the secretarial facilities which were so willingly made available to him.

Medical Research Council
Group for Research in Chemotherapy
Department of Organic Chemistry
University of Manchester
September, 1950

J. C. E. SIMPSON
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PART I

Cinnolines
CHAPTER I

General Introduction to Cinnoline Derivatives. Preparation and Properties of Cinnoline

1. General Introduction to Cinnoline Derivatives

So far as is known, no derivative of cinnoline occurs in nature. The cinnoline ring system was discovered in 1883 by von Richter, who, in the course of experiments designed to convert o-nitrophenylpropionic acid into o-hydroxyacetophenone, found that the diazonium chloride derived from o-aminophenylpropionic acid was transformed on heating into a nitrogenous derivative (Eq. 1). The new ring system so formed was named cinnoline (R.I. 976) from analogy with quinoline. In the following year, Widman prepared 4-methylcinnoline-7-carboxylic acid by diazotization of 1-methyl-1,2′-amino-4′-carboxyphenylethylene (Eq. 2). In 1909, Stoermer and his co-workers found that this reaction could also be used to prepare 4-arylcinnolines.

No further work was carried out in this field until 1941, when Borsche and Herbert found that diazotized 5-nitro-2-aminoacetophenone slowly cyclized on standing, yielding 6-nitro-4-hydroxycinnoline (Eq. 3). In
point of time, this observation may be said to have ushered in a new chapter in the chemistry of cinnolines, as, during the last few years, knowledge of this group of compounds has expanded considerably. The three reactions described above have been shown to be general synthetic routes, and the third reaction, leading to 4-hydroxycinnolines, has in particular been widely explored.

It is convenient to draw a sharp distinction between true cinnolines and a miscellaneous group of compounds which, although formally classifiable as cinnolines, contain additional rings fused to the cinnoline nucleus. The reasons for this distinction are: (1) such compounds are not prepared by the typical methods of cinnoline ring closure; (2) the characteristic reactions of true cinnoline derivatives frequently cannot be shown by cinnolines carrying additional fused rings owing to the fact that positions important for cinnoline reactivity (e.g., $C_3$, $C_4$) may be positions of ring fusion; and (3) these condensed cinnolines can, on occasion, be regarded equally logically as condensed phthalazines. The chapters which follow are therefore concerned with true cinnoline derivatives, and miscellaneous condensed cinnolines are grouped together in Chapter IX.

2. Preparation and Properties of Cinnoline

Cinnoline (I), the parent compound of the heterocyclic group to which it gives its name, may be prepared by two methods. The first of these, due to Busch and Rast, consists in the reduction of 4-chlorocinnoline (II)

with iron and 15% sulfuric acid to 1,2-dihydrocinnoline (III), which yields cinnoline on oxidation with mercuric oxide. The second method, devised by Jacobs et al., involves the synthesis of cinnoline-4-carboxylic acid (IV), which is then decarboxylated in benzophenone at 155–165°. Of the two methods, the latter is preferable as a preparative route.

Cinnoline is a pale yellow solid of geraniumlike odor which is soluble in water. It crystallizes from ether with 1 molecule of solvent, and then melts at 24–25°C; the solvent-free base melts at 39°C. [37–38°C.]. It tends to liquefy on exposure to air at 20–25°. The base forms stable salts; the hydrochloride melts at 156–160°C. (154–156°C.) and sublimes
at 110–115°/3 mm.; the picrate, yellow prisms from alcohol, has m.p. 196–196.5°C.\(^7\) (190°C.\(^9\)); and the methiodide, dark reddish-brown crystals, melts at 168–170.5° (dec.)\(^7\) [168°C.\(^4\)]. The chloroplatinate, m.p. 280° (dec.), and aurichloride, m.p. 146°, are also described.\(^8\) Busch and Rast\(^8\) state that cinnoline is a strong base, but this statement was clearly based on qualitative impressions, and recent quantitative work has established that the base is actually fairly weak \((pK_a = 2.51 \text{ at } 21–22° \text{ in } 50\% \text{ aqueous alcohol}; \text{ 2.70 at } 20° \text{ in water})\).

Cinnoline is distinctly toxic, and also shows appreciable antibacterial action against *Escherichia coli*.\(^6\)

References

CHAPTER II

4-Aryl-, 4-Acyl-, and 4-Carboxycinnolines

1. 4-Arylcinnolines

A. Synthesis. The first recorded examples of the synthesis of 4-aryl cinnolines are by Stoermer and Fincke,¹ who found that diazotization of o-aminoarylethylenes (I; \( R_1 = \text{aryl; } R_2 = \text{H or Me} \)) effected reaction

\[
\text{NH}_2 \quad \begin{array}{c} \quad \text{CR}_2 = \text{CHR}_2 \quad \text{N}_2X \\ \end{array} \quad \rightarrow \quad \begin{array}{c} \quad \text{NH}_2 \quad \begin{array}{c} \quad \text{CR}_2 = \text{CHR}_2 \quad \text{N}_2X \\ \end{array} \quad \quad \rightarrow \quad \text{N}_2X \\ \end{array} \quad \rightarrow \quad \text{N}_2X + \text{HX} \quad \text{(1)}
\]

(1), which is precisely the same reaction that was first observed many years earlier by Widman,² who prepared 4-methylcinnoline-7-carboxylic acid (II), and in consequence the reaction has come to be known as the Widman-Stoermer synthesis (2). A list of the known 4-arylcinnolines is given in Table II-1.

Recent investigations of the scope and mechanism of the reaction³,⁴,¹⁵ have shown that it proceeds successfully when \( R_1 \) is aryl or methyl and \( R_2 \) is alkyl, aryl, or aralkyl, but that it fails in cases so far investigated when \( R_1 \) is hydrogen or carboxyl (\( R_2 \) being aryl, \( \alpha \)-pyridyl, or \( \alpha \)-quinolyl). The reaction is usually very rapid, and it is seemingly independent of the geometrical configuration of the groups around the ethylenic linkage. It is concluded from these results⁶ that the ring closure is more or less ionic in character, and that it is induced by polarization of the diazonium salt of (I) as indicated below. The essential requisite which enables this polarization to be set up is, clearly, that \( R_1 \) must be an electron-donating group.
According to this mechanism, the coordination of the anionoid Cβ with the cationoid diazonium grouping should be retarded if R₂ has sufficient electron-absorbing powers. In agreement with this conclusion, it has been found that, whereas (I; R₁ = R₂ = Ph) yields 3,4-diphenylcinnoline almost quantitatively, the reaction with (I; R₁ = Ph; R₂ = α-C₆H₅) gives, in addition to the expected cinnoline, 2-phenylchrysene (III). This hydrocarbon arises through the agency of a competing Pschorr reaction, and is formed because an α-naphthyl residue on the β-carbon atom of the diazotized aminoethylene is more effective than a similarly placed phenyl group in absorbing the lone electron pair from Cβ, thus militating against the cinnoline ring closure.

B. Properties. No detailed study of the chemistry of 4-arylcinnolines has yet been made. In general, 4-arylcinnolines are, qualitatively, weak bases, although some compounds are soluble in dilute acids, and the basic strength seems to be enhanced by a 3-methyl or a 3-benzyl group. Usually they react as monoacid bases, but abnormal salts are also known. Thus 4-phenylcinnoline forms a hydrochloride, m.p. 130° (dec.), a hydrobromide, m.p. 202–204°, a hydriodide (dec. 150°), a nitrate, m.p. 156–157°, a picrate, m.p. 156–158°, a chloroaurate (melts gradually above 158°), and a chloroplatinate, m.p. > 300°; but it also yields a basic hydriodide (B₂HI), m.p. 93–95°, an acid sulfate, m.p. 181–182°, a chloroaurate (BHC₁₂AuCl₈), m.p. 145–147°, and an argentonitrate, BAgNO₃, m.p. 260° (dec.).

4-p-Anisylcinnoline forms a normal hydrochloride, m.p. 215°, a picrate, m.p. 150°, a nitrate, m.p. 151–152°, a chloroaurate, m.p. 120° (dec.), and a chloroplatinate (dec. 200°), an acid sulfate, m.p. 211° (dec.), and an argentonitrate, BAgNO₃ (dec. 250°). 3-Methyl-4-phenylcinnoline gives a chloroplatinate (dec. 180°); and 4-p-hydroxyphenylcinnoline yields a chloroplatinate (dec. 252°), an acid sulfate, m.p. 210°, and a sodium salt, m.p. 85°.
TABLE II-1. * 4-Arylcinnolines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>A</td>
<td>67–67.5</td>
<td>Yellow cryst.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>HO</td>
<td>H</td>
<td>230, 234–235</td>
<td>Yellow prisms</td>
<td>8, 10</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>85</td>
<td>Yellow needles</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>58–59</td>
<td>Yellow cryst.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>2'-Pyridyl</td>
<td>A</td>
<td>128–129</td>
<td>Picrate, m.p. 201–203°</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>Br</td>
<td>143.5–144.5</td>
<td>Yellow needles</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>OH</td>
<td>Cl</td>
<td>257–259 (dec.)</td>
<td>Yellow plates</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>260–261 (dec.)</td>
<td>Golden needles</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>134–136 135–136</td>
<td>Yellow cryst.</td>
<td>1, 4</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OH</td>
<td>H</td>
<td>241–242</td>
<td>Yellow prisms</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>131–133</td>
<td>Yellow leaflets</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>Ph</td>
<td>H</td>
<td>116.5–118</td>
<td>Pale yellow needles</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>A,C</td>
<td>149–150</td>
<td>Yellow rhombsh</td>
<td>6, 17</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>OH</td>
<td>H</td>
<td>283–286</td>
<td>—</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>OMe</td>
<td>H</td>
<td>169–170.5</td>
<td>Yellow needles</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1'-C₁₀H₂</td>
<td>Ph</td>
<td>H</td>
<td>178–179</td>
<td>Yellow cryst.</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>2'-Pyridyl</td>
<td>Ph</td>
<td>H</td>
<td>—</td>
<td>Picrate, m.p. 194–196°</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
TABLE II-1. 4-Arylcinnolines (continued)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2'-Pyridyl</td>
<td>-</td>
<td>OMe</td>
<td>H</td>
<td>A</td>
<td>157-158</td>
<td>Yellow tablets</td>
</tr>
<tr>
<td>2'-Quinolyl</td>
<td>-</td>
<td>OMe</td>
<td>H</td>
<td>A</td>
<td>151-152</td>
<td>Yellow tablets</td>
</tr>
</tbody>
</table>

* In this and in all other tables, plain hexagons are used to indicate substituent aryl groups.

 A, by the Widman-Stoermer reaction. B, by demethylation of the corresponding anisylcinnoline with hydrobromic acid. C, from benzil monophenylhydrazone by cyclo-dehydration with 75-80% (w/w) aqueous sulfuric acid.

TABLE II-2. 4-Arylcinnoline N-oxides

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>Color and cryat. form</th>
<th>M.p., °C.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td></td>
<td>Straw-colored needles</td>
<td>124-125</td>
<td>8</td>
</tr>
<tr>
<td>Me</td>
<td>-</td>
<td>OMe</td>
<td>Blades</td>
<td>161</td>
<td>8</td>
</tr>
<tr>
<td>CH₂Ph</td>
<td>Ph</td>
<td></td>
<td>Needles</td>
<td>110-111</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(clear at 130)</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td></td>
<td>Yellow needles</td>
<td>196-198</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OMe</td>
<td>Light brown blades</td>
<td>176-177</td>
<td>8</td>
</tr>
</tbody>
</table>

Quaternary salt formation occurs fairly readily in five cases so far examined, viz., 4-phenyl-, 4-phenyl-3-methyl-, 4-p-anisyl-, 4-p-hydroxyphenyl-, and 3-phenyl-4-p-hydroxyphenylcinnoline⁴,⁷,¹⁰ (see Chapter VII).

The formation of N-oxides is also a characteristic property of 4-aryl-cinnolines,⁸ as shown in Table II-2; these oxides are produced by oxidation of the cinnolines with hydrogen peroxide in acetic acid, but, unlike quinoxaline di-N-oxides, which are similarly formed (Chapter XXVI), they show no peroxidic properties. The oxidation is considered to occur at N₁ and not at N₂ by reason of the fact that the basic center of 4-substituted cinnolines is probably N₁⁷ (see Chapter VII). On nitration, 4-phenyl-3-methylcinnoline N-oxide yields, somewhat unexpectedly, four isomeric mono-nitro derivatives (m.p. 256-257°, 235-238°, 218-219°, and 198-199°), the orientations of which are unknown.
On oxidation with hot aqueous permanganate, 4-phenylcinnoline yields the acid (IV), and the analogs (V) and (VI) are produced by similar oxidation of 3-methyl-4-phenyl- and 4-p-anisyl-cinnoline. Degradation of (VI) ultimately yields pyridazine.

The most interesting known property of 4-arylcinnolines is their behavior on reduction with sodium and alcohol, whereby they are converted into the corresponding 3-arylinodoles. Table II-3 gives a list of cinnolines of which the behavior under these conditions has been investigated. It will be noted that 4-methylcinnolines undergo the same reaction; the ring contraction is thus characteristic of cinnolines carrying a hydrocarbon substituent at C_4, but it seems possible that substitution of both C_3 and C_4 by aryl groups has an inhibitory effect. Two cases have also been recorded of the conversion of cinnolines into indoles in acid reducing media; 4-phenylcinnoline gives 3-phenylindole when refluxed for 2 hours with 33% aqueous acetic acid and amalgamated zinc, and 3-hydroxycinnoline gives oxindole when refluxed 1 hour with red phosphorus and hydriodic acid (d 1.7); but no indole derivative could be obtained from 4-hydroxycinnoline.

TABLE II-3. Conversion of 4-Substituted Cinnolines into Indoles

<table>
<thead>
<tr>
<th>Cinnoline</th>
<th>Ammonia evolved (% of theoretical)</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Phenyl-3-methyl</td>
<td></td>
<td>3-Phenyl-2-methylindole + unchanged cinnoline</td>
</tr>
<tr>
<td>4-p-Anisyl-3-methyl</td>
<td>58</td>
<td>3-p-Anisyl-2-methylindole</td>
</tr>
<tr>
<td>4-p-Hydroxyphenyl-3-methyl</td>
<td>55</td>
<td>3-p-Hydroxyphenyl-2-methylindole + unchanged cinnoline</td>
</tr>
<tr>
<td>4-p-Hydroxyphenyl</td>
<td>53</td>
<td>3-p-Hydroxyphenylindole + unchanged cinnoline</td>
</tr>
<tr>
<td>4-p-Anisyl</td>
<td>15</td>
<td>Resin</td>
</tr>
<tr>
<td>3-Phenyl-4-p-anisyl</td>
<td>3</td>
<td>Unidentified mixture</td>
</tr>
<tr>
<td>3-Phenyl-4-p-hydroxyphenyl</td>
<td>1</td>
<td>Unchanged cinnoline + unidentified material</td>
</tr>
<tr>
<td>4-Methyl</td>
<td>65</td>
<td>Skatole + unchanged cinnoline</td>
</tr>
<tr>
<td>7-Chloro-4-methyl</td>
<td>60</td>
<td>Skatole + 4-methylcinnoline</td>
</tr>
<tr>
<td>6-Chloro-4-methyl</td>
<td>57</td>
<td>Skatole + unidentified material</td>
</tr>
</tbody>
</table>
2. 4-Acylcinnolines

4-Acetylcinnoline (I), m.p. 100–101°, is prepared from ethyl cinnoline-4-carboxylate (vide infra) by condensation with ethyl acetate, followed by acid hydrolysis of the intermediate keto ester (II) (m.p. 81.5–82°)\(^{11}\); it forms an oxime, m.p. 165–165.5° (corr.).

4′-Keto-6′-benzamido-n-hexylcinnoline (III), m.p. 115–116.5° (corr.), is formed by a similar condensation of ethyl cinnoline-4-carboxylate with ethyl o-benzamidocaprate, followed by hydrolysis.\(^{11}\)

4-Chloroacetylcinnoline (IV), m.p. 95–100° (dec.), results from interaction of diazomethane with the acid chloride of cinnoline-4-carboxylic acid, followed by treatment with hydrogen chloride and basification of the hydrochloride of IV.\(^{11}\)

3,4-Dibenzoylcinnoline (V) is prepared by oxidation of VI (Chapter IX) with nitric acid in acetic acid; it forms brown crystals, m.p. 163°, which give a blue coloration with concentrated sulfuric acid.\(^{12}\) Reactions of this compound are described in Chapter IX.

3,4-Di(thiobenzoyl)cinnoline (VII), which forms yellow crystals, m.p. 206–207° (dec.), is prepared by refluxing compound V with alcoholic ammonium sulfide.\(^{13}\)

3. 4-Carboxycinnolines (Cinnoline-4-carboxylic Acids)

Cinnoline-4-carboxylic acid (I) is prepared by oxidation of 4-styrylcinnoline (Chapter III) with permanganate in aqueous pyridine. It melts at 195–196° (dec., corr.) and gives an ethyl ester, m.p. 48.5–49.5°.\(^{11}\) When heated in benzophenone at 155–165° it is smoothly converted into cinnoline,\(^{11}\) a small amount of 4,4′-dicinnolyl (II) (m.p. 237–238°) being formed as a by-product.\(^{14}\)

3-Phenylcinnoline-4-carboxylic acid (III) is formed by the action of hot aqueous sodium hydroxide on N-benzylideneaminoisatin (IV)\(^{15}\); it forms yellow plates, m.p. 244° (dec.).
References