ISOQUINOLINES

PART ONE

This is the thirty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
Contributors

C. K. Bradsher, Department of Chemistry, Duke University, Durham, North Carolina

S. F. Dyke, School of Chemistry, The University of Bath, Claverton Down, Bath, United Kingdom

K. Fukumoto, Pharmaceutical Institute, Tohoku University, Aobayama Sendai, Japan

T. J. Kametani, Pharmaceutical Institute, Tohoku University, Aobayama Sendai, Japan

R. G. Kinsman, School of Chemistry, The University of Bath, Claverton Down, Bath, United Kingdom

E. McDonald, University Chemical Laboratory, Cambridge, United Kingdom
To Inge, Nadine, and Jeffrey
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 editions.

Research Laboratories
Eastman Kodak Company
Rochester, New York

Princeton University
Princeton, New Jersey

ARNOLD WEISSBERGER

EDWARD C. TAYLOR
Preface

The isoquinoline skeleton is found abundantly in the plant world and is widely incorporated into medicinally important compounds. Several excellent books on isoquinoline alkaloids and reviews on certain aspects of isoquinoline chemistry have been written but the significance of isoquinolines among heterocyclic compounds clearly merits a comprehensive and detailed study. This is the purpose of the books on isoquinolines. They are intended to serve a dual function, as an introduction for the beginner interested in the general chemistry of isoquinolines and as a source of detailed data for the frequent user. The individual chapters constitute a complete source on a specific subject of isoquinoline chemistry. They have been arranged in such a manner as to avoid overlapping as much as possible and to simplify literature searching.

The first two chapters deal with the general aspects of the chemistry of isoquinolines. A broad discussion of the physical and chemical properties of the ring system in the opening chapter is followed by a detailed coverage of the general and specific methods of synthesizing the isoquinoline nucleus. The other two chapters in Part I deal with the more specific subjects of isoquinoline biosynthesis and the chemistry of quaternary isoquinolinium derivatives. Subsequent chapters in future volumes will give a detailed coverage of the chemistry of substituted and fused isoquinolines and should be considered reference sources. To this purpose each of these chapters closes with an exhaustive tabulation of derivatives containing only the substituents discussed in that particular chapter and in the preceding ones.

These books are made possible only because of the untiring efforts of the expert authors, whose work I acknowledge with deep admiration and gratitude.

I thank Hoffmann-La Roche, Inc. for the use of the excellent library and the staff of the library for their continuous help. I owe my gratitude to Mrs. Claudette Czachowski for helping with the extensive correspondence connected with the editorial work. Special thanks are due to my family for their understanding and support during this long and sometimes difficult task.

GUENTER GRETHE

Nutley, New Jersey
November 1980
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ISOQUINOLINES

PART ONE

This is the thirty-eighth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
CHAPTER I

Properties and Reactions of Isoquinolines and Their Hydrogenated Derivatives

S. F. DYKE* AND R. G. KINSMAN

School of Chemistry, University of Bath, Bath, United Kingdom

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* Present address: Department of Chemistry, Queensland Institute of Technology, George Street, Brisbane, Queensland 4001, Australia.
I. INTRODUCTION

*Isoquinoline* (1)\(^1\) is the name given to 2-azanaphthalene, the benzopyridine in which a benzene ring is fused to the C-3 and C-4 atoms of the pyridine system. The numbering scheme of the atoms used throughout this chapter is in accordance with that currently accepted by *Chemical Abstracts*, although in earlier literature the atoms 4\(^a\) and 8\(^a\) at the ring junction were numbered both 9, 10 and 10, 9, respectively.

Isoquinoline, which occurs in the crude quinoline (2) fraction of coal tar, was first reported\(^2\) in 1885. It has been isolated by exploiting the greater basicity compared to quinoline and by the selective precipitation of certain isoquinoline salts. 1-Methyl-, 3-methyl-, and 1,3-dimethylisoquinolines have also been identified in coal-tar bases. Oxidation with alkaline potassium permanganate results\(^2\) in degradation to phthalic acid and pyridine-3,4-dicarboxylic acid (cinchomeronic acid). Certain chemical and physical properties of isoquinoline resemble those of both quinoline and naphthalene. Isoquinoline has been classified\(^3\) as a \(\pi\)-deficient system in common with quinoline and pyridine, and its properties reflect this definition.

This chapter is intended as an introduction to the general physical and
chemical properties of this heterocyclic system. Some characteristics of isoquinoline derivatives are incorporated, but a more detailed description is given in the appropriate chapters.

II. PHYSICAL PROPERTIES

A. General

Isoquinoline is a colorless, crystalline substance with melting point (m.p.) 26.48 ± 0.1°C. It has a density at 30°C of 1.09101 g/ml, and its viscosity is 3.2528 cP at the same temperature. The boiling point at 760 mm pressure is 243.25°C, and the heat of vaporization is 11.7 kcal/mole. The refractive index is $n_D^20 = 1.62078$. Critical temperatures of quinoline and isoquinoline, measured by observation of the disappearance and reappearance of the liquid–vapor meniscus, are 509 ± 2°C and 530 ± 5°C, respectively. A heat of atomization ($-\Delta H_a$) of 85.32 eV and a resonance energy ($E_R$) of 34.1 kcal/mole were calculated for isoquinoline by the SCF MO $\pi$-approximation method. By a different approach, using $pK_a$ values for equilibria 3 and 4, a value for the resonance energy of 48 ± 9 kcal/mole was suggested. Molar Cotton-Mouton constants for a series of solutes were determined and a value for the magnetic susceptibility for isoquinoline of $94.2 \times 10^{-6}$ derived (cf. quinoline, $112 \times 10^{-6}$).

\[
\begin{align*}
\text{3} & \quad \text{Me} & \text{OH} & \quad \text{H}^+ \\
\text{4} & \quad \text{Me} & \text{OH} & \quad \text{H}^+
\end{align*}
\]

B. X-Ray Crystallography

The structural analysis of 3-methylisoquinoline (5) shows it to be essentially planar, and the bond lengths resemble those of naphthalene (6). The three principal valence-bond structures of isoquinoline (7) are similar to those for naphthalene; and predictions of $\frac{2}{3}$ double-bond character for C₁–N, C₃–C₄, C₅–C₆, and C₇–C₈ bonds and $\frac{1}{3}$ double-bond character for all other bonds follow accordingly. The two C–N bond lengths, 1.300 Å for C₁–N and 1.366 Å for N–C₃, have the expected relationship to the 1.340-Å C–N
distance ($\frac{1}{2}$ double-bond character) in pyridines.\textsuperscript{11} The structure\textsuperscript{12} of isoquinoline hydrochloride (8) shows the increase in length of the C–N bonds expected to accompany protonation of the nitrogen lone-pair electrons. Papaverine has been examined,\textsuperscript{13} and its dimensions are as shown in structure 9.

The bond lengths in 2-(2',6'-dichlorobenzyl)-1-isoquinolone (10) are in fair agreement\textsuperscript{14} with those calculated\textsuperscript{15} by a semiempirical SCF MO $\pi$-approximation method for 1-isoquinolone (11) (Table I.1). In 2-methyl-1-

The bond lengths in 2-(2',6'-dichlorobenzyl)-1-isoquinolone (10) are in fair agreement\textsuperscript{14} with those calculated\textsuperscript{15} by a semiempirical SCF MO $\pi$-approximation method for 1-isoquinolone (11) (Table I.1). In 2-methyl-1-

phenyl-3-isoquinolone (12) the N–C\textsubscript{3} bond length (1.447 Å)$\textsuperscript{14}$ indicates an almost complete absence of conjugation between those two atoms; the suggested principal route for nitrogen–carbonyl conjugation is through the
benzenoid ring. The relevant bond lengths in 1-chloro-3-hydroxyisoquinoline (13) closely resemble those in 3-methylisoquinoline (5) and indicate that the compound exists in the lactim structure in the solid state.

TABLE 1.1. BOND LENGTHS OF ISOQUINOLONES

<table>
<thead>
<tr>
<th>Bond positions</th>
<th>10^14</th>
<th>11^15</th>
<th>12^14</th>
<th>13^14</th>
<th>3o</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-N</td>
<td>1.390</td>
<td>1.376</td>
<td>1.379</td>
<td>1.304</td>
<td>1.300</td>
</tr>
<tr>
<td>N-C3</td>
<td>1.383</td>
<td>1.412</td>
<td>1.447</td>
<td>1.366</td>
<td>1.366</td>
</tr>
<tr>
<td>C3-C4</td>
<td>1.334</td>
<td>1.348</td>
<td>1.433</td>
<td>1.366</td>
<td>1.360</td>
</tr>
<tr>
<td>C4-C4a</td>
<td>1.427</td>
<td>1.462</td>
<td>1.368</td>
<td>1.402</td>
<td>1.401</td>
</tr>
<tr>
<td>C4a-C5</td>
<td>1.403</td>
<td>1.403</td>
<td>1.412</td>
<td>1.416</td>
<td>1.434</td>
</tr>
<tr>
<td>C5-C6</td>
<td>1.373</td>
<td>1.393</td>
<td>1.338</td>
<td>1.350</td>
<td>1.374</td>
</tr>
<tr>
<td>C6-C7</td>
<td>1.382</td>
<td>1.400</td>
<td>1.432</td>
<td>1.416</td>
<td>1.379</td>
</tr>
<tr>
<td>C7-C8</td>
<td>1.379</td>
<td>1.393</td>
<td>1.350</td>
<td>1.354</td>
<td>1.349</td>
</tr>
<tr>
<td>C8-C8a</td>
<td>1.391</td>
<td>1.403</td>
<td>1.421</td>
<td>1.414</td>
<td>1.421</td>
</tr>
<tr>
<td>C8a-C1</td>
<td>1.466</td>
<td>1.466</td>
<td>1.379</td>
<td>1.405</td>
<td>1.405</td>
</tr>
<tr>
<td>C8a-C4a</td>
<td>1.413</td>
<td>1.403</td>
<td>1.426</td>
<td>1.436</td>
<td>1.414</td>
</tr>
</tbody>
</table>

A crystalline product from the reaction between 2-(4'-bromobenzyl)isoquinolinium bromide and carbon disulfide was obtained from dimethylformamide-acetonitrile solution, and its structure was shown by X-ray crystallographic analysis to be 2-(4'-bromobenzyl)isoquinolinium-4-dithiocarboxylate (14); the molecular geometry and dimensions are described.

\[
\text{S} \quad \text{C} \quad \text{S}^- \quad \text{Br}
\]

C. Dipole Moments

The dipole moment of isoquinoline is 2.49 D ± 0.01 D in benzene at 30.0°C. Values of 2.60 D, 2.65 D, and 2.61 D were found at 25°C for solutions in light petroleum, carbon tetrachloride, and benzene, respectively. Measurements in the vapor phase give values of 2.73 D and 2.75 D, compared with moments calculated by the valence electrons self-consistent field (VESC) method, of 2.41 D and 2.13 D, depending on the penetration terms adopted.
The dipole moments of several halogen-substituted isoquinolines have been measured\textsuperscript{19} at 30°C in benzene (Table 1.2), and using assumed\textsuperscript{20}

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$\mu$ (D)</th>
<th>$\alpha$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.53</td>
<td>—</td>
</tr>
<tr>
<td>1-Cl</td>
<td>3.35</td>
<td>108.5</td>
</tr>
<tr>
<td>3-Br</td>
<td>3.66</td>
<td>116.0</td>
</tr>
<tr>
<td>4-Br</td>
<td>2.70</td>
<td>105.0</td>
</tr>
<tr>
<td>5-F</td>
<td>2.10</td>
<td>123.5</td>
</tr>
<tr>
<td>5-Cl</td>
<td>2.35</td>
<td>114.5</td>
</tr>
<tr>
<td>5-Br</td>
<td>2.10</td>
<td>123.0</td>
</tr>
<tr>
<td>6-Br</td>
<td>1.24</td>
<td>98.0</td>
</tr>
<tr>
<td>7-Cl</td>
<td>1.92</td>
<td>109.0</td>
</tr>
<tr>
<td>8-Cl</td>
<td>3.15</td>
<td>98.0</td>
</tr>
</tbody>
</table>

moments for the C–F, C–Cl, and C–Br bonds, a mean value for the direction of the electric dipole moment in isoquinoline was derived, as shown in structure 15. The dipole moment of isoquinoline N-oxide was measured\textsuperscript{21} during an investigation into the double-bond character of N–O bonds in nitrogen heterocycles. The value of 4.47 D (cf. quinoline N-oxide, 4.07 D) compares favorably with that calculated\textsuperscript{22}; the direction of the moment was predicted to be at an angle of 33°41' with the $X$-axis, as indicated in structure 16. Schmitz\textsuperscript{23} measured the moment of 3,4-dihydroisoquinoline (17) by the Onsager method\textsuperscript{24} and obtained values of $\mu_{20}$ 1.78 D, $\mu_{30}$ 1.83 D, and $\mu_{40}$ 1.87 D. A value of $\mu = 1.99$ D was measured\textsuperscript{25} for 1-methyl-3,4-dihydroisoquinoline, and its direction was deduced from the dipole moment of 1-methyl-7-nitro-3,4-dihydroisoquinoline to act from C-4a through the nitrogen atom as shown in structure 18.

D. Ionization Constants

The lone-pair electrons of the nitrogen atom of isoquinoline are not delocalized into the $\pi$-aromatic system of this molecule but are present in
an orbital that has a large proportion of $s$-character. Thus isoquinoline should presumably be a much stronger base than indole ($pK_a = -2.4$) but weaker than a typical aliphatic amine (e.g., trimethylamine, $pK_a = 9.7$). The $pK_a$ value$^{26}$ of 5.40 (in water at 20°C) for isoquinoline is similar to that for pyridine ($pK_a = 5.23$)$^{27}$ but slightly higher than that for quinoline ($pK_a = 4.94$).$^{27}$ The ionization constant of isoquinoline has been determined$^{28}$ in a range of aqueous solvent mixtures, and the value for $\Delta pK/\Delta(1/D)$ (where $D$ is the dielectric constant of the solvent mixture) was shown to increase through the series ethanol $<$ 2-methoxyethanol $<$ 1,2-dimethoxyethane $<$ sulfolane $<$ $N$-methylpyrrolidone $<$ dimethylformamide $<$ $N$-butylacetamide. This sequence is the same as that for quinoline but different from that for pyridine.

A nitro-group substituent is capable of exerting only a base-weakening effect because both $-I$- and $-M$-mechanisms act in unison; $pK_a$ values for the nitroisoquinolines are 4-NO$_2$ 1.35,$^{29}$ 5-NO$_2$ 3.53,$^{30}$ 6-NO$_2$ 3.47, 7-NO$_2$ 3.61, and 8-NO$_2$ 3.59. 4-Bromoisoquinoline$^{29}$ ($pK_a = 3.31$) is also a weaker base than the unsubstituted molecule because of the $-I$-effect of the halogen atom. Comparison of the ionization constants of 4-nitro-, 4-bromo-, and 4-aminoisoquinoline as determined by a spectrophotometric method indicates that the Taft equation is followed with $\sigma = 0.95 \sigma_I + 0.38 \sigma_R$; an anomalous value of 4.70 for the 4-hydroxy compound is attributed to the contribution made by the zwitterion $^{19}$ (as much as 70%).

Protonation of aminoisouquinolines has been shown$^{26}$ to occur first at the ring nitrogen, and not at the substituent amino group. The first and second ionization constants of the aminoisouquinolines have been measured and are presented in Table 1.3. It is possible to rationalize the first $pK_a$ values using the concept of additional ionic resonance.$^{27}$ Thus amines with monocations from which additional ionic resonance is absent (4-, 5-, and 7-aminoisouquinolines) give $\Delta pK_a$ values of less than 1 unit. In contrast, 1-, 6-, and 8-aminoisouquinolines (cation resonance contributions $^{20, 21, 22}$
TABLE I.3. IONIZATION CONSTANTS OF AMINOISOQUINOLINES

<table>
<thead>
<tr>
<th>Substituent</th>
<th>First $pK_a$</th>
<th>Second $pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>5.40$^{26}$</td>
<td>--</td>
</tr>
<tr>
<td>1-NH$_2$</td>
<td>7.62$^{27}$</td>
<td>-9.59$^{31}$</td>
</tr>
<tr>
<td>3-NH$_2$</td>
<td>5.05</td>
<td>-4.20</td>
</tr>
<tr>
<td>4-NH$_2$</td>
<td>6.28</td>
<td>-2.29</td>
</tr>
<tr>
<td>5-NH$_2$</td>
<td>5.59</td>
<td>1.07</td>
</tr>
<tr>
<td>6-NH$_2$</td>
<td>7.17</td>
<td>-0.59</td>
</tr>
<tr>
<td>7-NH$_2$</td>
<td>6.20</td>
<td>1.13</td>
</tr>
<tr>
<td>8-NH$_2$</td>
<td>6.06$^a$</td>
<td>0.18</td>
</tr>
</tbody>
</table>

$^a$ From $\Delta pK_a$ value quoted and the rationale in the discussion section, this value should read 7.06.

respectively) have $\Delta pK_a$ values considerably greater than 1 unit. In the case of 3-aminoisoquinoline it is suggested that the ortho-quinonoid ionic resonance form 23 is not sufficiently favored for increase of the stability of the cation relative to that of the base. The second $pK_a$ of 1-aminoisoquinoline ($-9.59$) is similar to that of 2-aminopyridine$^{32}$ ($pK_a = -8.1$) and is probably due to the close proximity of the two positive charges on the molecule and some interaction with the perihydrogen atom. In the case of 3-aminoisoquinoline, where two close positive charges also exist, the second $pK_a$ is lower than expected. The value for 4-aminoisoquinoline ($pK_a = -2.29$) is in general agreement with that for 3-aminopyridine$^{32}$ ($pK_a = -1.5$). The second ionization constants of 6- and 8-aminoisoquinolines are lower than those of the 5- and 7-isomers because of the more facile second protonation of the additional ionic resonance forms 21 and 22.

The ionization constants of hydroxy$^{33-35}$ and mercaptoisoquinolines$^{36}$ and some of their $X$-$Me$ derivatives are shown in Table I.4.
The close similarities between the proton-gained $pK_a$ values for the $N$-unsubstituted and $N$-methyl derivatives of the 1-OH, 1-SH, 6-OH, and 8-OH isomers indicate that the neutral molecule exists predominantly in the forms containing an $N$-$H$ (25 and 26). If tautomer 24 were the dominant form, the $pK_a$ for the $X$-$Me$ derivatives would be more closely aligned to those of the corresponding unsubstituted molecules. A greater difference between the base strengths of the $N$-methyl and $N$-unsubstituted compounds is found in isomers where no tautomeric stabilization can occur (5- and 7-hydroxy), except for the anomalous behavior of 4-hydroxyisoquinoline (27), in which stabilization of the neutral molecule is achieved by contribution from the zwitterionic form 19. The 1-XH and 3-XH isomers, in which there is considerable stabilization of the neutral species by the amide tautomer 25, are also weaker acids than the other isomers.

The base strength of 1,2,3,4-tetrahydroisoquinoline (28) ($pK_a = 9.41$) is that expected for a cyclic alkyl derivative of benzylamine (29) ($pK_a = 9.34$).
Properties and Reactions of Isoquinolines

10

III. SPECTROSCOPIC PROPERTIES

A. Infrared Absorption

A total assignment of the vibrational spectrum of isoquinoline has been reported, and a comparison has been made with both quinoline and naphthalene. The frequency assignments of the 45 fundamental vibrations have been compared with those calculated by normal coordinate analysis and found to be in good agreement.

Of the substituted isoquinolines, only the hydroxyl and amino derivatives have been studied systematically. The hydroxyisoquinolines were examined to measure tautomerism in the system. Stretching frequencies in the O-H, N-H, and double-bond regions are shown (Table 1.5) for both solutions and solid state. There is no absorption in the O-H region (~3600 cm\(^{-1}\)) with either 1-hydroxyisoquinoline or homophthalimide, thus

TABLE 1.5. STRETCHING FREQUENCIES (cm\(^{-1}\)) OF HYDROXYISOQUINOLINES

<table>
<thead>
<tr>
<th>Compound</th>
<th>N-H</th>
<th>C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Solution</td>
<td>Solid</td>
</tr>
<tr>
<td>1-Hydroxyisoquinoline</td>
<td>3411</td>
<td>3278 w. 3150 s</td>
</tr>
<tr>
<td>Homophthalimide</td>
<td>3383</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Solution</th>
<th>Solid</th>
<th>Double-bond stretch</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-OH</td>
<td>3603</td>
<td>2900–2500 m, br</td>
<td>1626 m.</td>
</tr>
<tr>
<td>5-OH</td>
<td>3615</td>
<td>2950–2550 m, br</td>
<td>1623 m.</td>
</tr>
<tr>
<td>6-OH</td>
<td>3610</td>
<td>2920–2620 m, br</td>
<td>1625 m.</td>
</tr>
<tr>
<td>7-OH</td>
<td>3619</td>
<td>2900–2600 m, br</td>
<td>1628 m.</td>
</tr>
<tr>
<td>8-OH</td>
<td>3611</td>
<td>2920–2550 m, br</td>
<td>1621 m.</td>
</tr>
</tbody>
</table>