INDOLES
PART ONE

Edited by

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INDOLES

PART ONE

This is the twenty-fifth 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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Library of Congress Catalog Card Number: 76-154323

ISBN 0-471-37500-4

10 9 8 7 6 5 4 3 2 1

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

In 1954 "Heterocyclic Compounds with Indole and Carbazole Systems" was published as the eighth volume in the series The Chemistry of Heterocyclic Compounds. This text, edited and written by Profs. Ward C. Sumpter and F. M. Miller, summarized in a highly condensed form the literature on these topics through 1952. Since this time a large amount of new information relating to indoles and carbazole systems has been published. In order to make this new material available to the users of this Series and to widen the scope of Volume 8 it was decided to replace the earlier treatment by a more comprehensive and detailed presentation of indole chemistry. In addition the carbazole systems will be expanded to include condensed indoles, and isoindoles and condensed isoindoles will be added as part of the new enlarged coverage.

The material on indoles has been broken up into the three parts given on the Contents page. For organization of this subject matter the editor has borrowed heavily on the successful approach used by Dr. Erwin Klingsberg in preparing Volume 14 on Pyridine Chemistry in this Series.

Indoles Part One contains a broad coverage of the physical and chemical properties of this ring system together with general and specific methods for preparing an indole nucleus. It was assembled to provide the frequent user of indole chemistry a source of unified data and the beginner a framework of basic knowledge. Indoles Parts Two and Three will supply the detailed coverage that will allow this work to become a useful reference source.

The editor is grateful to Dr. Albert J. Frey, President, Sandoz-Wander, Inc. for allowing him free access to the excellent library and supporting facilities that are available in the Research and Development Division.

WILLIAM J. HOULIHAN

Hanover, New Jersey

Contents

Part One

I. Properties and Reactions of Indoles **1**

WILLIAM A. REMERS, Department of Medicinal Chemistry and Pharmacology, Purdue University, Lafayette, Indiana

II. Synthesis of the Indole Nucleus **227**

ROBERT K. BROWN, Department of Chemistry, University of Alberta, Edmonton, Canada

I. Index **559**

Part Two

III. Biosynthesis of Compounds Containing an Indole Nucleus
IV. Alkyl, Alkenyl and Alkynyl Indoles
V. Haloindoles and Organometallic Derivatives of Indoles
VI. Indoles Carrying Basic Nitrogen Functions
VII. Oxidized Nitrogen Derivatives of Indole

Part Three

VIII. Indole Alcohols and Thiols
IX. Indole Aldehydes and Ketones
X. Dioxindoles and Isatins
XI. Oxindoles, Indoxyls and Isatogens
XII. Indole Acids

INDOLES

PART ONE

CHAPTER I

Properties and Reactions of Indoles, Isoindoles, and Their Hydrogenated Derivatives

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I. Introduction 3
A. Structures and Numbering 3
B. General Considerations 4
C. Historical 6
II. Physical Properties 7
A. X-Ray Crystallography 7
B. Dipole Moments 8
C. Melting Points and Boiling Points 9
D. Solubility 11
E. Acidity and Basicity 11
F. Spectroscopic Properties 15
1. Infrared Absorption 15
2. Ultraviolet Absorption 19
3. Fluorescence, Phosphorescence, and Chemiluminescence . . . 24
4. Nuclear Magnetic Resonance 33
5. Electron Spin Resonance 40
6. Mass Spectrometry 41
G. Stereochemistry 47
H. Tautomerism 48
I. π-Molecular Complexes 51
III. Theoretical Treatments of Properties and Reactions 55
A. Resonance 55
B. Molecular Orbital Theory 57
1. Introduction 57
2. Calculation of Properties 58
3. Calculation of Reactivity 60
IV. Reactions 63
A. Protonation 63

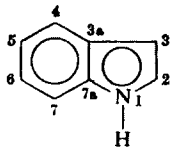
B. Dimerization and Trimerization 66
C. Electrophilic Substitution 70
1. General Considerations 70
2. Halogenation 71
a. Bromination 71
b. Chlorination 77
c. Iodination 78
3. Nitration 78
4. Nitrosation 84
5. Diazo Coupling 86
6. Electrophilic Sulfur and Selenium Reagents 86
a. Sulfur Trioxide 86
b. Thionyl Chloride 87
c. Sulfur Monochloride 88
d. Thiocyanogen and Selenocyanogen 88
e. Sulfur 89
f. Fuming Sulfuric Acid 90
7. Alkylation and Arylation 90
a. Alkylation 90
b. Arylation 93
8. Mannich and Related Reactions 95
9. Michael-type Reactions 100
10. Reactions with Aldehydes and Ketones 105
a. Aldehydes 105
b. Ketones 109
11. Acylation 111
a. Acid Chlorides and Anhydrides 111
b. Friedel-Crafts 114
c. Diketene 114
d. Reactions with Nitriles 115
e. Vilsmeier-Haack Formylation 116
f. Cyclodehydration 119
g. Other Methods of Acylation 120
12. Reactions with Carbenes 121
a. α-Carbonylcarbenes 121
b. Halocarbenes 122
13. Miscellaneous Electrophilic Substitutions 125
a. Sulfomethylation 125
b. Reaction with Ethoxycarbonyliminotriphenylphosphorane . . 125
c. Hexamethyldisilazane 125
d. Mercuration 126
D. Indolyl Anions 126
1. Introduction 126
2. Structure and Protonation. 127
3. Alkylation 128
4. Acylation and Carboxylation 133
5. Nitrogen, Phosphorus, and Sulfur Derivatives 134
E. Rearrangements 135
F. Oxidation 145
1. Autoxidation and Catalytic Oxidation 145

2. Chemical Oxidation 153
3. Dehydrogenation of Indolines and Other Reduced Indoles . . . 160
G. Reduction 163
1. Catalytic 163
2. Chemical 166
H. Cycloadditions 172
I. Metalation 176
J. Aryne Formation 178
K. Free Radical Reactions 179
L. Photochemical Reactions 181
M. Reactions Involving the Carbonyl Systems of Indoles with Oxygen at $C_{(2)}$ and $C_{(3)}$ 184
1. Carbonyl Reactivity of Isatin 184
2. Reactions of the Methylene Groups of Oxindole and Indoxyl . . 186
N. Ring Expansion of the Pyrrole Ring of Indoles 189
O. Addition Reactions of the C=N Bonds of Indolenines and Isatogens . . 191
V. The Effects of the Indole Nucleus upon Substituents 194
A. Substituents at $C_{(3)}$ 194
1. Carbonyl Groups 194
2. Alkylations with Gramine and Related Compounds 200
3. Cleavage of 3-Substituents 203
B. Substituents at $C_{(2)}$ 205
C. Substituents on the Benzenoid Ring 210
1. Nucleophilic Displacement 210
2. Other Reactions 210
D. Substituents on $N_{(1)}$ 212
References 212

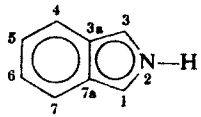
1. Introduction

A. Structures and Numbering

Indole (**1**) is the commonly used name for the benzopyrrole in which the benzene ring is fused to the 2- and 3-positions of the pyrrole ring. Fusion at the 3- and 4-pyrrole positions gives isoindole (**2**). These two benzopyrroles and their simpler derivatives and hydrogenation products are the subjects of this chapter. A third benzopyrrole, with ring fusion involving the pyrrole nitrogen, known as pyrrocoline, has been treated in the volume on heterocyclic compounds with bridgehead nitrogen.[1] Numbering of the atoms in



1



2

indole and isoindole begins with the atom next to the ring junction in the pyrrole ring and proceeds around the nucleus as shown in **1** and **2**.

B. General Considerations

Isoindole itself has not been isolated, but its existence has been shown by trapping with dienophiles.[2] A number of substituted isoindoles are known, the simplest of which is *N*-methylisoindole.

Both indoles and isoindoles have ten π-electrons free to circulate throughout the molecules. Two of these electrons originate from the nitrogen atom. That these molecules are aromatic is shown by the effect of their ring currents in nmr spectra, appreciable resonance energy of 47 kcal/mol for indole[3] and 50 kcal/mol (calculated) for isoindole,[4] and their behavior in chemical reactions such as halogenation (Section IV.C.2). They belong to the group of heterocycles designated π-excessive heteroaromatics,[5] which means that the π-electron densities on their carbon atoms is greater than that on the carbon atoms of benzene.

As anticipated for π-excessive compounds, both indoles and isoindoles are highly reactive toward electrophilic reagents, including acids and certain oxidants. They are protonated by strong acids, which in some cases results in dimerization or polymerization. However, indoles appear to have appreciable stability in concentrated acids where they are completely protonated.[6]

N-Substituted isoindoles are appreciably more stable toward heat and air oxidation than their *N*-unsubstituted counterparts. It is thought[4] that the source of instability for the latter type is the isoindolenine tautomers with which they are in equilibrium (Section II.H).

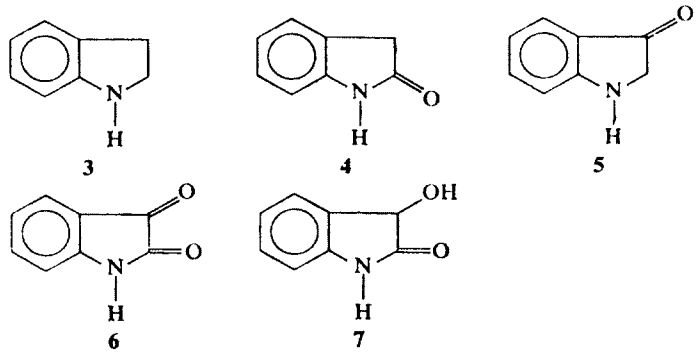
Indoles give many of the same electrophilic substitution reactions as does pyrrole, but in indole $C_{(3)}$ is the preferred site. Isoindoles are able to act as dienes in Diels-Alder reactions, but indoles lack this property.

The NH group of indoles (and presumably isoindoles) is relatively acidic ($pK_a = 17$) and forms the anion in the presence of strong bases.[7] Although the electron pair of this anion is orthogonal to the π-system, it nevertheless increases reactivity at $C_{(3)}$ toward electrophiles. As a consequence, the indolyl anion has ambident properties in alkylation and acylation reactions.

The 2,3-dihydro derivative (**3**) of indole is known as indoline. Indoline has most of the properties and reactions typical of an alkylaniline.

Indoles oxygenated at the 2 and at the 3 positions are commonly named oxindole and indoxyl, respectively. These compounds exist in the carbonyl forms **4** and **5**, rather than in the tautomeric hydroxypyrrole forms. They give many reactions typical of carbonyl compounds, although under certain

conditions they react as the tautomers. For example, both oxindole and indoxyl undergo condensations at the active methylene groups adjacent to their carbonyl groups. Indoxyl reacts as the tautomeric hydroxypyrrole in forming an *O*-acetyl derivative. Isatin (**6**) is indole-2,3-dione, and it exists completely in the dicarbonyl form (Section II.H). The 3-carbonyl group of isatin is more reactive than the 2-carbonyl group toward nucleophiles. 3-Hydroxyoxindole (**7**) is commonly known as dioxindole.

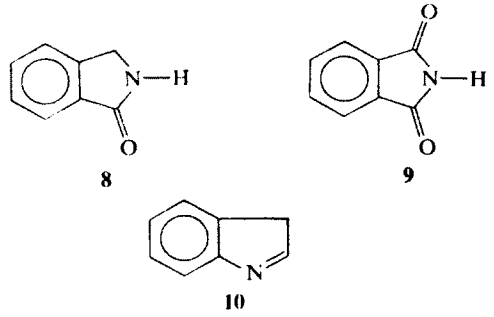


3 **4** **5**

6 **7**

Phthalimidine (**8**), the equivalent of oxindole in the isoindole series, behaves as a weak secondary base, resembling an *N*-alkylacetamide in its reactions. The corresponding dione is phthalimide (**9**). This imide is a weak acid due to considerable delocalization of charge in the anion formed by removal of its NH proton.

The indole tautomer in which a hydrogen has moved from nitrogen to $C_{(3)}$ is named indolenine (more properly 3*H*-indolenine). Indolenine itself (**10**) is unstable with respect to indole; however, 3,3-disubstituted indoles possess indolenine structures. In these indolenines the nitrogen atom has an unshared pair of electrons which imparts basic properties to the molecules.[8] They readily form acid-addition salts and react with methyl iodide to give quaternary salts.[9]



8 **9**

10

C. Historical

The development of indole chemistry began in the mid-nineteenth century with intensive research on the dye indigo. This dye had been highly valued since ancient times, but meaningful investigations of its chemistry had to await the establishment of a structural theory of organic chemistry.[10]

In 1841 indigo was oxidized to isatin by nitric acid,[11] and in 1866 isatin was reduced to dioxindole and oxindole.[12] Later in 1866 Baeyer prepared the parent substance, indole, by zinc dust pyrolysis of oxindole.[13] He proposed the presently accepted formula of indole in 1869.[14] Reductive cyclization of 2-nitrophenylacetic acid to oxindole in 1878 provided the first synthesis of an indole derivative.[15]

Indole chemistry continued to be important in the dyestuff industry until the beginning of the twentieth century when newer dyes supplanted the indoles. A brief decline in indole research then occurred, but in the 1930s the discovery that many alkaloids contain the indole nucleus led to a notable revival.[16] During this period recognition of the essential amino acid, tryptophan,[17] and the plant growth hormone, heteroauxin,[18] as indole derivatives added stimulus to this research. Many important methods of indole synthesis were developed in order to prepare these substances and their analogs.

In more recent years indoles have achieved increased significance in medicinal chemistry. The identification of serotonin (5-hydroxytryptamine) as a metabolite important in brain biochemistry[19] and the discovery of the psychotomimetic indoles psilocin and psilocybin[20] have led to extensive investigations of tryptamine derivatives. Several potential central nervous system depressants have resulted from these investigations. A valuable anti-inflammatory agent was found in 1-*p*-chlorobenzoyl-5-methoxy-2-methylindole-3-acetic acid.[21] The thiosemicarbazone of 1-methylisatin showed promising antiviral activity.[22] Several important pigments including the melanins[23] and adrenochromes[24] were found to be indole derivatives which resulted from oxidative cyclization of oxygenated phenethylamines.

Significant advances in understanding the properties of indoles have been brought about by recent breakthroughs in instrumentation. Nuclear magnetic resonance and mass spectrometry have been added to infrared and ultraviolet spectroscopy as valuable methods for structure determination, including subtle aspects of tautomerism and stereochemistry. Fluorescence and phosphorescence are now easily measured and interpreted. Molecular orbital theory has been applied to indoles, enabling both their properties and reactions to be better understood and in some cases predicted. Finally, the continually increasing knowledge of reaction mechanisms and the introduction of radioisotopes into the study of mechanisms have allowed reinterpretation of a number of indole transformations.

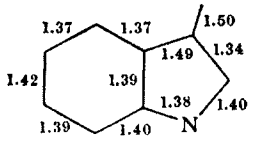
In this chapter particular emphasis will be placed on the application of recently developed physical methods and theoretical approaches to the description of the properties and reactions of indoles.

II. Physical Properties

A. X-Ray Crystallography

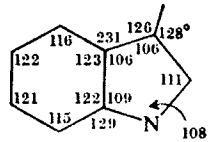
The crystal structures of 1:1 complexes of indole and of 3-methylindole with 1,3,5-trinitrobenzene have been determined by X-ray analyses.[25] In both cases it was observed that the constituent molecules overlap with average interplanar spacing of 3.30 Å, and the relative orientations suggested decisive attraction between the indole or 3-methylindole nitrogen atom and a non-substituted carbon position of 1,3,5-trinitrobenzene. The indole complex was disordered, with two alternative orientations found.

Both the indole and 3-methylindole molecules are planar. The bond lengths and angles for 3-methylindole in the complex are depicted in **11** and **12**



11

bond lengths (Å) in 3-methylindole

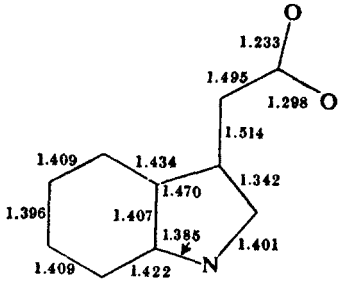


12

bond angles in 3-methylindole

Indole-3-acetic acid has also been examined by X-ray crystallography.[26] The molecules were found to exist as dimers, hydrogen bonded between the carboxylic acid groups. Hydrogen bonding was not observed for the indole NH. Two planes, one through the indole nucleus and the other through the carboxyl group, at a dihedral angle of 62°52′ to each other, characterized the molecular structure. High precision bond lengths and angles for this molecule are given in **13** and **14**.

Bond lengths and angles for the indole nucleus as determined from indole-3-acetic acid and from the skatole complex are in good agreement. They show the six-membered ring of indole to have geometry which is reasonable for a fully aromatic ring. The pyrrole ring is rather distorted from a regular pentagon, with the 2,3 bond showing more double bond character and the 3,3*a* bond showing more single bond character than the corresponding bonds in pyrrole. Conjugation through the nitrogen atom is indicated by the



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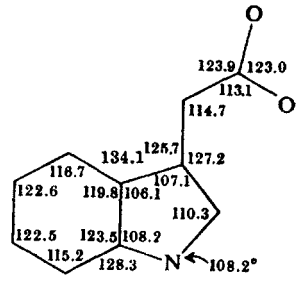
bond lengths (Å) in indole-3-acetic acid

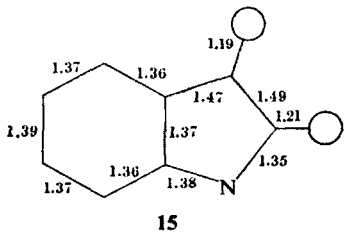


14

bond angles in indole-3-acetic acid

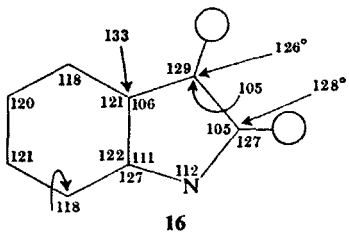
lengths of the two C—N bonds, which are shorter than normal C—N single bonds.

X-Ray crystallographic determination of the isatin structure showed that it is a nearly planar molecule existing almost entirely in the dione form.[27] The benzene ring geometry is little distorted from that of benzene itself. In the crystal, isatin molecules are linked in pairs across a symmetry center by two hydrogen bonds of 2.93 Å length. These bonds are formed between the 2-oxygen and the NH hydrogen.



15

bond lengths (Å) in isatin



16

bond angles in isatin

B. Dipole Moments

The dipole moment of indole is 2.38 D in dioxane at 25°.[28] In benzene it is 2.11 D at 25° [29] and 2.05 D at 20°. The moment in dioxane was resolved into a π moment of 2.15 D at an angle of 40° with the internal bisector of the CNC angle and a σ moment of 0.45 D directed from H to N. The latter moment was estimated to be lowered about 0.3 D due to the effect of dioxane.[28] A calculated π moment for indole[29] is in reasonable agreement with the experimental values given above.

Dipole moments of 2.08 and 3.05 D were found for 3-methylindole and 2,3-dimethylindole, respectively, in benzene.[30] From the series of 4-, 5-, 6-, and 7-nitro-2,3-dimethylindoles, having moments of 6.56, 7.37, 6.58, and 4.00 D, respectively, it was concluded that the interaction between the nitro and imino groups was small, with the effect of the imino group largely confined to the pyrrole ring. The 7-NO_2 group is in the plane of the indole nucleus and is probably hydrogen bonded to the NH.[30]

The relatively high dipole moment of isatin, 5.72 D at 20° in dioxane, was considered important evidence for the existence of this compound in the dicarbonyl form.[31]

Excited-state dipole moments of 5.6 D for indole and 8.5 D for tryptophan were determined from temperature changes of the absorption and fluorescence spectra.[32]

C. Melting Points and Boiling Points

Crystallinity of compounds is dependent upon, among other factors, shape, symmetry, and polarity. Indole is flat and moderately polar (dipole moment of 2.38 D), but it has a low order of symmetry. It has a melting point of 52–54°C, which is somewhat lower than that of the more symmetrical, but less polar naphthalene (80–81°), but higher than that of the less polar, unsymmetrical indene (−5 to −3°).

Indoline has a 5-membered ring which is not planar. The molecules are less able to pack closely than are molecules of indole, consequently indoline is a liquid at room temperature.

Substitution of indole with small groups which do not significantly change the polarity or introduce intermolecular hydrogen bonding does not greatly increase the melting point. For example, 2-methylindole melts at 58–60°, 5-methoxyindole at 56–58°, and 5-chloroindole at 69–71°. In contrast, substituents that engage in strong intermolecular hydrogen bonding afford much higher melting points. Thus indole-3-carboxaldehyde and indole-3-carboxylic acid melt at 198–199 and 235–236°, respectively. Smaller increases in melting point are obtained with substituents such as 5-hydroxy and 5-amino which give weaker hydrogen bonds. Their melting points, 107–108 and 131–133°, respectively, are nonetheless higher than that of 5-chloroindole.

The isomeric acetylindoles show a wide range of melting points, which may be partly explained by differences in polarity and hydrogen bonding among the isomers. A melting point of 74–76° for 5-acetylindole is not greatly different from that of indole and indicates only small interaction between the substituent and indole NH. 3-Acetylindole, with a much higher melting point of 188–192°, is known from infrared studies to be strongly hydrogen

TABLE I. Melting Points of Selected Indoles

Compound	Melting point (°C)
Indole	52–54
2-Methylindole	58–60
3-Methylindole	97–98
5-Methylindole	59–60
5-Aminoindole	131–133
5-Chlorindole	69–71
5-Hydroxyindole	107–108
3-Acetylindole	188–192
5-Acetylindole	74–76
Isatin	201–203
Indoxyl	125–127
Oxindole	85
Indole-3-carboxaldehyde	198–199
Indole-3-carboxylic acid	235–236
Indole-3-propionic acid	85.5
Indole-3-acrylic acid	185 (dec)
2-Phenylindole	186–188
2,3-Diphenylindole	124–125

bonded. The carbonyl group of this molecule is in direct conjugation with the nitrogen and is therefore highly polarized. Hydrogen bonding is not possible in 1-acetylindole. Furthermore, the N—CO dipole is opposed to the indole dipole. This combination of factors helps to make 1-acetylindole a liquid.

Differences in the extent of hydrogen bonding are also evident in the series isatin, oxindole, indoxyl, which melt at 201–203, 125–127, and 85°, respectively.

Extending the length of side-chain carboxylic acid derivatives of indole results in a decrease in melting point, due to the high entropy needed to fix the chains in the crystal. Thus indole-3-carboxylic acid melts at 235–236°, indole-3-acetic acid has a melting point of 165–169°, and indole-3-propionic acid melts as low as 85.5–88°. The less flexible chain of indole-3-acrylic acid affords melting with decomposition at 185°.

TABLE II. Boiling Points of Selected Indoles

Compound	Boiling point (°C)
Indole	254
Indoline	220–221
2-Methylindoline	228–229
1-Methylindole	101–103 (5 mm)
1-Acetylindole	153 (14 mm)

A lower melting point for 2,3-diphenylindole (124–125°) than that of 2-phenylindole (186–188°) is probably a consequence of steric interaction between the phenyl groups in the former compound. One or both of its phenyl groups must turn out of the plane of the indole nucleus, thus increasing the thickness of the molecule and making packing in the crystal more difficult. Tables I and II give melting and boiling points of some selected indoles.

D. Solubility

The low melting point and moderate polarity of indole afford good solubility in a wide range of solvents, including petroleum ether, benzene, chloroform, and alcohol. It has slight solubility in water at 20° (1 part in 540), but good solubility in boiling water.[33] This solubility difference is useful in its recrystallization from water.

Isatin and oxindole may also be crystallized from water. Whereas oxindole is soluble in most organic solvents, the more highly polar isatin has better solubility in alcohol and acetic acid and lower solubility in ether and hydrocarbons. Isatin also dissolves in concentrated sulfuric and hydrochloric acids and forms soluble salts in alkaline solutions.

Indoline is miscible with most organic solvents and is slightly miscible with water. Unlike indole, it has an electron pair on nitrogen which may readily bond with a proton, and the resulting salt formation accounts for its solubility in dilute acids.

Indole derivatives such as indole-3-carboxaldehyde, which have relatively acidic NH protons ($pK_a = 12$), are soluble in strongly alkaline solutions.

As expected, salts derived from basic or acidic groups in side-chain substituents on indoles render the molecules soluble in water. For example, tryptamine hydrochloride and sodium indole-3-acetate have good water solubility.

The very low solubility of certain indole-3-carboxaldehydes and indole-3-ketones in most organic solvents is due to strong intermolecular hydrogen bonding in their crystals. These compounds show shifts of over 100 cm^{-1} for their NH infrared absorption upon going from the solid state into solution.[34] Strong intermolecular hydrogen bonds are also responsible for the low solubilities of indole carboxylic acids. Hydrogen-bond breaking solvents such as pyridine, dimethyl sulfoxide, and dimethylformamide are useful in dissolving these compounds.

E. Acidity and Basicity

Indoles may be converted into both their conjugate acids and conjugate bases. Aqueous solutions of appropriate strong acids or bases in high concentration usually will effect these conversions.

In contrast to alkylamines or nitrogen-containing heterocycles such as pyridine, the lone pair of electrons on the indole nitrogen is an integral part of the π-electron system and is not readily available for salt formation. A high concentration of hydrogen ions is therefore necessary to afford protonation of indoles.[6] Such protonation occurs mainly on $C_{(3)}$ in solution, but salts in which the proton was on nitrogen could be isolated from certain solutions by precipitation.

Thermodynamic pK values for the protonation of a number of indole derivatives were determined in sulfuric acid solution and in perchloric acid solution using an ultraviolet technique to give indicator ratios at various acid concentrations.[35] An acidity function H_I was derived for certain indoles. Indole itself and certain other derivatives did not follow H_I. Their pK's were also determined and, while these are not thermodynamic values, they appear to be reasonably accurate for most purposes. Selected pK values are given in Table III.

TABLE III. Selected pK Values for the Protonation of Indoles[35]

Compound	pK
Thermodynamic	
1,2-Dimethylindole	+0.30
2-Methylindole	−0.28
2,3-Dimethylindole	−1.49
1-Methylindole	−2.32
3-Methylindole	−4.55
Tryptamine	−6.31
Indole-3-CO_2H	−6.13
Not thermodynamic	
Indole	−3.5
5-Methylindole	−3.3
5-Nitroindole	−7.4
1,3-Dimethylindole	−3.3

It is also possible to estimate indole pK's by reference to the H_0 scale since the intercept in a plot of log ([ind H^+]/[ind]) + H_0 against log [H^+] + H_0 is the pK. Only the ratio of [ind H^+]/[ind] as a function of acid concentration need be measured.[36]

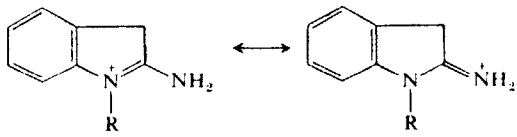
The effect of substituents on the pK values for the protonation of indoles is pronounced, particularly for substituents in the pyrrole ring. Methyl groups in this ring have additive effects which are of use in predicting pK's of unknown indoles.[35]

Methyl groups on nitrogen or on $C_{(2)}$ increase the pK by 0.7 and 2.9 units, respectively, whereas a methyl group on $C_{(3)}$ decreases the pK by 1.1 units. These effects may be related to the differences in energy between the neutral indoles and their conjugate indoleninium cations, with the contributions made by the methyl groups to each species depending upon their relative positions. Thus the remarkable base-strengthening of the 2-methyl group is due in part to perturbation of the π-electron system of the neutral indole. It repels electron density from $C_{(2)}$ and increases it at $C_{(3)}$ (the site of protonation). In the indoleninium cation this group possibly stabilizes the relatively large positive charge at $C_{(2)}$ by hyperconjugation. Similar effects are afforded by the *N*-methyl group, although their magnitude is less since they must operate through the heteroatom. With the 3-methyl substituent, electron density in the indole is decreased at the site of protonation, thus rendering this process more difficult. Furthermore, the resulting indoleninium cation has one fewer hydrogen at $C_{(3)}$ available for hyperconjugation.[35]

At the 5-position a methyl group is sufficiently remote from the site of protonation that it has only a slight base-strengthening effect (0.2 units).

A 5-nitro substituent, as anticipated, makes the protonation of indole more difficult.

The relatively high pK (8.5) of 2-aminoindole is explained by the fact that it exists as the 2-aminoindolinine tautomer. Its *N*-methyl derivative, which has a pK of 9.60, is an iminoindoline. Both of these compounds upon protonation afford cations **17** and **18** which are stabilized by delocalization of the charge.[37]



17 **18**

Loss of the hydrogen from the N—H bond of indoles occurs in the presence of concentrated aqueous alkali or in systems containing stronger bases. Indoles are thus more acidic than aliphatic amines, and this is because the resulting anion is stabilized by delocalization over the aromatic system.[38]

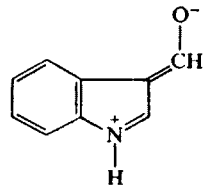
Derivatives of indole were found suitable for the determination of indicator activity of very basic aqueous solutions. An H_- acidity scale was derived for them and thermodynamic pK's were obtained. For substituted indolecarboxylic acids an H_{2-} scale was derived.[38]

Selected pK's for indole and derivatives are presented in Table IV. A plot of pK versus σ constants gave a reasonable Hammett relation ($p = 1.75$) for 5-substituted indoles. However, the pK's for the 3-formyl and 3-acetyl indoles were much lower than anticipated from this plot. The relatively high acidity

TABLE IV. Selected pK Values for Deprotonation of Indoles[38]

Compound	pK
Indole	16.97
3-Methylindole	16.60
Serotonin	18.25
Tryptophan	16.82
Indole-2-CO_2H	17.13
Indole-5-CO_2H	16.92
5-Nitroindole	14.75
Indole-3-CHO	12.36
Indole-3-$COCH_3$	12.99

of these compounds may be explained by the high degree of intermolecular hydrogen bonding between the N—H and carbonyl groups (Section II.F.1) which imparts certain properties typical of the hydroxymethylene group to these compounds. Evidently the polarized structure **19** is an important



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contributor to the resonance hybrid of these compounds, accounting for the low bond order of the carbonyl group and the strong hydrogen bonding.

An ultraviolet study of the acidity of nitroindoles has been made, but pK values were not given.[39]

The Hammett equation has been applied to the ionization of the carboxyl groups of 5- and 6-substituted indole 3-carboxylic acids.[40] Transmission of substituent effects appeared to be directed through the 3-position by the shortest route, not the longer route involving the nitrogen atom. For substituted indole 2-carboxylic acids an excellent Hammett relation was obtained using a two-term equation for transmission both through the nitrogen and the alternate route. Selected values of the apparent pK's of indolecarboxylic acids are given in Table V. It may be noted in this table that the 2-carboxylic acids are considerably stronger than the corresponding 3-carboxylic acids. This is a probable consequence of the higher electron density on the 3-position of indoles.

A thermodynamic pK_a for indole-2-carboxylic acid has been given as 3.870.[41]

TABLE V. Selected Apparent pK_a Values for the Carboxyl Groups of Indolecarboxylic Acids in 50% Aqueous Ethanol at 25°C[40]

Compound	pK_A
Indole-3-CO_2H	7.00
5-Nitroindole-3-CO_2H	6.50
5-Ethoxyindole-3-CO_2H	6.98
Indole-2-CO_2H	5.28
5-Nitroindole-2-CO_2H	4.10
5-Methoxyindole-2-CO_2H	5.24

The first excited singlet of indole has a pK_a which is 7.5 units lower than that of indole in the ground state.[42] This substantial increase in acidity is due to the greater importance of polar forms to the indole structure in the excited state (Section II.F.3).

F. Spectroscopic Properties

1. *Infrared Absorption*

Infrared (ir) spectroscopy has been of considerable value in the determination of indole structures, particularly where a choice between possible tautomeric forms was required. The indole NH stretching frequency band has been extensively studied and correlated with substituent and solvent effects. It is often shifted due to the formation of hydrogen bonds with proton acceptors. Carbonyl derivatives of indole have also been carefully investigated with particular reference to the extent of their enolization. Correlations have been made which allow determination of 2 or 3 substitution on the indole nucleus, but substitution in the benzene ring has not been correlated with ir absorption frequencies, except where there is no substituent.

The ν_{NH} for indole is a sharp peak and is much more intense (ϵ_A 140–210) than that of saturated amines or aniline.[43] This property probably reflects the donation of electrons from the nitrogen atom to the indole nucleus. Solvent effects on the NH band have been explained in terms of intermolecular hydrogen bonding with the solvent.[44] Red shifts are particularly pronounced where proton acceptors such as dioxane ($\Delta\nu = -152\ cm^{-1}$), acetone, and ethyl acetate are used.[45] Such poor hydrogen bonding solvents as carbon tetrachloride and carbon disulfide give only minimal shifts. The stretching

frequencies in these solvents ($c = 0.6$ m) are 3554 and 3550 cm^{-1}, respectively.[45] In more concentrated solutions in carbon disulfide a weak but sharp band appears at 3480 cm^{-1}. This band has been attributed to intermolecular interactions between the solute molecules.[45]

The interaction of the indole NH with various carbonyl compounds in carbon tetrachloride solution has been correlated with the proton donor ability (D) of indole and the proton acceptor ability (A) of the carbonyl compounds in terms of a product rule $\Delta\nu = D \cdot A$ cm^{-1}.[46] The enthalpy, free energy, and entropy of hydrogen bond formation of indole with certain proton acceptors including carbonyl compounds have been determined.[47]

Substitution about the indole nucleus has pronounced effects on the NH stretching frequency. For a wide variety of solid 2- and 3-substituted compounds, ν_{NH} falls in the range of 3425–3144 cm^{-1}. The particular frequency within this range depends upon the electronic nature of the substituents; electron acceptors cause lower frequencies than electron donors.[48] This effect is larger for 3 than for 2 substituents, as may be seen in Table VI. Indole

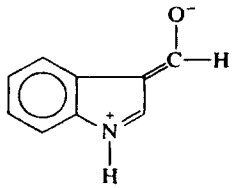
TABLE VI. Selected ν_{NH} for Solid Indole Derivatives[48]

Substituent	ν_{NH} (cm^{-1})
3-CH_3	3425
2-CH_3	3401
None	3390
2-CHO	3185
3-CHO	3144

2-carboxylic esters show ν_{NH} at 3460–3430 cm^{-1} and at 3350–3300 cm^{-1} in carbon tetrachloride. The latter band is weakened upon dilution, which indicates that it arises from hydrogen bonding to the carboxyl group.[49] Similar behavior is exhibited by the NH bands of isatin at 3430 and 3270 cm^{-1}, respectively, in chloroform solution.[50] Oxindoles show in chloroform a sharp NH band at 3478–3440 cm^{-1} and a broad maximum at 3320–3220 cm^{-1} due to hydrogen bonding.[51] Strong hydrogen bonding between the indole NH and the basic nitrogen atom of tryptamines in the solid state is shown by the complete disappearance of the sharp indole NH band at 3500 cm^{-1} in potassium bromide disks. A broad band in the region 3000–2400 cm^{-1} is observed instead. In dilute chloroform solutions of tryptamines the band at 3500 cm^{-1} is present.[52]

The acid addition salts obtained by instantaneous precipitation from ether of strong perchloric acid solutions of alkylindoles showed weak immonium

bands around 2080 cm^{-1} and strong bands for $C{=}\overset{+}{N}<$ at 1640 cm^{-1}, indicating protonation at $C_{(3)}$. Similarly precipitated acid sulfate salts showed protonation at either $C_{(3)}$ or nitrogen, depending upon the indole. Thus 1,2,3-trimethylindole showed only ammonium bands at 2390–2460 and 2570 cm^{-1} (both medium intensity), characteristic of N protonation. Ammonium bands and $>C{=}\overset{+}{N}<$ bands (1632 cm^{-1}) indicated protonation at both sites for 1,2-dimethylindole. 2-Methylindole had absorption in both these regions, plus a weak immonium band at 2080 cm^{-1}, which suggested 3-protonation.



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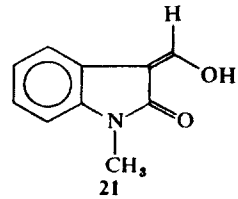

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The C=O stretching frequency of carbonyl derivatives of indole varies greatly with hydrogen bonding, tautomerism to enolic forms, and contributions from dipolar forms. Oxindole exists completely in the carbonyl form, showing intense absorption in the 1690–1725 cm^{-1} region. It had three bands in dilute chloroform solution, which changed when the concentration was varied. In contrast, 1-methyloxindole gave only one carbonyl band under comparable conditions. These observations suggest that intermolecular hydrogen bonding occurs with oxindole.[53] The effects of benzene-ring substituents upon the carbonyl absorption of oxindole have been correlated by a Hammett $\sigma\rho$ relationship. Isatin also shows no evidence of an enol form. It has carbonyl frequencies at 1727 and 1745 cm^{-1} in the solid and these shift to 1742 and 1759 cm^{-1} in chloroform.[50] The higher frequency is assigned to the α-carbonyl group. In contrast to isatin, tetrahydro-*N*-phenylisatin is considered to exist as the 3-enol, which is strongly hydrogen bonded in the solid form. Carbonyl frequencies (for the α-carbonyl) in carbon tetrachloride at 1689 and 1709 cm^{-1} show that both the hydrogen-bonded dimer and free carbonyl forms are present.[54]

Indole-3-carboxaldehyde has the surprisingly low carbonyl stretching frequency of 1631 cm^{-1} as a solid. This frequency changes to 1655 cm^{-1} in chloroform. It has been suggested that dipolar form **20** makes a large contribution to the resonance hybrid.[54] Dipolar association can readily occur to give in the solid an extensive H-bonded polymer.

For *N*-methyloxindole-3-carboxaldehyde the enolic form **21** of the aldehyde exists both in the solid and in solution.[54] The absence of any band above

3100 cm^{-1} shows that there is no free OH, but an intense, broad band between 2600 and 2400 cm^{-1} indicates strong hydrogen bonding. The carbonyl frequency of the α-carbonyl is at 1680 cm^{-1}.

3-Acyl indoles are also strongly hydrogen bonded in the solid state. They undergo shifts from 3130 to 3290 cm^{-1} in the NH band and from 1614 to 1662 cm^{-1} in the carbonyl band upon solution in tetrahydrofuran.[55]

Increase of the carbonyl frequency to 1640–1620 cm^{-1} upon methylation of 3-acylindoles is another indication that hydrogen bonding is strong in this type of compound.[55] The lower carbonyl frequency for 3-acylindoles (1620–1590 cm^{-1}) compared with 2-acylindoles (1630 cm^{-1}) in nujol is probably a consequence of greater electron density at the 3-position. Relatively high frequencies in the range 1730–1750 cm^{-1} for *N*-acylindoles indicates that the electron pair on nitrogen is involved in delocalization within the nuclear π-electron system to such an extent that it is unable to conjugate with the acyl groups to the same degree as electron pairs on the nitrogen atoms of typical alkyl- and aryl-substituted amides.

A study of the keto–enol equilibrium of indolepyruvic acid in different organic solvents was made by comparing the relative intensities of the C=O group absorption at 1720 cm^{-1} and the C=C group absorption at 1640 cm^{-1}.[56] The enol form is predominant in nujol; the keto form is predominant in decreasing extent in nitromethane, tetrahydrofuran, and dioxane.

Correlations of ir absorption maxima in the 2000–920 cm^{-1} region with substituents on the indole nucleus have not been made. In the 900–700 cm^{-1} region, however, bands characteristic of the substitution pattern were assigned.[43] A band at 725–710 cm^{-1} indicates no substituent in the pyrrole ring, one at 785–770 cm^{-1} signifies a substituent at 2, and one at 810–760 cm^{-1} shows a substituent at 3. An unsubstituted benzene ring also gives a band at 725–710 cm^{-1}.

Exchange of the indole 3-proton with deuterium caused loss of bands at 766 and 703 cm^{-1} (characteristic of indoles unsubstituted at 2 and 3) and new bands appeared at 830 and 808 cm^{-1}.[57] The latter band is characteristic of 3-substituted indoles, and confirms the assignments noted above.

Of 23 different indoles studied in the 400–700 cm^{-1} region, all had characteristic bands at 620 ± 20 and 575 ± 25 cm^{-1}.[58]

The ir absorption by methyl groups at various positions on the indole nucleus was studied in the region 3200–2800 cm^{-1} and correlated with the effect of the nitrogen atom on the electron density at these positions.[59] A methyl group on the indole nitrogen shows characteristic absorption at 2820–2810 cm^{-1}.

Stretching and scissoring frequencies for several types of amino-substituted indoles are given in Table VII.

Indolenines substituted at position 2 with alkyl groups show $\nu_{C=N}$ at

TABLE VII. Infrared Absorption Maxima of the Amino Groups of Aminoindoles[43]

Compound	Stretching (cm^{-1})		Scissoring (cm^{-1})
	Sym	Assym	
2-Aminoindole	3448	3378	1577
2-Aminoindoline	3509	3390	1592
1-Aminooxindole	3384	3347	1657

1640–1660 cm^{-1} in chloroform.[60] For 2-aminoindolenines in methylene chloride this band is at 1642 cm^{-1} with a ring mode at 1615 cm^{-1}.[43]

Isoindoles have NH bands at 3445–3460 cm^{-1} and C=C stretching bands at 1595 cm^{-1} in chloroform.[62] The isoindolenine tautomers have no NH band, but show aromatic ring and conjugated azomethine bands at 1610, 1570, and 1500 cm^{-1} in potassium bromide.[63]

2. *Ultraviolet Absorption*

The ultraviolet (uv) absorption spectra of indole derivatives are highly characteristic and sensitive to changes in substitution on the indole nucleus. They are therefore important in the identification of indole structures, and have been a particularly valuable aid in the classification of indole alkaloids. Since both the conjugate acids and bases of indoles absorb at different wavelengths from the neutral species, the variation in uv spectra with acidity or basicity has provided the basis for determination of indole pK_a's. Such spectra have also aided in determining the position of protonation of indoles.

Theoretical interpretation of the uv absorption spectrum of indole presents some difficulty because it is not obvious whether the group of bands at 262, 275, and 288 mμ represents several electronic transitions or merely the vibrational structure of a single electronic transition.[64] The superficial resemblance of this region to the *p* band (Clar nomenclature) region of naphthalene (Fig. 2) might suggest that only one such transition causes all these maxima; however, most authors agree that indole shows both α and *p* bands in this region, with the *p* band partially obscured.[65–67] This assignment is also in harmony with the fluorescence emission spectrum of indole (Section II.F.3). The wavelengths of bands derived from singlet-singlet transition energies calculated by the SCF-MO method with limited configuration interaction are in good agreement with assignment of the 262 mμ maximum as the *p* band and the 288 mμ maximum as the α band.[68] The β band then corresponds to the intense maximum at 220 mμ and the β' band occurs in the

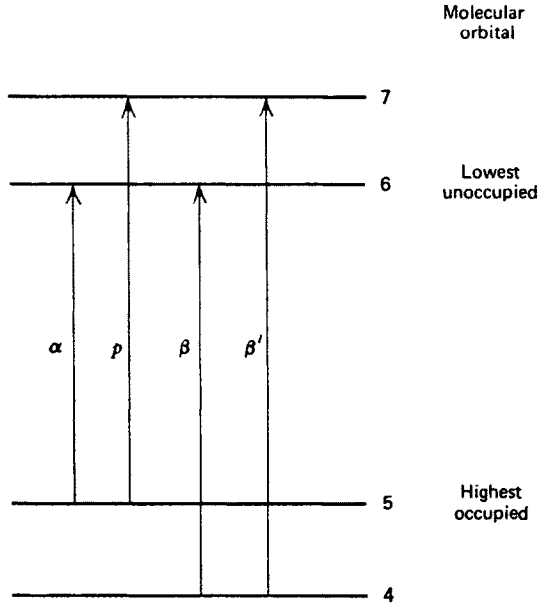


Figure 1. Electronic transitions responsible for the uv absorption bands of indole.

vacuum uv region. A schematic diagram of the electronic transitions responsible for these bands is given in Figure 1.

The uv spectrum of indole has also been calculated in terms of an indenyl anion model, with which it is isoelectronic.[65] These calculations also predict the occurrence of both the *p* and α bands. The vapor phase uv spectrum of indole has been analyzed in shape and fine structure in the 280 mμ region.[69] This analysis shows the transition from the zero vibrational level of the ground state to the zero vibrational level of the first excited singlet state (0–0 band) is the strongest, and the vibrational structure extends approximately 2500 cm^{-1} to the violet of this band.

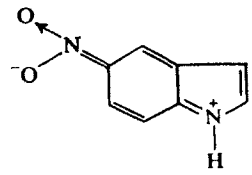
The effects of alkyl substituents on the indole uv spectrum have been studied.[70] Little change occurs in the maxima of 3-alkyl derivatives, but 2-alkyl derivatives exhibit bathochromic shifts. Alkylation of the indole nitrogen produces bathochromic shifts of 5 to 10 mμ of the α and *p* bands, but effects only slightly the β band. In contrast, *N*-acetylation causes only slight displacement of the α and *p* bands, but produces a large bathochromic shift in the β band.[67] Table VIII gives data on a variety of substituted indoles. It may be noted that most indoles give characteristic absorption bands near 280–290 mμ, but the band near 260 mμ is modified or absent in many substituted indoles.

TABLE VIII. Ultraviolet Absorption Maxima of Selected Indoles and Their Conjugate Acids[35]

Indole	Maxima in mμ and Log ε		M^a
	95%Ethanol	Sulfuric acid	
Indole	216(4.54), 266(3.76), 287(3.68), 276(3.76)	233(3.59), 238(3.58), 280(3.68)	12
1-Methyl	219(4.54), 275(3.77), 293(3.66), 282(3.78)	233(3.59), 238(3.52), 282(3.78)	9
3-Methyl	222(4.50), 275(3.73), 290(3.69), 282(3.78)	236(3.60), 240(3.58), 286(3.68)	12
1,3-Dimethyl	225(4.50), 278(3.68), 288(3.72)	232(3.58), 237(3.55), 273(3.69)	10
6-Nitro	248(4.03), 324(3.92), 358(3.88)	254(3.08)	12
5-Nitro	254(4.20), 264(4.24), 322(3.90)	211(3.99), 278(3.99)	12
3-Acetic acid	222(4.51), 273(3.77), 294(3.71), 279(3.78)	234(3.65), 239(3.63), 281(3.67)	12
Tryptamine	218(4.53), 272(3.72), 286(3.65), 277(3.73)	234(3.64), 239(3.62), 288(3.68)	12

[a] Molarity of sulfuric acid solution.

Indoles with strong electron-withdrawing substituents such as a nitro group at the 5 position have uv spectra that differ widely from those of most other indoles. The importance of contributors such as **22** to the resonance



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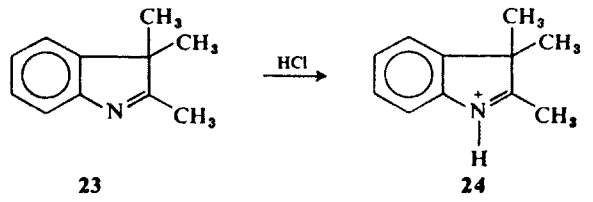
hybrid probably account for these differences. An extensive study on the uv spectra of nitroindoles has been reported.[39]

In acid strong enough to completely protonate alkyl indoles, the uv maximum at 220 mμ is replaced by two maxima of much lower intensity near 230 and 237 mμ. The shape of absorption maxima near 280 mμ changes to a very broad band near 275 mμ. These spectra resemble closely those of 2,3,3-trimethylindolenine (**23** → **24**) in 0.1 *N* hydrochloric acid (229, 235, 275 mμ; log ε 4.00, 3.95, 3.91) and its methiodide (**25**) in water (229, 236, 273 mμ; log ε 3.78, 3.73, 3.77), and they do not resemble the spectrum of 1,1-dimethylindolium perchlorate (**26**) in ethanol.[35] These findings helped to establish that the site of protonation of these alkylindoles is at the 3 position.[6]



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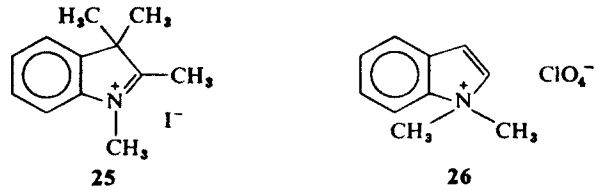

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The marked decrease in the intensity of the uv absorption of indoles near 220 mμ upon protonation was used as the basis for determining the indicator ratios and thence the pK_a's of a number of indoles (Section II.E). Table VIII lists the uv absorption maxima of certain indoles and their conjugate acids.

Advantage was also taken of the shift in uv absorption spectrum upon formation of the conjugate bases of indoles to determine the pK_a's of the NH groups.[7, 38]

The peak near 280 mμ is shifted to around 295 mμ and an additional peak appears at 310–320 mμ. Since the neutral indoles generally do not absorb in the latter region, the ionization ratios and pK_a's were determined by measuring uv absorption as a function of base strength in this region (Section II.E).

The chromophore of indoline is essentially that of an alkyl aniline, and it possesses a strong electron transfer (β) band at 254 mμ (ϵ 25,000) characteristic of this system. Additional bands are at 210 (ϵ 32,000) and 306 mμ (ϵ 5500) in alcohol.[71] α-Methyleneindoline (**27**) is isoelectronic with indole, but has a different chromophore. This chromophore is distinguished by intense absorption at 293 mμ (ϵ 45,000) in alcohol.[71]

Both oxindoles and *N*-acylindolines have the chromophore of the alkyl acetanilide system. However, the acylindolines may possess steric inhibition of resonance, which will cause the spectrum to more nearly resemble that of a xylene. For *N*-acylindolines in which the *N*-acyl group is in a relatively coplanar relationship with the benzene ring, a strong electron transfer band occurs near 255 mμ (ϵ 10,000), and other bands are present at 281 (ϵ 4200) and 290 (4300) mμ. The spectra of oxindoles have maxima nearly identical to these.[71]

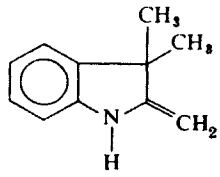
Isatin absorbs at 245, 310, and 420 mμ in chloroform solution. Its long wavelength absorption (orange color) is indicative of π-electron conjugation

between the benzene ring and α-dicarbonyl system. Substituents in the benzene ring produce significant changes in the visible absorption band of isatins, which is further evidence for such conjugation.

Indolenines absorb at shorter wavelengths and lower intensities than indoles. A band at 255 mμ (ε 4000) in alcohol is typical. As noted above, the protonated indolenine chromophore is shifted to 275 mμ.[71]

In indoles with 3-acyl substituents, polarized forms make important contributions to the resonance hybrid. Their excited states apparently reflect this polarization, since their uv spectrum is unlike that of most other indoles. An intense maximum at 270 mμ (ε 13,600), along with maxima at 251 (ε 17,800) and 297 (ε 9600), is characteristic of this chromophore in alcohol. In alkaline solution the anionic form of 3-acyl indoles exists largely as the hydroxymethylene indolenine enolate and gives rise to absorption at 252 (ε 7500), 275 (ε 17,000), and 317 (ε 11,000) mμ.[72] 2-Acetyl-3-methylindole absorbs at 238 (ε 15,000) and 312 (ε 21,000) mμ in ethanol, indicating a different degree of conjugation with the indole π-electron system.[73]

The adrenochrome system (**28**) shows absorption maxima at 215, 305, and



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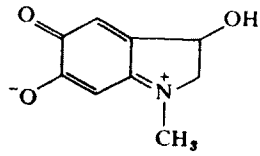

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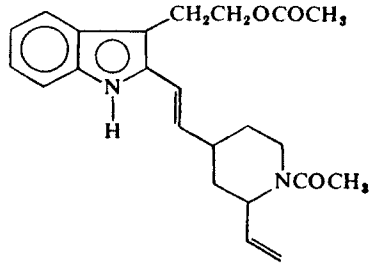
473–475 mμ in water.[74]

The effect upon the indole uv chromophore by conjugation with a double bond depends upon the position to which the substituent group is attached. Thus 3-vinylindole has absorption maxima at 225 (ε 25,000), 258 (ε 16,000), and 282 (ε 8900) mμ, with inflections at 253, 278, 289, and 297 mμ.[75] In contrast, the 2-vinylindole system of alkaloid degradation product **29** has λ_{max} 305 (ε 25,000) and 315 (ε 25,000) mμ.[75] Uleine (**30**) has a slightly different



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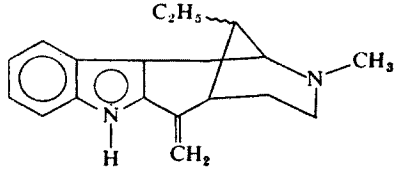
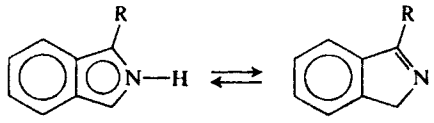


30

2-vinylindole chromophore, λ_{max} 209 (ϵ 24,000) and 309 (ϵ 20,000) mμ, due possibly to the geometrical constraints imposed by the bridged structure upon conjugation in the chromophoric system.[77]

Since the highest occupied molecular orbital of isoindole lies at a position ($\alpha - 0.29\beta$) much higher than that in indole, while its lowest unoccupied orbital has approximately the same energy as that of indole (Fig. 10), it is anticipated that electronic transitions between its orbitals would be easier than in indole, and that it would therefore absorb light at longer wavelengths. This is indeed the case, for isoindoles show a 0–0 band in the 350–370 mμ region.[62] For 1-phenylisoindole, maxima are present at 357 (log ϵ 3.10), 325 (2.99), 282 (2.92), and 272 (2.86) mμ.[62] A tautomeric equilibrium occurs between *N*-unsubstituted isoindoles (**31**) and the corresponding isoindolenines (**32**). The latter form absorbs at shorter wavelengths and it is therefore



31 **32**

possible to determine the position of equilibrium between these tautomeric forms in various solvents by comparing the ratios of absorption at several wavelengths (Section II.H).

3. *Fluorescence, Phosphorescence, and Chemiluminescence*

The fluorescence and phosphorescence properties of indoles have been valuable in their detection and identification, especially in biological systems. At the simplest level of investigation, the presence of certain indoles on paper or thin-layer chromatograms may be detected by their fluorescence under uv light. However, much more information than this is potentially available. Characteristic fluorescence excitation and emission spectra distinguish the indoles, and these spectra are sensitive to substituents as well as changes in pH of the medium. Fluorescence analysis is extremely sensitive, with the lower limits of detection in the parts per billion range. The increased sensitivity over uv absorption spectroscopy derives in part from the fact that fluorescence emission is measured against a dark background, whereas the uv absorption is measured by difference in light intensity.[76] Phosphorescence analysis is equally sensitive.[76] In addition to characteristic exciting and emitting wavelengths, phosphorescence has a measurable half-life that is specific for each compound. The main disadvantage of this method is that the sample must be