INDOLES

PART ONE

This is the twenty-fifth volume in the series
THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
INDOLES
PART ONE

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The Chemistry of Heterocyclic Compounds

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

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

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

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Preface

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
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INDOLES

PART ONE
CHAPTER I

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

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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 isoiindole (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

\[ \text{Indole} \quad (1) \]

\[ \text{Isoindole} \quad (2) \]
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. A number of substituted isoindoles are known, the simplest of which is N-methylisoindole.

Both indoles and isoindoles have ten \( \pi \)-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 and 50 kcal/mol (calculated) for isoindole, and their behavior in chemical reactions such as halogenation (Section IV.C.2). They belong to the group of heterocycles designated \( \pi \)-excessive heteroaromatics, which means that the \( \pi \)-electron densities on their carbon atoms is greater than that on the carbon atoms of benzene.

As anticipated for \( \pi \)-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. N-Substituted isoindoles are appreciably more stable toward heat and air oxidation than their \( N \)-unsubstituted counterparts. It is thought 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. Although the electron pair of this anion is orthogonal to the \( \pi \)-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.

\[
\begin{align*}
3 & \quad \text{N} & \quad H \\
4 & \quad \text{N} & \quad \text{O} & \quad H \\
5 & \quad \text{N} & \quad \text{O} & \quad H \\
6 & \quad \text{N} & \quad \text{O} & \quad \text{O} \\
7 & \quad \text{N} & \quad \text{O} & \quad \text{OH} \\
8 & \quad \text{N} & \quad \text{O} & \quad \text{H} \\
9 & \quad \text{N} & \quad \text{O} & \quad \text{H} \\
10 & \quad \text{N} & \quad \text{N} & \quad \text{H}
\end{align*}
\]

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 3H-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. They readily form acid-addition salts and react with methyl iodide to give quaternary salts.
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.\textsuperscript{10}

In 1841 indigo was oxidized to isatin by nitric acid,\textsuperscript{11} and in 1866 isatin was reduced to dioxindole and oxindole.\textsuperscript{12} Later in 1866 Baeyer prepared the parent substance, indole, by zinc dust pyrolysis of oxindole.\textsuperscript{13} He proposed the presently accepted formula of indole in 1869.\textsuperscript{14} Reductive cyclization of 2-nitrophenylacetic acid to oxindole in 1878 provided the first synthesis of an indole derivative.\textsuperscript{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.\textsuperscript{16} During this period recognition of the essential amino acid, tryptophan,\textsuperscript{17} and the plant growth hormone, heteroauxin,\textsuperscript{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\textsuperscript{19} and the discovery of the psychotomimetic indoles psilocin and psilocybin\textsuperscript{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-\textit{p}-chlorobenzoyl-5-methoxy-2-methylindole-3-acetic acid.\textsuperscript{21} The thiosemicarbazone of 1-methylisatin showed promising antiviral activity.\textsuperscript{22} Several important pigments including the melanins\textsuperscript{23} and adrenochromes\textsuperscript{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. 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.

Indole-3-acetic acid has also been examined by X-ray crystallography. 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 3,3a bond showing more single bond character than the corresponding bonds in pyrrole. Conjugation through the nitrogen atom is indicated by the
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.\textsuperscript{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.

B. Dipole Moments

The dipole moment of indole is 2.38 D in dioxane at 25°.\textsuperscript{28} In benzene it is 2.11 D at 25°\textsuperscript{29} and 2.05 D at 20°. The moment in dioxane was resolved into a \( \pi \) moment of 2.15 D at an angle of 40° with the internal bisector of the CNC angle and a \( \sigma \) 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.\textsuperscript{28} A calculated \( \pi \) moment for indole\textsuperscript{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. 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-NO₂ group is in the plane of the indole nucleus and is probably hydrogen bonded to the NH.

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.

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.

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
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Boiling point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indole</td>
<td>254</td>
</tr>
<tr>
<td>Indoline</td>
<td>220–221</td>
</tr>
<tr>
<td>2-Methyldolene</td>
<td>228–229</td>
</tr>
<tr>
<td>1-Methyldolene</td>
<td>101–103 (5 mm)</td>
</tr>
<tr>
<td>1-Acetyldolene</td>
<td>153 (14 mm)</td>
</tr>
</tbody>
</table>
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. 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 (pKₐ = 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. 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 $\pi$-electron system and is not readily available for salt formation. A high concentration of hydrogen ions is therefore necessary to afford protonation of indoles. 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. 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>
<thead>
<tr>
<th>Compound</th>
<th>$pK$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermodynamic</td>
<td></td>
</tr>
<tr>
<td>1,2-Dimethylindole</td>
<td>+0.30</td>
</tr>
<tr>
<td>2-Methylindole</td>
<td>−0.28</td>
</tr>
<tr>
<td>2,3-Dimethylindole</td>
<td>−1.49</td>
</tr>
<tr>
<td>1-Methylindole</td>
<td>−2.32</td>
</tr>
<tr>
<td>3-Methylindole</td>
<td>−4.55</td>
</tr>
<tr>
<td>Tryptamine</td>
<td>−6.31</td>
</tr>
<tr>
<td>Indole-3-CO$_2$H</td>
<td>−6.13</td>
</tr>
<tr>
<td>Not thermodynamic</td>
<td></td>
</tr>
<tr>
<td>Indole</td>
<td>−3.5</td>
</tr>
<tr>
<td>5-Methylindole</td>
<td>−3.3</td>
</tr>
<tr>
<td>5-Nitroindole</td>
<td>−7.4</td>
</tr>
<tr>
<td>1,3-Dimethylindole</td>
<td>−3.3</td>
</tr>
</tbody>
</table>

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.

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.
Properties and Reactions of Indoles

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 $\pi$-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.

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.

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.

Derivatives of indole were found suitable for the determination of indicator activity of very basic aqueous solutions. An $H_L$ acidity scale was derived for them and thermodynamic $pK$'s were obtained. For substituted indolecarboxylic acids an $H_{3L}$ scale was derived.

Selected $pK$'s for indole and derivatives are presented in Table IV. A plot of $pK$ versus $\sigma$ 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

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indole</td>
<td>16.97</td>
</tr>
<tr>
<td>3-Methylindole</td>
<td>16.60</td>
</tr>
<tr>
<td>Serotonin</td>
<td>18.25</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>16.82</td>
</tr>
<tr>
<td>Indole-2-(\text{CO}_2\text{H})</td>
<td>17.13</td>
</tr>
<tr>
<td>Indole-5-(\text{CO}_2\text{H})</td>
<td>16.92</td>
</tr>
<tr>
<td>5-Nitroindole</td>
<td>14.75</td>
</tr>
<tr>
<td>Indole-3-CHO</td>
<td>12.36</td>
</tr>
<tr>
<td>Indole-3-(\text{COCH}_3)</td>
<td>12.99</td>
</tr>
</tbody>
</table>

of these compounds may be explained by the high degree of intermolecular hydrogen bonding between the N—H and carbonyl groups (Section II.F.I) which imparts certain properties typical of the hydroxymethylene group to these compounds. Evidently the polarized structure 19 is an important 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. An ultraviolet study of the acidity of nitroindoles has been made, but pK values were not given. An ultraviolet study of the acidity of nitroindoles has been made, but pK values were not given. An ultraviolet study of the acidity of nitroindoles has been made, but pK values were not given.

The Hammett equation has been applied to the ionization of the carboxyl groups of 5- and 6-substituted indole 3-carboxylic acids. 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.