INDOLES

PART ONE

This is the twenty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors



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.

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INDOLES

PART ONE

Chemistry of Heterocyclic Compounds, Volume 25
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CHAPTER I

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

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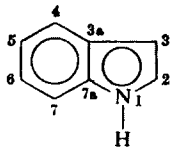
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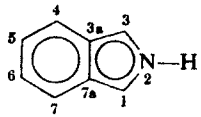
1. Introduction

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 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).

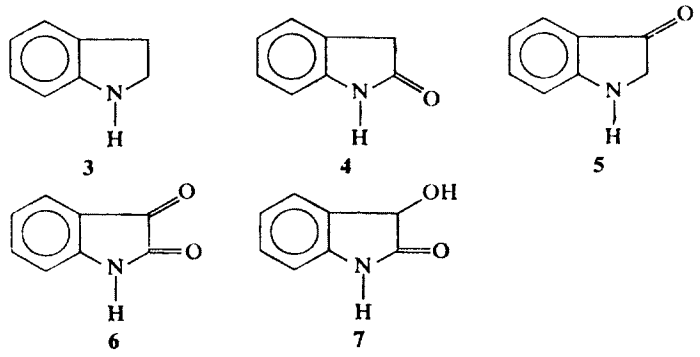
Indoles give many of the same electrophilic substitution reactions as does pyrrole, but in indole $C_{(3)}$ is the preferred site. Isoindoles are able to act as dienes in Diels-Alder reactions, but indoles lack this property.

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.

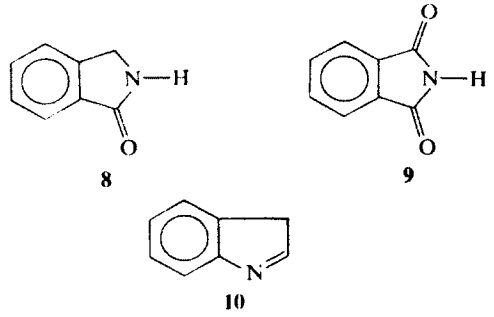


3 **4** **5**

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.

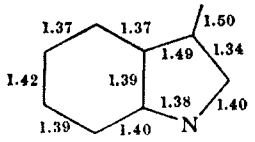
In this chapter particular emphasis will be placed on the application of recently developed physical methods and theoretical approaches to the description of the properties and reactions of indoles.

II. Physical Properties

A. X-Ray Crystallography

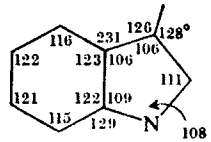
The crystal structures of 1:1 complexes of indole and of 3-methylindole with 1,3,5-trinitrobenzene have been determined by X-ray analyses.[25] In both cases it was observed that the constituent molecules overlap with average interplanar spacing of 3.30 Å, and the relative orientations suggested decisive 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

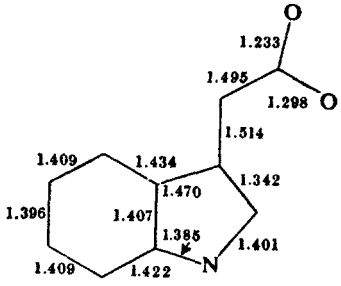


12

bond angles in 3-methylindole

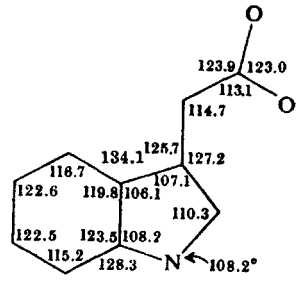
Indole-3-acetic acid has also been examined by X-ray crystallography.[26] The molecules were found to exist as dimers, hydrogen bonded between the carboxylic acid groups. Hydrogen bonding was not observed for the indole NH. Two planes, one through the indole nucleus and the other through the carboxyl 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



13

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

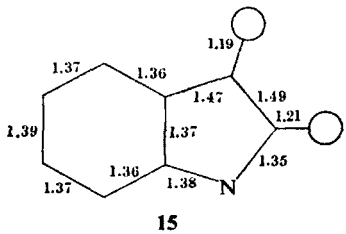


14

bond angles in indole-3-acetic acid

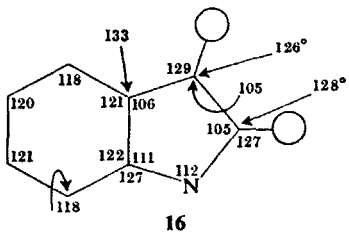
lengths of the two C—N bonds, which are shorter than normal C—N single bonds.

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]

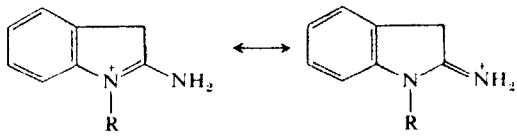
The effect of substituents on the pK values for the protonation of indoles is pronounced, particularly for substituents in the pyrrole ring. Methyl groups in this ring have additive effects which are of use in predicting pK's of unknown indoles.[35]

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]

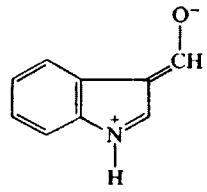
Derivatives of indole were found suitable for the determination of indicator activity of very basic aqueous solutions. An H_- acidity scale was derived for them and thermodynamic pK's were obtained. For substituted indolecarboxylic acids an H_{2-} scale was derived.[38]

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



19

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

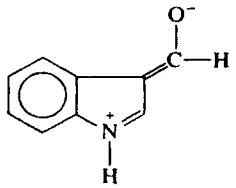
TABLE VI. Selected ν_{NH} for Solid Indole Derivatives[48]

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

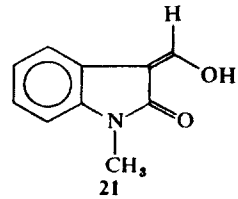
2-carboxylic esters show ν_{NH} at 3460–3430 cm^{-1} and at 3350–3300 cm^{-1} in carbon tetrachloride. The latter band is weakened upon dilution, which indicates that it arises from hydrogen bonding to the carboxyl group.[49] Similar behavior is exhibited by the NH bands of isatin at 3430 and 3270 cm^{-1}, 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.



20



21

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

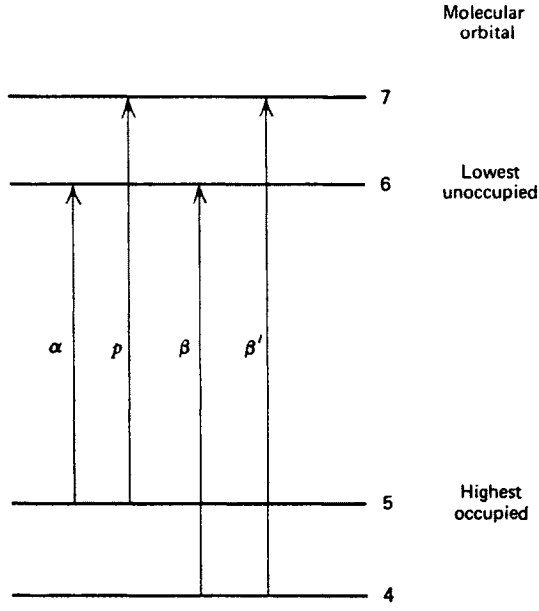


Figure 1. Electronic transitions responsible for the uv absorption bands of indole.

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.

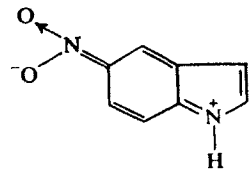
The effects of alkyl substituents on the indole uv spectrum have been studied.[70] Little change occurs in the maxima of 3-alkyl derivatives, but 2-alkyl derivatives exhibit bathochromic shifts. Alkylation of the indole nitrogen produces bathochromic shifts of 5 to 10 mμ of the α and *p* bands, but effects 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.

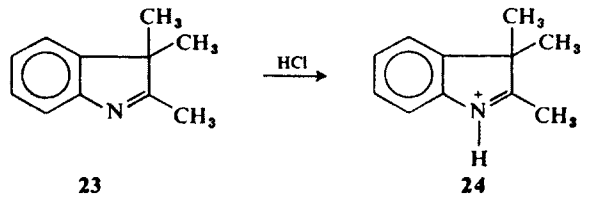
Indoles with strong electron-withdrawing substituents such as a nitro group at the 5 position have uv spectra that differ widely from those of most other indoles. The importance of contributors such as **22** to the resonance



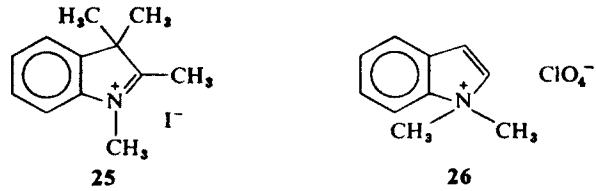
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hybrid probably account for these differences. An extensive study on the uv spectra of nitroindoles has been reported.[39]

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]



23 24



25 26

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]

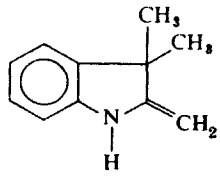
Isatin absorbs at 245, 310, and 420 mμ in chloroform solution. Its long wavelength absorption (orange color) is indicative of π-electron conjugation

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.

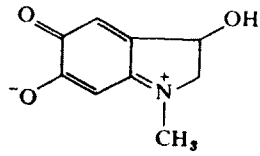
Indolenines absorb at shorter wavelengths and lower intensities than indoles. A band at 255 mμ (ε 4000) in alcohol is typical. As noted above, the protonated indolenine chromophore is shifted to 275 mμ.[71]

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



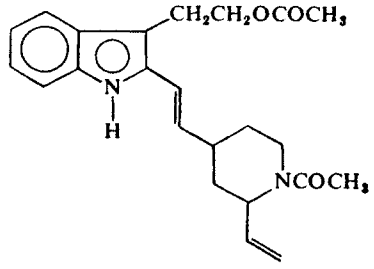
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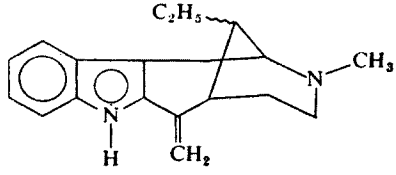
28

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



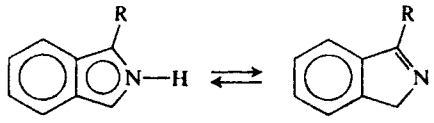
29



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

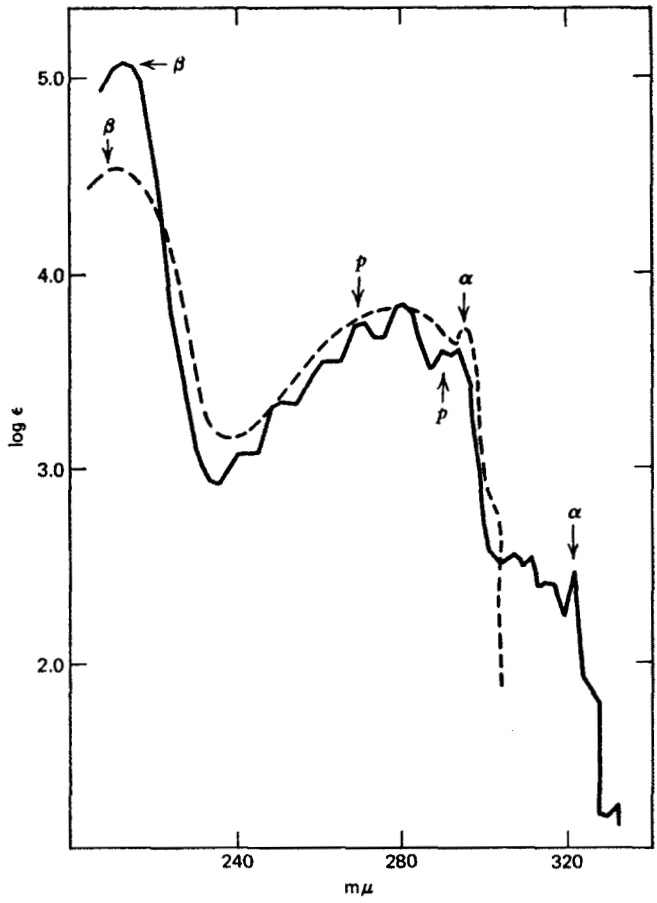


Figure 2. Ultraviolet absorption curves of naphthalene (———) and indole (- - -) in 95% ethanol.

analyzed in a rigid glass at 77°K in order to minimize the loss of excitation energy by collisional transfer.[76, 77]

A schematic diagram of the luminescence properties of indole is given in Figure 3. The excitation of π electrons from the zeroth vibrational level of the ground state to the vibrational levels of the excited singlet states is responsible for its uv absorption. The transition to the zeroth vibrational level of the first excited singlet state accounts for the absorption associated with the longest wavelength peak (0–0 band) at 288 mμ. Transitions to higher vibrational levels (0–1 band, etc.) are responsible for the 279 mμ and any shorter wavelength peaks. (In the uv spectrum of indole shown in Fig. 2 the bands around

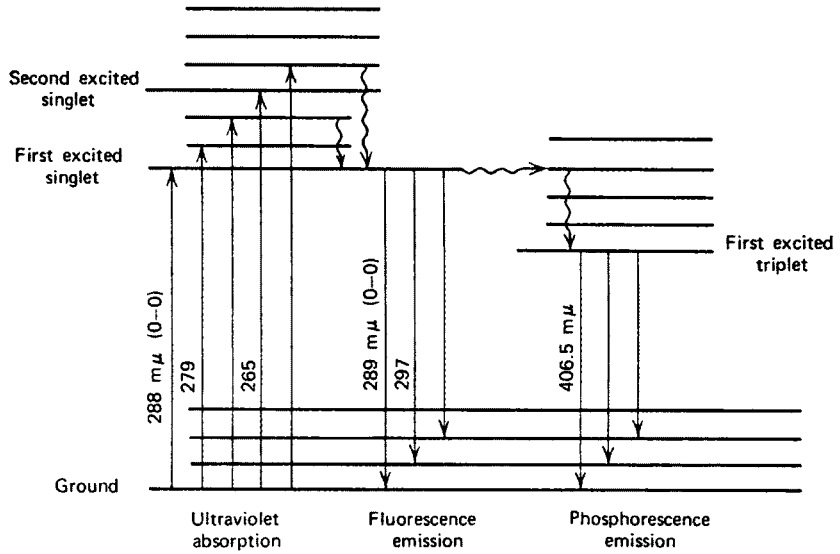


Figure 3. Schematic diagram of the light absorption and emission properties of indole.

265 mμ result from excitation to the second excited singlet, and there is probably overlap of vibrational levels between the first and second excited singlets.) Since the vibrational relaxation process is rapid compared with emission of a photon, electrons excited to vibrational levels higher than the lowest (zeroth) vibrational level of the first excited singlet state will fall to this level (wavy arrow in Fig. 3) and fluorescence emission will occur from this level.[76] The transition of the molecule from this level to the zeroth vibrational level of the ground state is responsible for the shortest wavelength peak (0–0 band) in the fluorescence emission spectrum (Fig. 3). This band is almost exactly the same wavelength in cyclohexane (289 mμ) as the 0–0 absorption band (288 mμ) which is the reverse transition. Longer wavelength bands in the fluorescence emission spectrum, such as the maxima at 297 mμ, are the result of electrons falling to higher vibrational levels of the ground state from the zeroth level of the first excited singlet.

In addition to undergoing fluorescence or certain radiationless transitions to the ground state, electrons in the zeroth vibrational level of the first excited singlet state can undergo intersystem crossing to a higher vibrational level of the first excited triplet state.[76, 77] This process is spin forbidden, but the time for it to take place is nevertheless of the same order as fluorescence emission (10^{-8} sec) and the two processes are therefore competitive.[76] Once the triplet state is populated the molecule rapidly falls to the zeroth vibrational level of this triplet state. The lifetime of a triplet state is much longer than that

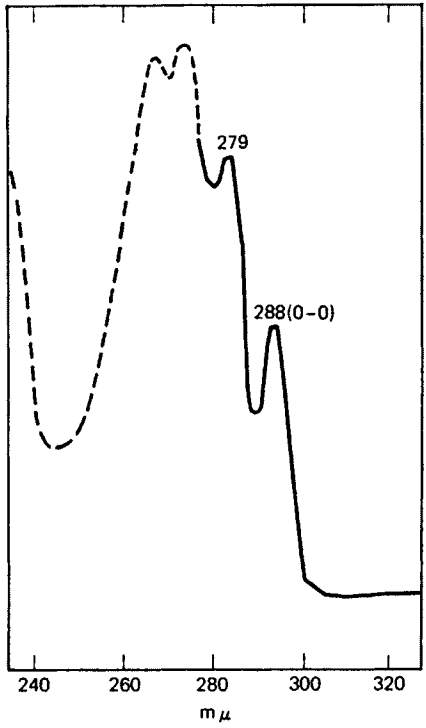


Figure 4. Ultraviolet absorption spectrum of indole in cyclohexane.

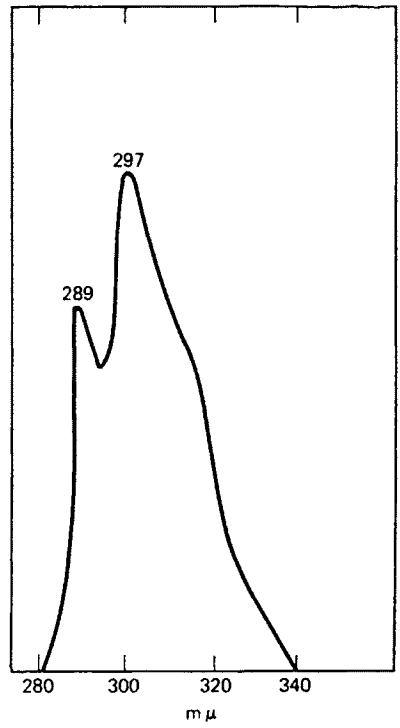


Figure 5. Fluorescence emission spectrum of indole in cyclohexane.

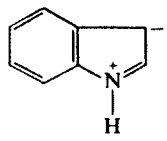
of a singlet state and therefore collisional deactivation becomes a significant factor in the triplet state. Consequently the phosphorescence emission spectra of indoles must be determined in rigid glasses at 77°K. This phosphorescence has a decay time approximately equal to the lifetime of the lowest triplet state, which varies for indoles from 1.4 to 7.1 sec for a drop to 36.8% of the initial intensity.[78] The 0–0 band for phosphorescence emission of indole is at 406.5 mμ[79] and longer wavelength bands correspond to transitions to higher vibrational levels of the ground state (Fig. 3).

Examples of the uv absorption and fluorescence emission spectra of indole are given in Figures 4 and 5. Typically such spectra have a "mirror-image" relationship with reference to the 0–0 band, due to the nature of transitions from zeroth levels of one state to a spectrum of vibrational levels of the other state (Fig. 3). This is probably also the case with indole, except that transitions to the second excited singlet state (dotted portion of the curve in Fig. 4) obscure the relationship.

Although the uv absorption and fluorescence excitation spectra of indoles

do not undergo pronounced shifts with changes in solvent polarity, fluorescence emission is markedly effected. Thus the fluorescence excitation maximum of indole is 285 mμ in each solvent of the series hexane, benzene, dioxane, ethanol, water; however, the fluorescence emission maxima are 297, 305, 310, 330, and 350, respectively, in this same solvent sequence.[80] The fluorescence intensity decreases moderately with increasing polarity except in benzene where considerable quenching occurs. Chloroform, carbon tetrachloride, acetone, and certain acids also strongly quench indole fluorescence.

Since the ground state of indole does not change appreciably in different solvents (the uv absorption spectra are little affected), the pronounced influence of solvents on the emission spectrum means that the excited state is highly polarized.[81] Presumably polarized forms such as **33** make larger



33

contributions to the structure of indole in the excited state than they do in the ground state. The incidence of forms bearing positive charge on the indole nitrogen is also consistent with the high acidity of indole in the excited state (Section II.E). Thus an enhancement of pK_a by 7.5 units is calculated from the shifts in absorption and fluorescence spectra upon ionization.[42]

N-Alkyl indoles undergo the same type of shifts in fluorescence emission as does indole, which rules out hydrogen bonding as a major cause of this phenomenon. Formation of excited-state solute–solvent complexes, which are intermediates in the process of electron transfer from indole to solvent, has been postulated as an explanation for the large shifts in polar solvents.[81] The observed stoichiometry of indole–solvent complexes is 1:2 in associating solvents and 1:1 in nonassociating solvents.[81]

The fluorescence activation and emission maxima and quantum efficiencies of selected indole derivatives is given in Table IX. This table shows that the alkyl-substituted indoles absorb and fluoresce at longer wavelengths than indole. Electron withdrawing groups decrease the quantum efficiency of fluorescence. This effect is particularly notable in the ionization of carboxyl groups wherein the free acid fluoresces less efficiently than the anion.[80]

5-Hydroxyindoles absorb at longer wavelengths than the corresponding indoles, but fluoresce at shorter wavelengths, a property which is useful in their identification,[82] The wavelength of fluorescence emission of hydroxyskatoles varies widely with the position of the hydroxyl group,[83] ranging from 315 mμ for the 7-isomer to 375 mμ for the 6-isomer (Table IX).

TABLE IX. Fluorescence Excitation and Emission Maxima of Indoles

Indole	Solvent	Excitation max (mμ)	Emission max (mμ)	Quantum efficiency (%)	Ref.
Indole	Water	287	355	46.0	82
Indole	Cyclohexane	285	297		80
Indole anion	Water	290	400	14.5	82
1-Methyl	Water	287	350	47.0	82
3-Acetic acid	Water	292	356	30.7	82
3-Acetic acid anion	Water	292	362	56.5	82
Tryptamine cation	Water	290	360	35.0	82
Tryptamine	Water	291	362	37.3	82
Tryptamine anion	Water	291	408	5.1	82
2-Methyl	Ethanol	280	335		80
3-Methyl	Ethanol	280	350		80
1-Methyl-2-phenyl	Ethanol	310	370		80
4-Hydroxy-3-methyl	Water	290	320		83
5-Hydroxy-3-methyl	Ethanol	295	360		83
6-Hydroxy-3-methyl	Water	300	375		83
7-Hydroxy-3-methyl	Ethanol	290	315		83

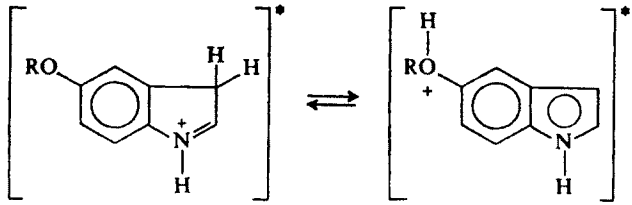
A detailed study of the changes in excitation and fluorescence wavelengths and fluorescence intensities of indoles over a wide pH range has been reported.[82] In strong sulfuric acid most indoles (except for the 5-hydroxyindoles described below) are nonfluorescent. As the pH is increased, fluorescence appears and rapidly reaches maximum intensity. For indole this appearance is at pH 0.3 and maximum intensity (355 mμ) occurs in the region of pH 3.3 to 11. Above pH 11 the indole fluorescence at 355 mμ diminishes due to an excited state reaction, reaching zero at pH 15. Fluorescence of the indole anion (400 mμ) appears at pH 14 and increases in intensity to the limit of alkalinity used (H_0 17.4). *N*-Alkyl indoles cannot form the anion in strong alkali. Then give one fluorescence of maximal intensity at 350 mμ from pH 4.5 to the limit of alkalinity.[82]

The fluorescence curve of tryptamine shows four different molecular species as the pH is varied. Below pH 0 the dication is nonfluorescent. At pH 0 the monocation appears and fluoresces maximally (360 mμ) from pH 4 to pH 9. The un-ionized form appears at pH 9, reaches maximum intensity at pH 10.4 (362 mμ), and diminishes to zero near H_0 16. Fluorescence of the anion (408 mμ) occurs at H_0 16–17.[82]

Indole-3-acetic acid gives typical indole fluorescence, with ionization of the carboxyl group indicated by a pronounced increase in the intensity.

Tryptophan fluorescence shows features anticipated for an amino acid: a nonfluorescing dication, monocation fluorescing at 345 mμ from pH 1 to pH 4, zwitterion (352 mμ) from pH 4.1 to pH 8.6, intensely fluorescing anion (359 mμ) over the short range pH 10.7–11.0, and a dianion above H_0 15.[82]

Anomalous behavior is exhibited by 5-hydroxy- and 5-alkoxyindole derivatives in strong aqueous or ethanolic acids where they fluoresce at 520–540 mμ. This fluorescence has been ascribed to an excited-state phenomenon involving proton transfer of the type **34** ⇆ **35** wherein the oxo-



34 **35**

nium ion is the emitting species. The long wavelength of the fluorescence is thought to be due to energy loss in the proton transfer.[83]

Fluorescence-polarization spectra of indole and certain derivatives have been analyzed in terms of overlap between two independent electronic transitions.[84]

The phosphorescence excitation and emission characteristics of certain 3-substituted indoles in rigid ethanol glasses at 77°K are given in Table X.

TABLE X. Phosphorescence Excitation and Emission of Indoles in Ethanol at 77°K[78]

Indole	Excitation max (mμ)	Emission max (mμ)	τ_e (sec)[a]
3-Acetic acid	285	436	7.1
3-Proprionic acid	285	441	6.5
5-Hydroxy-3-acetic acid	304	445	4.9
3-Carboxylic acid	283	424	5.5
L-Tryptophan	289	435	6.4

[a] τ_e is the time required for the phosphorescence intensity to decrease to 36.8% of initial intensity.

Excitation maxima were in the range 278–304 mμ and emission maxima were in the range 424–445 mμ. The levels of detection were very low.[78]

Theoretical treatments of indole phosphorescence[79, 85] have described the observed spectrum as a progression of eight bands, with the 0–0 band at 406.5 mμ. The vibrational structure of the ground state is consistent with values from ir and Raman spectroscopy. Figure 6 shows the phosphorescence emission spectrum of indole-3-acetic acid.

A large number of indoles afford chemiluminescence in the presence of

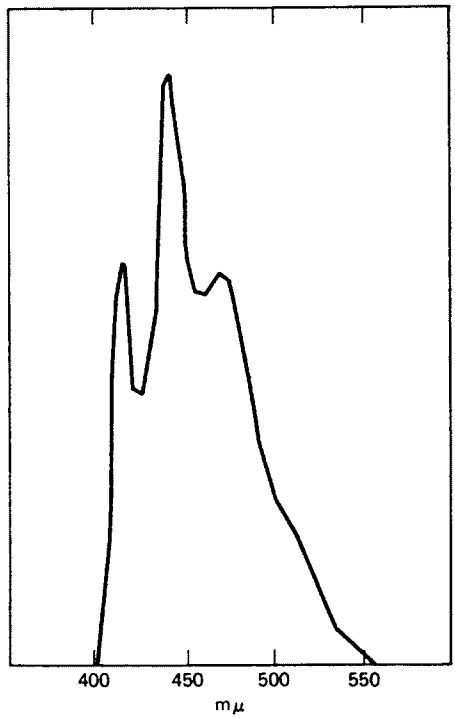
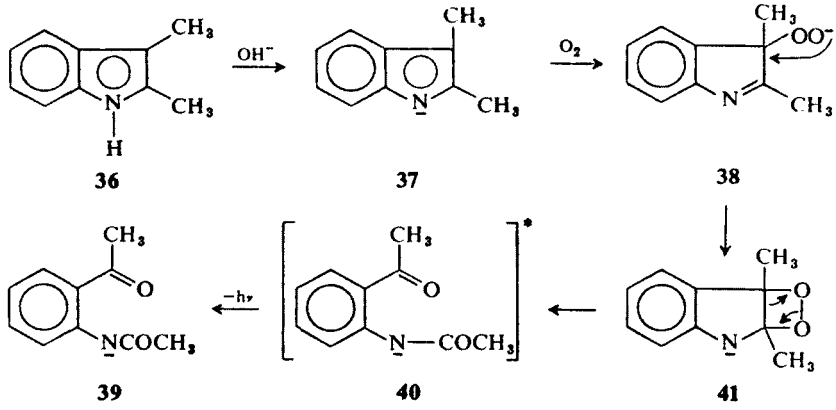


Figure 6. Phosphorescence emission spectrum of indole-3-acetic acid in ethanol at 77K.

alkali and a suitable oxidizing agent.[86–92] In dimethylsulfoxide (DMSO) solution 3-methylindole luminesced with only base added,[70] but other indole derivatives required oxygen or potassium peroxydisulfate as well.[86, 88, 89] A system composed of ethanol, potassium hydroxide, hydrogen peroxide, potassium ferricyanide, and indole derivatives also produced chemiluminescence of the same wavelengths as were obtained in DMSO, although different intensities and quantum efficiencies were recorded.[86]

The comparative chemiluminescence of 2,3-dimethylindole (**36**) and its corresponding 3-hydroperoxyindolenine in DMSO containing potassium hydroxide was studied.[87] Both compounds emit the same amount of light at the identical wavelength (520 mμ) in an oxygen atmosphere, although only the hydroperoxide luminesced in a hydrogen atmosphere. An excellent correlation was obtained between this luminescence spectrum and the fluorescence emission spectrum of *o*-acetamidoacetophenone. These observations led to the proposal of the following scheme for the chemiluminescence reaction.[87] In alkaline solution in the presence of oxygen or an oxidizing agent 2,3-dimethylindole anion (**37**) is converted in a rate-determining step

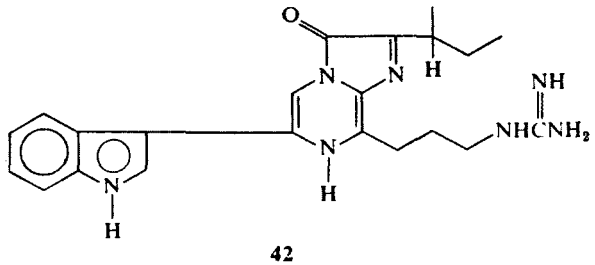
to the hydroperoxide anion (**38**), which proceeds in faster steps to the first excited singlet state of *o*-acetamidoacetophenone anion (**40**). The excited **40** then falls to the ground state (**39**) with emission of light (Scheme 1).



Scheme 1

Excellent agreement between the chemiluminescence spectrum of skatole and the fluorescence emission spectrum of *o*-formamidoacetophenone[92] suggests that a similar mechanism is operating with this molecule, and possibly this type of mechanism is general for the chemiluminescence of simple indoles. A kinetic study on the chemiluminescence of indole 5-carboxylic acid established the relationship $I_{max} = k$[substrate][base][peroxydisulfate], where I_{max} is the intensity of luminescence.[88] This relationship is consistent with the above-described type of mechanism. Because of the low quantum efficiency and number of products produced in the alkaline oxidations of indoles, it is thought that the chemiluminescence reaction corresponds to only a small part of the total oxidation process.[88]

The naturally occurring indole derivative cypridina luciferin (**42**) undergoes



spontaneous chemiluminescence in dimethylsulfoxide. It is considered, however, that the luminescence is due to the dihydroimidazo[1,2-*a*]pyrazineone moiety rather than the indole moiety.

TABLE XI. Maximum Chemiluminescent Intensities of Indoles[88]

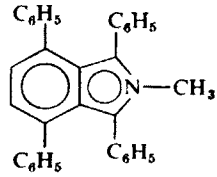
Indole	Aqueous system[a]	DMSO system[b]
Indole	135	105
2-Methyl	40	2,100
3-Methyl	80	10,000
1,2-Dimethyl	55	300
2,3-Dimethyl	0	3,000
2,5-Dimethyl	0	600
3-Acetic acid	0–10	95
L-Tryptophan	25	0
3-Chloro	0	0
5-Nitro	0	0
5-Carboxylic acid	60	0

[a] Solutions 2.5×10^{-3} *M* in the indole, 0.50 *M* in sodium hydroxide, and 0.08 *M* in potassium peroxydisulfate.

[b] Solutions 0.05 *M* in dimethylsulfoxide treated with 0.5 g of solid potassium hydroxide.

The chemluminescence properties of selected indoles are given in Table XI.

Electrochemiluminescent emission was observed when *N*-methyl-1,3,4,7-tetraphenylisoindole (**43**) was oxidized at a platinum electrode in DMF solution. This emission was identical with the fluorescence emission of **43** at 490 mμ.[93]



43

4. *Nuclear Magnetic Resonance*

Proton magnetic resonance (pmr) spectra of indoles have been thoroughly investigated, and interpreted in considerable detail. Since the indole nucleus bears relatively few hydrogens, and their environment changes significantly according to the position on the nucleus, it is frequently possible to assign every proton in the spectrum of a simple indole and to determine the positions of substitution on the nucleus. Subtle effects in longe-range coupling and in the solvent and concentration dependence of chemical shifts have been carefully studied.

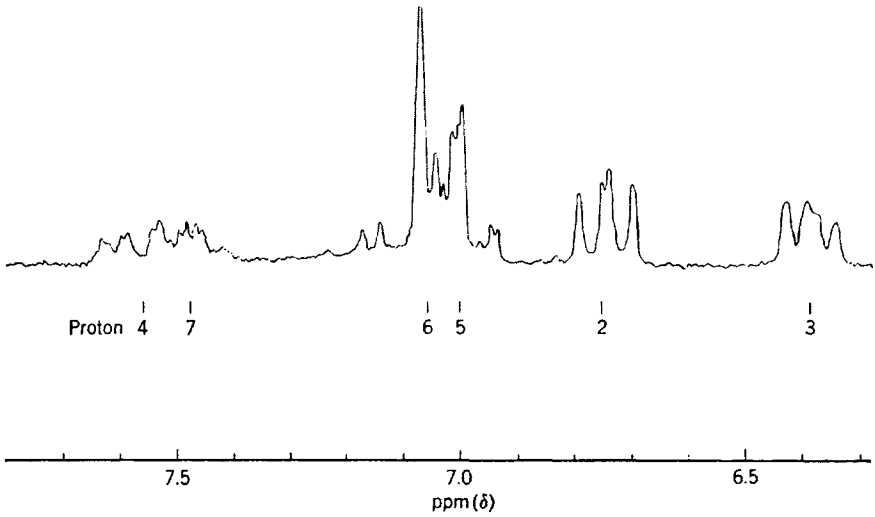


Figure 7. 60 MHz nmr spectrum of indole in carbon tetrachloride.

The 60 MHz spectrum of indole in CCl_4 is shown in Figure 7. Since the ring current in the pyrrole ring is less than that in the benzene ring, the 2 and 3 protons are less deshielded and appear at higher fields than the other protons, with the considerable electron density at 3 being reflected in the higher field of this proton, despite the fact that it is deshielded more by the benzene ring current than is the 2 proton. Protons at 5 and 6 appear next in order, followed by those at 7 and 4 which are strongly deshielded by the currents in both rings.

The chemical shifts of certain indole protons, relative to those in benzene, have been estimated from calculated ring currents and calculated π-electron densities.[94] Furthermore, the electron densities have been calculated by the reverse process, using observed chemical shifts.[95] Agreement between theoretical and experimental values has been reasonable in these cases. The choice of chemical shifts determined in acetone, which selectively deshields the 2, 3, and 7 protons, caused one set of calculations[95] to appear somewhat poorer than it actually was.

In Figure 8 the effect of deuterium exchange on the pmr spectrum of indole in acetone is shown. The multiplets of the 2- and 3-protons are particularly simplified, demonstrating that the NH proton is strongly coupled to both of them. Careful study of the effects of substituents at specific positions on the multiplicities of certain peaks in the pmr spectrum,[96, 97] and particularly double resonance experiments,[98] have revealed the complex pattern of

TABLE XII. Spin-Spin Coupling Constants of Protons on Indole[98]

Coupling	Value in Hz
1,2	2.5
1,3	2.0
1,4	0.8
2,3	3.1
2,6	[a]
3,7	0.7
4,5	7.8
4,6	1.2
4,7	0.9
5,6	7.1
5,7	1.3
6,7	8.1

[a] Not described for indole. In 5-methoxyindole a value of 0.4 Hz was found.[99]

couplings between various protons on the indole nucleus. Of unusual interest are the long-range couplings between the 1- and 4-,[98] 3- and 7-,[97] and even the 2- and 6-protons.[99] Table XII gives the coupling constants for indole protons. The small values for coupling between the 1- and 2-protons and the 1- and 3-protons are characteristic of the pyrrole ring. The pmr spectrum of indole has been calculated from reasonable values for chemical shifts and coupling constants and is in good agreement with the observed spectrum.[98]

Solvent and concentration effects on the chemical shifts of indole protons are pronounced, particularly in hydrogen-bonding and other polar solvents.[100] Figure 8 shows the pmr spectrum of indole in acetone. Comparison of this spectrum with Figure 7 reveals that, although all protons are deshielded on going from CCl_4 to acetone, the NH proton is deshielded much more than any other, the 2-proton is deshielded more than any other proton on carbon, and the 7- and 3-protons are also strongly deshielded. In a solvent like acetone a strong hydrogen bond with the indole NH is apparently formed. Consequently the acetone molecule is held in such a way that the diamagnetic anisotropy of its carbonyl group exerts the observed deshielding effects. If the indole has an alkyl substituent on nitrogen, these deshielding effects are considerably diminished, although the order is preserved.[101] Deshielding in this case is probably due to dipolar interaction which holds the molecules in such a way that a selective effect occurs. Chemical shift changes for the

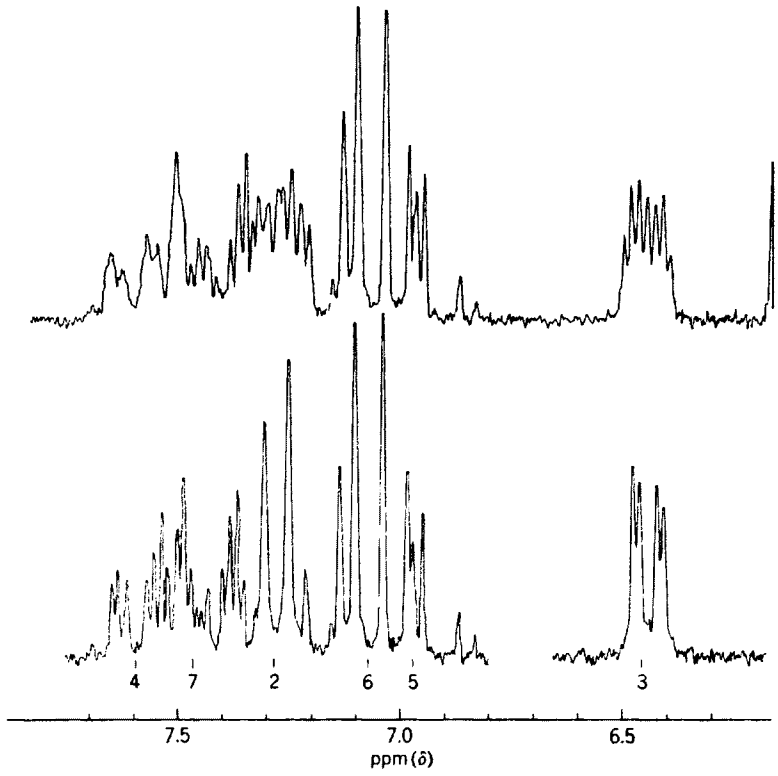


Figure 8. Upper curve: 60 MHz nmr spectrum of indole in acetone. Lower curve: Same spectrum after addition of CD_3OD and D_2O.

2- and 3-protons of a series of NH indoles in various solvents are given in Table XIII.

The chemical shifts of the 2- and 3-protons of indoles are also affected by concentration.[102] In a nonassociating solvent (CCl_4) the 3-proton is unchanged by variation in concentration, but the 2-proton is strongly shielded as the solute concentration increases to 30 mol%. The chemical shift of the 3-proton varies with a minimum near 30 mol% in tetrahydrofuran, while the 2-proton again experiences strong shielding as concentration increases.[102]

It has been suggested that the relative magnitude of changes due to solvent on the chemical shifts of the 2- and 3-protons is a useful guide in determining the position of a substituent (or rather the remaining proton) at one of these sites.[100] However, caution is recommended in applying this rule, particularly in view of the concentration effects.[102] It must also be kept in mind whether an NH- or N-substituted indole is being studied since the changes may be much smaller in the latter case.[101]

TABLE XIII. Effects of Solvents on the Chemical Shifts of 2- and 3-Protons for Selected Indoles[100]

Compound	Proton	Chemical shifts in solvents (δ)[a]						
		CCl_4	$CDCl_3$	Acetone	DMSO	Dioxane	CS_2	Over-all Δδ
Indole	2	6.54	6.74	⩾7.25	>7.29	>7.11	6.55	0.76
Indole	3	6.30	6.41	6.48	6.47	6.48	6.29	0.19
3-Methylindole	2	6.35	6.61	⩾7.0	7.06	6.87	6.37	0.71
2-Methylindole	3	5.94	6.05	6.14	6.12	6.12	5.90	0.24
3-Bromoindole	2		7.02	7.43	7.58	7.23	6.87	0.54
3-Acetylindole	2			8.18	8.34			0.17
Indole-2-carboxylic acid	3			7.21	7.19	7.26		0.08
Ethyl indole-3-carboxylate	2		7.82	8.01	8.12	7.90		0.25
Ethyl indole-2-carboxylate	3		7.23	7.22	7.20	7.20		0.03

[a] Center of doublet or multiplet is given.

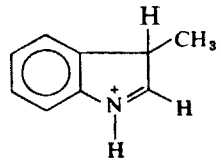
The effect on chemical shift obtained by adding benzene to a carbon tetrachloride solution of an indole or monomethyl indole has also been suggested as diagnostic for substitution at the 2- or 3-position.[103] Thus a 3-proton or methyl group experiences small positive or negative shifts (+0.5 to −0.54 ppm), while a 2-proton or methyl group experiences positive shifts (+0.03 to +0.45 ppm). *N*-Alkylation produces increased negative shifts at the 3-position. These effects are explained by the alignment of benzene to solvate the positive end (nitrogen) of the indole dipole, with the benzene ring as far as possible from its negative end.[103]

The pmr spectra for a number of alkyl,[104] hydroxyl,[105] carboxy,[106] and other substituted indoles have been interpreted. These substituents cause significant shielding or deshielding of the remaining protons, depending upon their electronegativity and position. For example, in 5-methoxy-1-methylindole the 4- and 6-protons are shifted to higher fields ($\Delta\delta = 0.57$ and 0.36 ppm, respectively) than the corresponding protons in 1-methylindole, whereas the 2-, 3-, and 7-protons are little affected.[100]

A proton on a carbon atom adjacent to that bearing a methyl substituent in the 5-membered ring experiences a small spin-spin coupling (ca. 1.0 Hz) with this substituent.[96]

The chemical shifts of indole *C*-methyl groups fall in the region of δ 2.3 to 2.1, but that of the *N*-methyl group is near δ 3.4.[107] A method for distinguishing methyl groups on basic nitrogen atoms from methyl groups on more neutral nitrogens such as in indoles is founded in the solvent shifts afforded on going from deuteriochloroform to perdeuterioacetic acid to trifluoroacetic acid.[108] The methyl groups on more neutral nitrogens are subject to less deshielding than are those on basic nitrogens. Exceptions to this rule are 1,2-dimethylindole and 5-benzyloxy-1-methylindole which give fairly large shifts in trifluoroacetic acid[108]; however, these electron-rich molecules might be undergoing protonation at $C_{(3)}$ in such a strong acid.

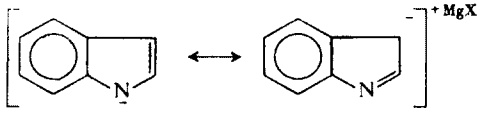
A study of the pmr spectra of certain alkylindoles in 12 *M* sulfuric acid has demonstrated that the protonation of these compounds occurs at the 3-position.[109] Thus in 3-methylindole the 3-methyl group is shifted to higher field and split into a doublet ($J = 7.5$ Hz), while the added proton is split into a quartet with the same coupling and the 2-proton is a doublet coupled with the NH. These data all fit Structure **44**. Results consistent with 3-proton-



44

ation were also obtained with 1,2- and 1,3-dimethylindoles, 1,2,3-trimethyl indole, and tryptamine.[109]

Nuclear magnetic resonance was utilized in a study of the structures of indolylmagnesium bromide and indolylsodium in tetrahydrofuran.[110] Both species gave closely similar spectra which showed no NH proton, but did show the 3-proton. Strong deshielding of the 2- and 7-protons was noted, and both of these shifts were concentration dependent. A structure which is a hybrid of forms **45** and **46** was suggested for indolylmagnesium bromide in



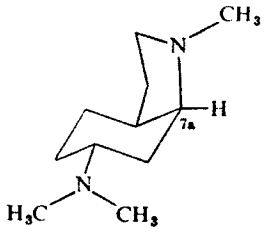
45 **46**

tetrahydrofuran.[110]

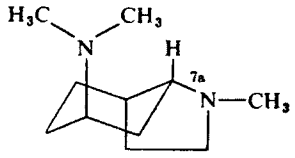
The pmr spectra of indoline and indolinium ion suggest that considerable puckering occurs in the 5-membered ring.[111] Thus the sums of coupling constants between *cis* and *trans* protons at the 2 and 3 positions were 17.0 and 15.6 Hz, respectively, for these species. In *cis* and *trans* 2,3-dimethylindolines, the coupling constant $J_{2,3}$ depends strongly on the substituent on the nitrogen.[112] For 2,3-dimethylindolines unsubstituted on nitrogen, $J_{2,3}$ is large and nearly identical for the *cis* (8.83 Hz) and *trans* (8.85 Hz) isomers. These values indicate that C-2 is appreciably out of the plane of the other atoms, and they are consistent with a nearly sp^3 hybridized nitrogen. If the nitrogen is substituted with a *p*-toluenesulfonyl or nitroso group, $J_{2,3}$ is much larger for the *cis* isomers (8.61 and 8.22 Hz, respectively) than for the *trans* isomers (2.71 and 3.02 Hz, respectively). These values indicate a nearly planar 5-membered ring and an sp^2 nitrogen, caused by appreciable resonance interactions with the substituents. A general method for determining the stereochemistry of 2,3-disubstituted indolines was suggested from these observations.[112]

A study of *N*-acetylindolines in chloroform revealed strong deshielding of the 7-proton ($\Delta\delta = -0.93$ ppm) compared to the other protons ($\Delta\delta$ ca. 0.22 ppm). The 2 and 3 protons gave pairs of triplets anticipated for an A_2B_2 system approaching the A_2X_2 limit, at 3.27 and 4.15 ppm, respectively.[113]

The structures of the isomeric perhydroindole derivatives **47** and **48** were



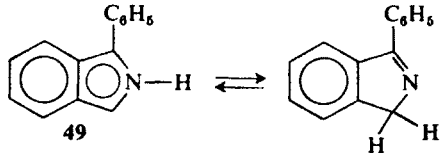
47



48

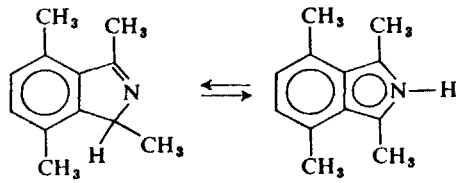
differentiated on the basis that **47** had a one-proton sextet at 3.16 ppm (7*a*-proton), whereas **48** lacked any peaks at this low field.[114] This finding is consistent with the general rule that in six-membered ring systems equatorial protons absorb at lower fields than do their epimeric axial counterparts.

The pmr spectra of several isoindoles have been analyzed.[115, 116] They indicate facile tautomerism between isoindole and isoindolenine forms. This behavior is in contrast to the spectra of indoles which show no contribution from the corresponding indolenines.[107] The spectrum of 1-phenylisoindole (**49**) in deuteriochloroform shows a broad NH band from 0.0 to +0.9 τ, aromatic protons in the region 1.9 to 3.2 τ, and a peak at 5.13 τ due to the CH_2 of tautomeric isoindolenine **50**.[115]



49 **50**

For 1,3,4,7-tetramethylisolindolenine (**51**), relative areas of the aromatic hydrogens at δ 7.02 ppm, aliphatic hydrogen at 4.74 ppm, two methyl groups on an aromatic ring at 2.58 and 2.56 ppm, one methyl group on a double bond at 2.39 ppm, and one aliphatic methyl group at 1.44 ppm show it to be the predominant tautomer. The presence of a small amount of tautomeric isoindole **52** was shown by olefinic hydrogens at 6.38 ppm, an NH at 3.26



51 **52**

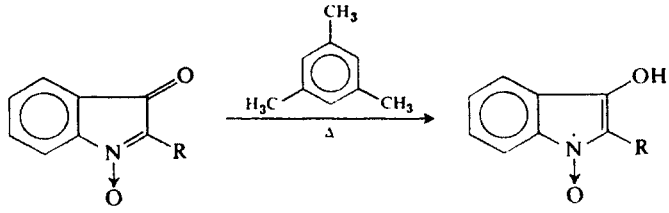
ppm, and methyl groups at 2.69 and 2.61 ppm.[116]

5. *Electron Spin Resonance*

Despite the increasing importance of electron spin resonance (esr) in the detection of radicals and in the understanding of the properties and distribution of unpaired electrons in aromatic systems, few applications of this technique have been made with indoles.

In the most important application thus far, it was found that when solutions of 2-carbomethoxyisatogen (**53a**) or 2-phenylisatogen (**53b**) in aromatic

hydrocarbons capable of proton transfer (such as mesitylene and xylene) were heated, the formation of free radicals with a lifetime of several months occurred (Eq. 1). The esr signals were nearly identical for the free radicals from both isatogens, indicating that the unpaired spins were not delocalized onto their substituent groups. Analysis of the signals revealed three main groups of bands with intensity ratios 1:1:1, which were attributed to coupling with ^{14}N. Each group of bands contained 18 individual bands, and these bands were resolved into coupling of the unpaired electron with two sets of equivalent protons H_5, H_7 and H_4, H_6. A further splitting of about 0.5 G was assigned to coupling with a hydrogen not originally present in **53a** and **53b**. On the basis of the above data, the most likely structures for the radicals were considered to be **54a** and **54b** (Eq. 1). Radicals resulting from



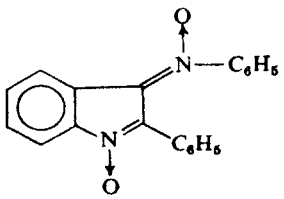
(1)

53a; R = CO_2CH_3 **54a**; R = CO_2CH_3

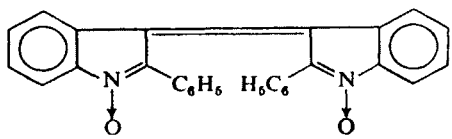
53b; R = C_6H_5 **54b**; R = C_6H_5

the aromatic hydrocarbons were not detected due to their much shorter lifetimes.[117]

Another interesting example of esr spectroscopy in indole chemistry was the demonstration that bisnitroxides **55** and **56** are biradicals.[118] A strong esr signal was detected from the black complex formed when indole and iodine were combined, but no interpretation of this signal was made.[119]



55

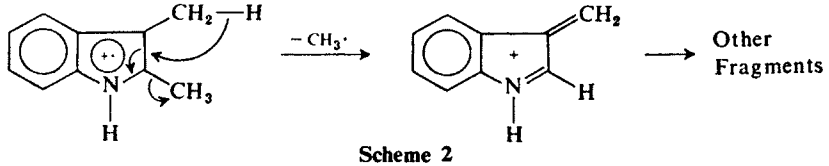


56

6. *Mass Spectrometry*

The first electron removed from indoles under electron impact probably originates from the nitrogen atom.[120] Large molecular ion peaks in all mass spectra of indoles reflect their aromatic nature. Some of these spectra show

a large number of "half masses" due to doubly charge ions, which is a typical behavior of nitrogen-containing compounds, and especially aromatic compounds.[121] Indoles substituted with more than one methyl group undergo facile methyl cleavage; however, monomethylindoles do not. It has been suggested that such methyl group cleavage involves participation of the neighboring methyl group (Scheme 2).[121] The observation that the M-15 peak is greatest for these compounds is consistent with this suggestion.

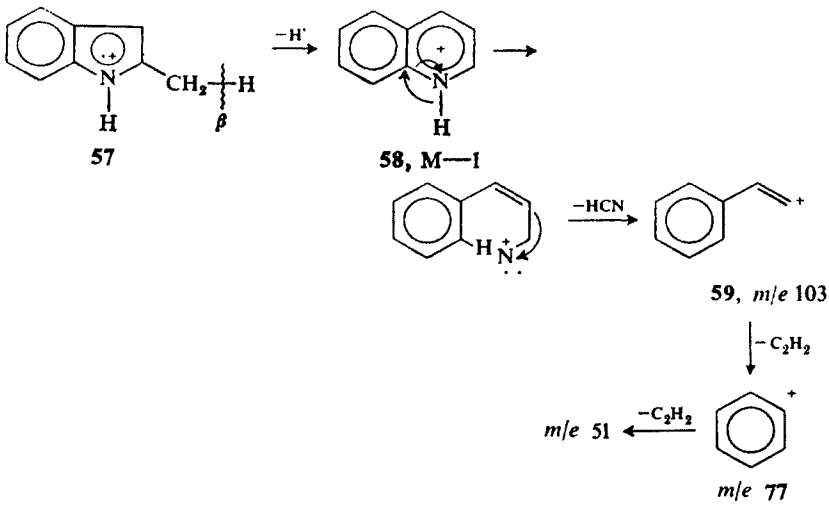


Scheme 2

For indole itself the molecular ion is the base peak and the most abundant fragment (M-27) arises from expulsion of HCN.[123] Relatively abundant peaks at *m/e* 28 and 39 have been ascribed to the formation of $HCNH^+$ and cyclopropenium cation, respectively.[123] Studies with 1-deuterioindole and with 3-deuterioindole indicated that 79% of the 1-deuterium, 21% of the 2-hydrogen, and none of the 3-deuterium were present in the HCN fragment.[124]

Indoles substituted with alkyl groups at the 2 and/or 3 positions readily undergo β-cleavage. If only methyl substituents are present, a hydrogen atom is expelled and a large M-1 peak is observed. Longer-chain alkyl substituents expel the appropriate alkyl fragments for β-cleavage; for example, a 2- or 3-butylindole loses C_3H_7.[122]

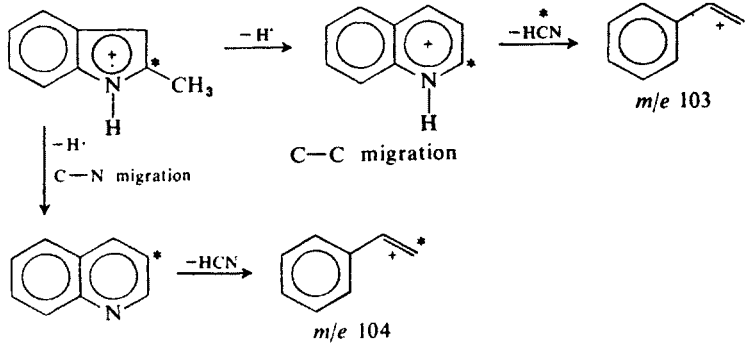
The stepwise decomposition of 2-methylindole (**57**) has been established by



Scheme 3

observation of the appropriate metastable ions. For the M-1 peak resulting from β-cleavage, quinolinium cation **58** was suggested,[122] since loss of HCN from it gives the next fragment (**59**) by way of a stable intermediate. This route is also consistent with the ^{13}C labeling experiment described below. Subsequent loss of two successive molecules of acetylene accounts for the more important smaller fragment ions of *m/e* 77 and 51 (Scheme 3).

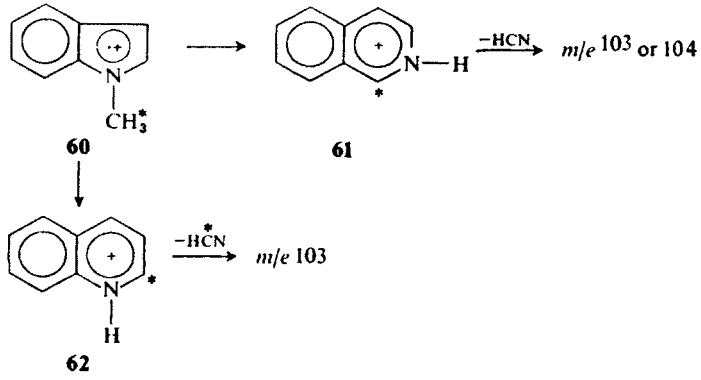
When 2-methylindole was labeled at $C_{(2)}$ with ^{13}C, elimination of HCN from the intermediate quinolinium ion gave much more of a fragment at *m/e* 103 than it gave of a *m/e* 104 fragment.[125] This result shows that C—C migration predominates over C—N migration in formation of the quinolinium ion, as depicted in Scheme 4. When the 2-methylindole had ^{13}C in the methyl



Scheme 4

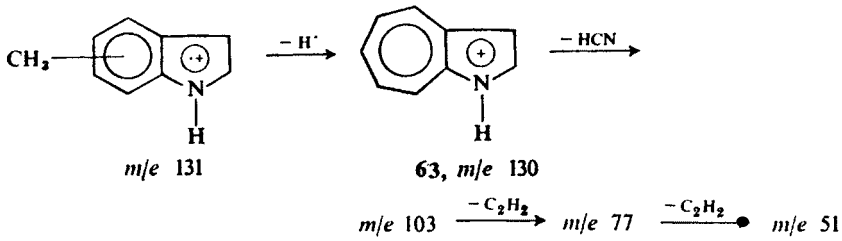
group, the fragment resulting from expulsion of HCN was mainly *m/e* 104, confirming the preference of C—C migration.

For *N*-methylindole labeled in the methyl group (**60**), elimination of HCN gave a roughly equal mixture of ions at *m/e* 103 and 104, indicating that formation of **61** is more probable than formation of **62**, which should have given all but a small percentage of *m/e* 103[125] (Scheme 5).



Scheme 5

The mass spectra of the four isomeric indoles with methyl groups in the benzene ring were closely similar. In all cases the M-1 peak was the base peak. A suggested pathway (Scheme 6) for their fragmentation features ring

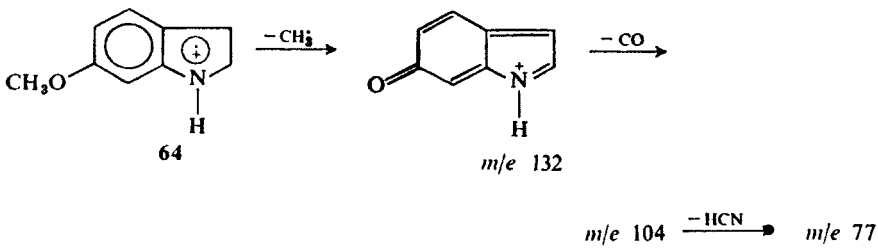


Scheme 6

expansion to azaazulinium ion **63**, followed by loss of HCN and two molecules of acetylene.[124]

The molecular ion is the base peak in the spectra of 1-, 2-, and 3-phenylindole and the predominant fragment ($C_{13}H_9^+$) is the result of CH_2N loss from it. In 2,3-diphenylindole the M-1 peak predominates, but this peak disappears if a 6-nitro group is present.[124]

6-Methoxyindole (**64**) may be readily distinguished from its 5 and 7 isomers because it readily loses a methyl radical to give *m/e* 132 as the base peak (Scheme 7). The other isomers also lose this radical, but for them the



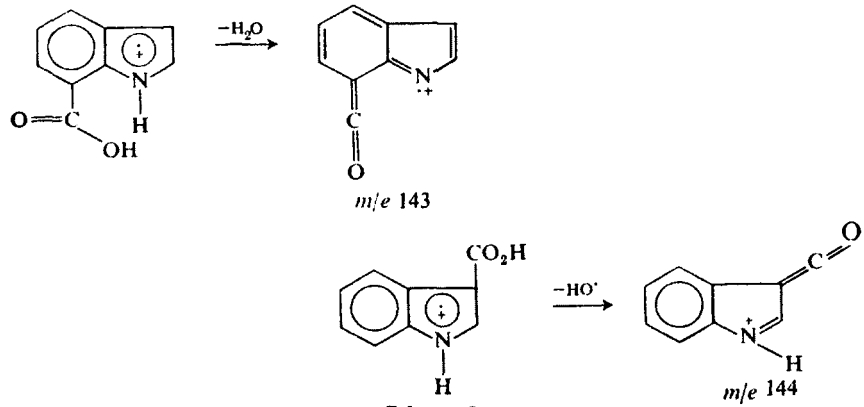
Scheme 7

molecular ion is the base peak.[124]

Isomeric indole carboxaldehydes gave either the molecular ion or M-1 peak as the base peak. Loss of CO from the M-1 peak, followed consecutively by loss of HCN and C_2H_2, accounted for the major fragments in all cases examined.[124]

Very intense M − CO_2 peaks observed for indole 2- and 3-carboxylic acids were attributed to decarboxylation in the inlet system. Other indolecarboxylic acids show weaker M − CO_2 peaks. The 2- and 7-carboxylic acids give intense ions due to loss of H_2O from the molecular ion ("ortho effect"),

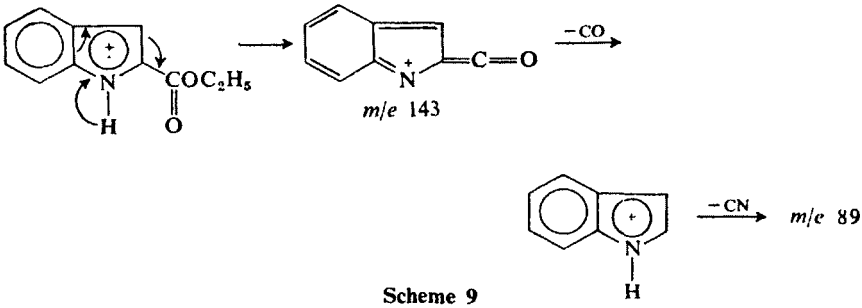
whereas the isomeric acids lose OH instead[124] (Scheme 8).



Scheme 8

A detailed study of various indole carboxaldehydes and indole esters has provided a guide to differentiation between the 2- and 3-isomers.[126]

The mass spectrum of ethyl indole-2-carboxylate has a base peak at M-46, indicating the loss of the elements of ethanol in a primary process. Further fragmentation proceeds with consecutive losses of carbon monoxide and a neutral cyanide radical (Scheme 9). Metastable peaks appropriate to each of



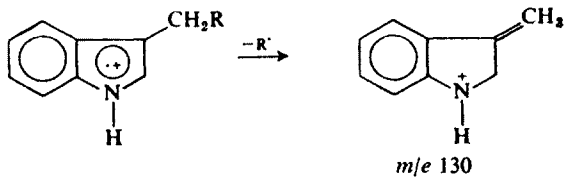
Scheme 9

these processes have been observed.[127]

Cyanoindoles undergo fragmentation by successive loss of two HCN fragments. Indole carboxamides either lose water to give an ion corresponding to the nitrile (*m/e* 142) or they lose NH_2 to give an ion at *m/e* 144. From this point fragmentation is related to that of the corresponding nitrile or acid.[124]

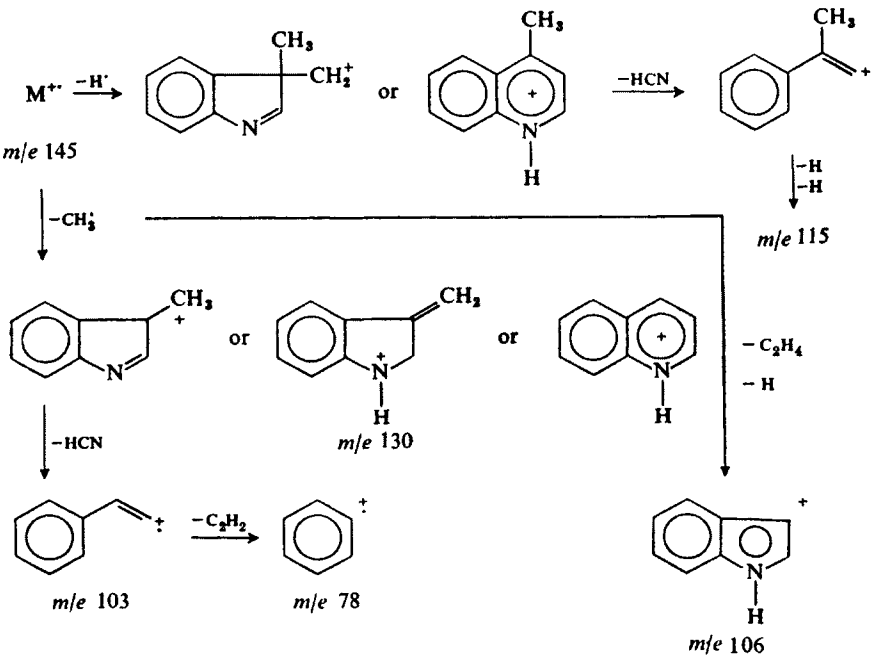
A number of 3-substituted indoles such as tryptophan, methyl indole-3-acetate, and indolmycin show a strong peak at *m/e* 130, resulting from *β*-cleavage (Scheme 10).

3,3-Disubstituted indolenines give mass spectra which are similar to those of the isomeric 2,3-disubstituted indoles. It is likely that both systems rearrange to the same ions.[128]



Scheme 10

Accurate masses have been determined for important fragments derived from both 2,3-dimethylindole and 3,3-dimethylindolenine. Scheme 11

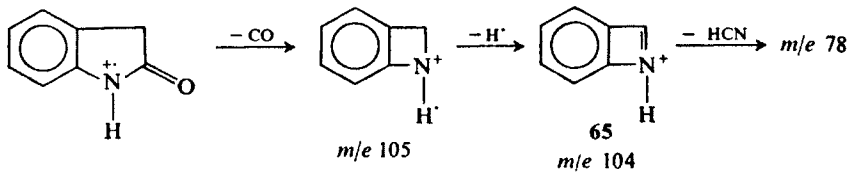


Scheme 11

accounts for certain of these fragments.

Indolines with a methyl group and either an allyl or isopropyl group at C-3 undergo facile cleavage of the entire allyl or isopropyl group, affording the ion with *m/e* 130. However, other alkyl groups in the same situation generally suffer the β-cleavage.[128]

Fragmentation of the molecular ion of oxindole (base peak) involves expulsion of CO followed by loss of H· (Scheme 12). The resulting benzazetinium ion **65** is characteristic of oxindoles, appearing in the mass spectra of a variety of oxindole derivatives.[124]



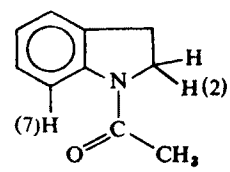
Scheme 12

G. Stereochemistry

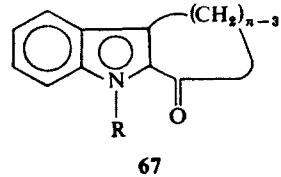
Although indoles are planar molecules, indolines may have $C_{(2)}$ appreciably out of the plane of the other atoms.[112] In 2,3-dimethylindolines with unsubstituted nitrogen, this puckering of the 5-membered ring reflects nearly sp^3 geometry of the nitrogen atom. However, if these same 2,3-dimethylindolines are substituted on nitrogen by nitroso or *p*-toluenesulfonyl groups, this ring becomes nearly planar due to conjugation of the nitrogen with the substituents. The nitroso derivative shows restricted rotation at room temperature.[112]

Restricted rotation of *N*-acylindolines was shown by the appreciable selective deshielding (1.77 ppm) of the proton on $C_{(7)}$. Deshielding of this magnitude indicates that the acetyl group must be nearly in the plane of the indole nucleus with its carbonyl group turned toward $C_{(7)}$, as illustrated in **66**. A much lower deshielding (0.68 ppm) of the protons on C-2 was observed. Similar observations were made for a variety of N-acetyl- and *N*-benzoylindolines; however, 1-formylindoline appears to exist as a 1:3 mixture in which the configuration with the carbonyl group directed toward C-2 predominates.[129]

For the series of cyclic 2-acylindoles represented by structure **67**, it was



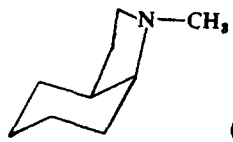
66



67

observed that as *n* increased from 5 to 8 steric crowding caused loss of coplanarity between the carbonyl group and the indole nucleus. The resulting steric inhibition of resonance was manifested in an increase of the carbonyl stretching frequency in the ir, bathochromic and hypochromic shifts in uv absorption maxima, and certain shifts in the line positions of methylene protons in the NMR.[130]

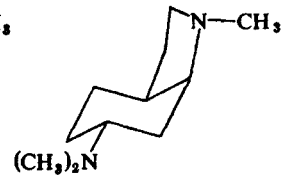
The octahydroindoles formed by catalytic hydrogenation of indolines have a *cis*-ring junction and the nitrogen atom is axial to the six-membered ring. Suggested preferred conformations for 1-methyloctahydroindole (**68**) and its 5- and 6-dimethylamino derivatives (**69** and **70**, respectively) are indicated.



68



69



70

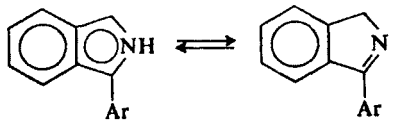
The dimethylamino substituents are thought to be equatorial.[114]

H. Tautomerism

Prior to the widespread use of spectroscopy in structure determination, the tautomerism of compounds was usually decided on the basis of their chemical reactions. This procedure frequently led to error because the predominant tautomer of a molecule is not necessarily its more reactive form. The ambident behavior of certain molecules further complicated the understanding of their structures. However, the techniques of ir, uv, and nmr spectroscopy have now provided a convenient and reliable basis for investigating tautomerism. Dipole moments and X-ray crystallography have also been useful in this respect.

Thus indole was once considered to exist in equilibrium with its tautomer indolenine on the basis of its chemical reactivity. However, the nmr spectra of indole shows no trace of indolenine.[107] Isatin, oxindole, and indoxyl were also considered to exist in tautomeric (enolic) forms, but were later shown by ir and uv studies to be in the keto forms.[54, 51, 131] X-Ray and dipole moment data also confirmed the existence of isatin in the dicarbonyl form.[27, 31]

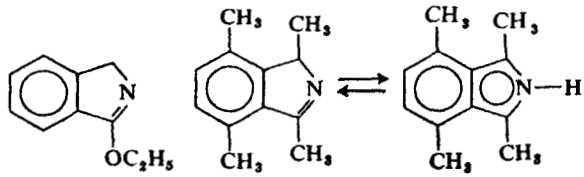
In contrast to the indoles, simple isoindoles (unsubstituted on nitrogen) do exist in measurable equilibrium with tautomeric isoindolenines.[62] For example, the isoindole form of 1-phenylisoindole (**71**) is present to the extent of 91% in ether-d_{10} and 96% in $CDCl_3$ in equilibrium with the isoindolenine form (**72**). A more pronounced variation in the tautomeric



71 **72**

equilibrium with solvent was observed for 1-*p*-methoxyphenylisoindole which had 100, 90, 87, and 70% of isoindole form **72** in ether, ethanol, acetonitrile, and $CDCl_3$, respectively.

Electron-releasing substituents appear to enhance the relative amount of isoindolenine tautomer, since 1-ethoxyisoindolenine (**73**) occurs without any trace of the tautomeric isoindole. Furthermore, the isoindolenine form (**74**) of 1,3,4,7-tetramethylisoindole predominates over its tautomer (**75**) by a

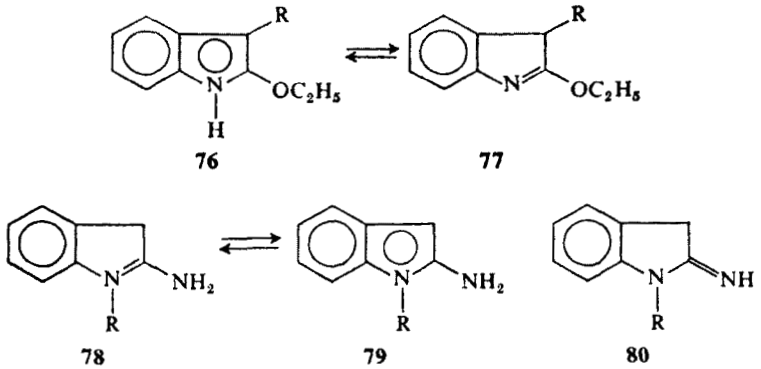


73 **74** **75**

substantial factor according to ir and nmr spectra.[116]

The tautomerism of isoindoles appears to be important in determining their stability.[4] The isoindolenine form is generally more reactive due to a large electron deficiency at its 1-position, hence those compounds that exist mainly in the isoindole form (such as 1-phenylisoindole) have been the ones stable enough for isolation. *N*-Methylisoindole, which is fixed in its form, also has appreciable stability. Those isoindolenines that have been isolated possess electron-donating substituents such as ethoxy at the 1-position.[4]

Certain electron-releasing substituents at the 2-position of indoles increase the stability of the tautomeric indolenine. An interesting example of this effect is 2-ethoxyindole (**76**, R = H) which is present in a ratio of 1:2 with 2-ethoxyindolenine (**77**, R = H) in CCl_4 at 35°.[132] The indolenine tautomer of 2-ethoxy-3-methylindole (**77**, R = CH_3) is likewise predominant.[133] 2-Aminoindole exists as the 2-aminoindolenine tautomer (**78**, R = H) by a



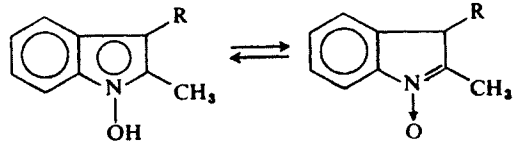
76 **77**

78 **79** **80**

Scheme 13

factor of at least 10 over the indole form (**79**, R = H) and the amidine form (**80**, R = H). Since 2-amino-1-methylindole cannot assume the indolenine form without separation of charges, it is more stable as the indole (**79**, R = CH_3); however, as the solvent polarity increases, the amidine tautomer (**80**, R = CH_3) becomes increasingly important[37] (Scheme 13).

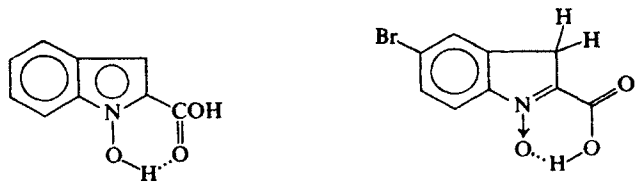
Tautomeric equilibria which are readily detected by ir and nmr also exist for 1-hydroxy-2-methylindole (**81**, R = H) and its 3-methyl derivative (**81**,



81 **82**

R = CH_3). These forms are favored in proton donor solvents such as $CDCl_3$ and phenol, whereas the tautomeric nitrones (**82**) predominate in proton acceptor solvents such as pyridine, acetonitrile, and nitromethane.[134, 135]

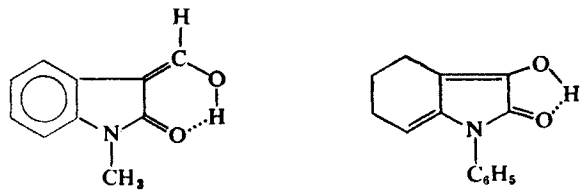
Although the hydroxyindole form (**83**) of 1-hydroxyindole-2-carboxylic acid is stable in $CDCl_3$ according to its nmr spectrum, the nitrone form (**84**)



83 **84**

of 5-bromo-1-hydroxyindole-2-carboxylic acid is the stable one in the same solvent.[136] The reason for this pronounced effect of the bromine group is not apparent.

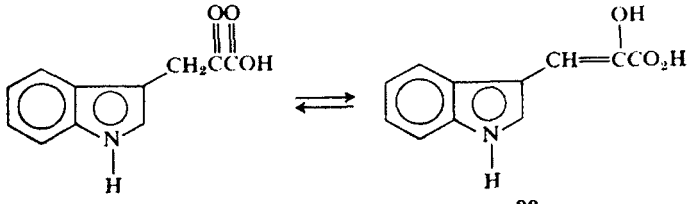
Strong intramolecular hydrogen bonding is responsible for the stability of the hydroxymethylene form (**85**) of *N*-methyloxindole-3-carboxaldehyde,[54] and it is responsible for form (**86**) of *N*-phenyl-4,5,6,7-tetrahydroisatin.[54]



85 **86**

The long conjugated system present in the enol form (**87**) of indole-3-pyruvic acid provides the stability of this form in aprotic solvents or methanol.

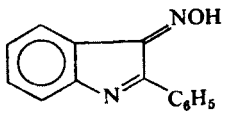
However, the keto form (**88**) is more stable in protophilic solvents such as



87 **88**

nitromethane and tetrahydrofuran. This effect of protophilic solvents has been attributed to their promotion of carboxylate anion formation, which inhibits enolization by way of a carbanion.[56]

3-Nitroso-2-phenylindole exists mainly as the indolenine form **89**.[137]



89

I. π-Molecular Complexes

Since indoles have extended π-electron systems which are appreciably polarized, they are able to form π-molecular complexes of moderate stability. Generally the other member of the complex is a good electron acceptor such as a quinone or polynitrobenzene. These complexes are characterized by enthalpys of formation in the range −1.9 to −4.2 kcal/mol and frequently show long-wavelength (visible) absorption bands. Such bands are called charge-transfer bands and are considered to arise from promotion of an electron from the highest occupied molecular orbital of the indole (donor) to the lowest unoccupied molecular orbital of the other member of the complex (acceptor).

Some controversy exists concerning the importance of the charge-transfer bands in the formation and stabilization of such complexes. Thus it has been indicated that they should be regarded as a special kind of donor–acceptor complex held together by charge-transfer forces.[138] However, a recent critique[139] points out that there is no compelling evidence for this interpretation. Rather, the complexes are held together by van der Waals forces of the types: (*1*) simple electrostatic interactions between polar molecules (dipole-dipole interactions), (*2*) dipole-induced dipole forces (where one

molecule is polar), and (*3*) Heitler-London dispersion forces between nonpolar molecules. The only requirement for the new long-wavelength bands is that the molecules be close together, which is easy in a complex held together by van der Waals forces. The terms donor–acceptor complex, charge transfer complexes, and π-complexes are considered to be misleading.[139]

In the case of indole complexes with polar molecules such as quinones, nitrobenzenes, and tetracyanoethylene, the dipole-dipole interaction forces should predominate over the other two types. With the indole-iodine complex the forces might be of the dipole-induced dipole type. The dispersion forces should be less important with polar molecules like indoles. Although there may be no enhancement of stability for these complexes in the ground state by charge transfer, it is known (Section II.F.3) that indole is highly polarized in the first excited singlet state, so the fraction of complexes existing in the excited state may be more tightly held together than those in the ground state.

Benzoquinone solutions containing indole, tryptophan, or indole-3-acetic acid showed no visible evidence of complex formation at room temperature, but gave colored complexes when frozen. This complex formation was reversible and not dependent upon time.[140] Chloranil in carbon tetrachloride at 20° gave a colored complex (λ_{max} 496 mμ) with indole, which intensified in color upon cooling.[141] Thermochemical data for this complex are given in Table XIV. Colored complexes were also observed between a series of

TABLE XIV. Thermodynamic Values for Indole π-Molecular Complexes

Complex	Solvent	Temp. (°C)	K (l./mol)	ΔH	ΔS	Ref.
Chloranil–Indole	CCl_4	20	2.86	−1.9	−4.4	145
TCNE[a]–Indole	CH_2Cl_2	25	2.75	−3.1		141
TCNE–4-Methoxyindole	CH_2Cl_2	6	8.27			141
TCNE–5-Methoxyindole	CH_2Cl_2	25	5.05	−4.2		141
Riboflavin–2-Methylindole	6:4 Ethanol-12 *M* HCl	27	603	−1.02	+9.3	148
Lumiflavin–3-Methylindole		27	67.1	−1.99	+1.7	148
Riboflavin–3-Methylindole		27	35.5	−1.92	+0.7	148
Lumiflavin–Tryptophan		27	28.2	−2.60	−2.0	148
Riboflavin–Tryptophan		27	15.3	−2.22	−2.0	148

[a] Tetracyanoethylene.

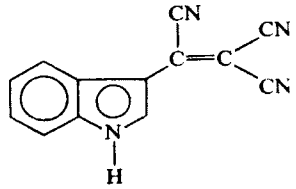
methyl-substituted indoles and a series of benzoquinones in methylene chloride. The wavelengths of charge-transfer bands for a given quinone

acceptor showed bathochromic shifts with increased methylation of the indole donor.[141]

Association constants for complexes of indole and simple alkylindoles with 1,4-dinitrobenzene and 1,3,5-trinitrobenzene in chloroform were determined from chemical shifts in the nmr spectrum of the indole protons at $C_{(3)}$ and on the benzene ring.[142] These constants varied from 2.40 kg/mol for 3-methylindole to 1.65 kg/mol for indole with 1,3,5-trinitrobenzene and from 0.47 to 0.32 kg/mol for the same indoles with 1,4-dinitrobenzene. Localized interactions in the formation of these complexes were indicated by pronounced chemical shifts in the protons at $C_{(2)}$ and $C_{(3)}$.[142] The π-electron distribution at these indole positions is expected to be most readily perturbed according to molecular orbital calculations of superdelocalizability. X-Ray crystallographic analysis of indole and 3-methylindole complexes with 1,3,5-trinitrobenzene (Section II.A) also indicates localized interaction between the indole 3-position and an unsubstituted carbon atom of 1,3,5-trinitrobenzene.[25] The internuclear distances of 3.30 Å are the right order for complexes held together by van der Walls forces.

Stable crystalline orange complexes were observed between 1-fluoro-2,4-dinitrobenzene and indole or its methyl homologs. The infrared spectra of these complexes did not contain any bands other than those of the components.[143]

When methylene chloride solutions of indole (1 *M*) and tetracyanoethylene (5×10^{-4} *M*) are mixed, a royal blue color (λ_{max} 560 mμ) appears immediately. This color gradually fades and after several days a yellow solution containing 3-tricyanovinylindole (**90**) is obtained. These observations



90

have been interpreted as indicating that the π-molecular complex initially formed proceeds by way of a σ complex to the observed product.[144]

Comparison of the association constants with the charge-transfer band wavelengths for a series of complexes of indole and monó- and dimethoxyindoles with tetracyanoethylene (TCNE) indicated no direct correlation between these two properties.[145] Methoxy groups increased stability of the complexes, apparently by enhancing the polarity of the indole molecules.

Thermochemical data for several of these complexes are given in Table XIV. Association constants in methylene chloride varied from 4.20 l/mol for indole at 4.75° to 17.29 l/mol for 4,5-dimethoxyindole at 6°.[145]

Complexes between indole and iodine absorb light around 370 mμ. The exact wavelength and intensity of this absorption is uncertain because the I_3^- ion absorbs at 367 mμ. A black solid which also forms shows a large unpaired-electron concentration. This solid is not considered to be the simple π-molecular complex.[141]

Correlation of the wavelengths of charge-transfer bands of indole π-molecular complexes with calculations of the relative energy levels of the highest occupied molecular orbital of the indoles has received attention.[138–145] When a series of complexes involving the same acceptor but different (indole) donors is used, there is generally a linear correlation between the ionization potential of the donor and the position of the charge-transfer band. The calculated values of the appropriate molecular orbitals are related to the ionization potentials and may be used instead.[146] With indoles the correlations are generally good.

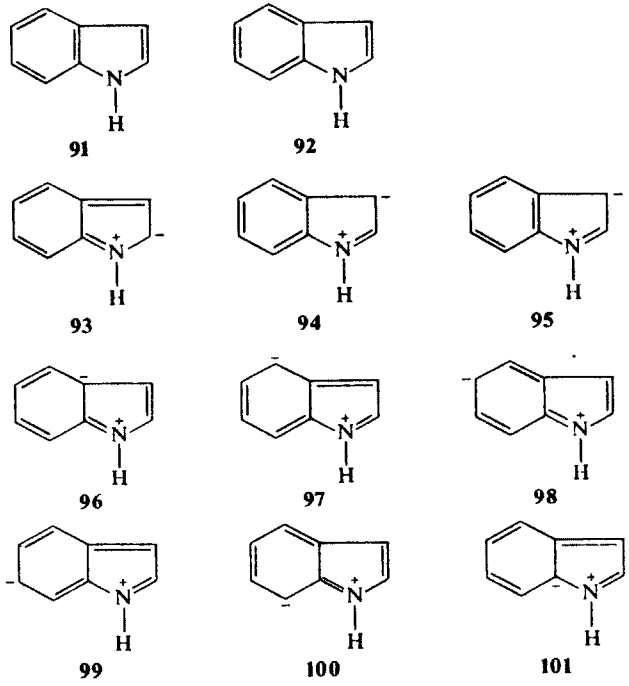
Complex formation between diphosphopyridine nucleotide or *N*-methylnicotinamide and indoles such as serotonin, tryptamine, and tryptophan has been studied (147). Intense yellow color (310–450 mμ) which varied in intensity with pH and concentration was observed for these complexes. In neutral or acidic aqueous alcohol, 1 : 1 complexes between certain indoles and riboflavin, lumiflavin, and FMN were observed. Those complexes involving lumiflavin and 3-methylindole or tryptamine hydrochloride could be obtained in crystalline form.[148] The visible spectra of the various complexes showed the flavin absorption tailing into the longer-wavelength region. Several new bands at longer wavelength were present, but they were considered not to be charge-transfer bands. Stabilities of the complexes were in the range 10–1000 l/mol.[148] Their thermodynamic properties are listed in Table XIV. It is apparent from this table that entropy is the principal factor in determining stability of the indole–flavin complexes.

An evocative hypothesis concerning the mode of action of certain drugs, including indole derivatives, proposes that they form "charge-transfer complexes" with biological acceptors, and that their ability to form such complexes is related to the energy of their highest occupied molecular orbitals.[149] Following this hypothesis a number of attempts to correlate the biological activities of indoles with their electronic properties, including not only orbital energies but also reactivity indices relating to localized interactions, have been made.[138, 145, 150, 151] These attempts have met with limited success,[145] probably because complex formation is only one of the factors involved in drug action even in a closely related series of compounds.

III. Theoretical Treatments of Properties and Reactions

A. Resonance

Resonance theory has been valuable in explaining certain of the properties and reactions of indoles qualitatively. In this theory the mathematical function that represents the properties of the π-electrons of an aromatic system is approximated as a linear combination of the functions of suitable contributing structures. For indole many contributing structures are possible. The two main uncharged contributors and nine contributors with separation of charge are depicted in Scheme 14. These charged contributors bear the



Scheme 14. Resonance contributors to the indole hybrid structure.

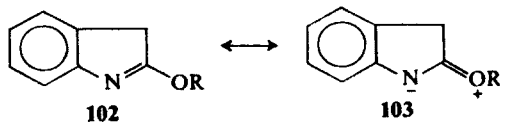
positive charge on nitrogen, reflecting the known electron-donating properties of the indole nitrogen. Not shown are contributors bearing positive charge on

carbon and contributors with interactions across the rings (Dewar structures).

Contributors **91** and **92**, which do not have separation of charges, are undoubtedly the most important two. Since they both have the 2,3-double bond intact, it is expected that in the resonance hybrid a high degree of double-bond character will be found for this bond, and the 3, 3*a* bond will have appreciable single-bond character. These expectations are realized in the X-ray crystallographic determination of indole structures (Section II.A).

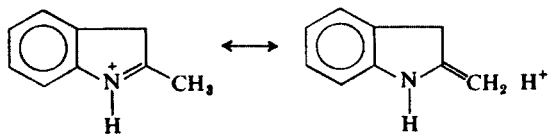
The most important charged forms should be **94** and **95**, which maintain an unbroken benzene ring. Since both of these forms bear the negative charge on $C_{(3)}$, it is anticipated that this position should be the most electron rich. Observation that the proton on $C_{(3)}$ of indole is the one most highly shielded in the nmr spectrum (Section II.F.4) is consistent with this concept.

The interactions of the indole nucleus with substituents are readily understood in terms of resonance. Thus the high melting points, relative acidity, and decreased carbonyl group reactivity of indole-3-carboxaldehydes and 3-acylindoles reflect the importance of contributors such as **19** in which electrons have moved from the nitrogen to the carbonyl oxygen. The relative stability of the indolenine tautomers of indoles with electron-donating substituents such as methoxy and amino at $C_{(2)}$ may be due to the importance of resonance interaction between the indolenine nuclear nitrogen and the substituent (**102** → **103**). A similar interaction explains the stability of the



102 **103**

cations derived from 2-aminoindoles (Section II.E).[37] The effect of a 2-methyl group in enhancing indole basicity has been attributed to its ability to stabilize the indolium salt by hyperconjugation (**104** → **105**).[35]



104 **105**

Ambident-type reactivity of indolyl anion is best understood in terms of a resonance hybrid formed from contributors bearing negative charge on the nitrogen and contributors negatively charged on $C_{(3)}$ (Section IV.D).

B. Molecular Orbital Theory

1. *Introduction*

Although resonance theory is useful for a qualitative understanding of certain molecular properties and reactions, it is of less value in their quantitative estimations because the relative contributions of various charged structures can not be simply determined. For a molecule such as indole the charged structures are particularly important, hence a different theoretical approach is required for its quantitative treatment. The Hückel molecular orbital theory has filled this requirement with some success.

In the Hückel theory the atoms of a conjugated hydrocarbon are firmly bonded by a σ-electron framework in which sp^2 bonding is localized between adjacent atoms. The remaining $2p_z$ orbitals are combined in linear fashion to form molecular orbitals which extend over all of the conjugated portion of the molecule. These LCAO (linear combination of atomic orbitals) molecular orbitals are equal in number to the atoms in the system and they are assumed not to interact with the σ-electron framework. Each atom contributes one π-electron to the molecular orbital system, and these electrons are placed two in each orbital (paired spins), starting with the lowest energy level, until all have been allocated according to the Pauli exclusion principle.

The N linearly independent molecular orbitals are assumed to have the form $\psi(j) = C_{j1}\varphi_1 + C_{j2}\varphi_2 + \cdots + C_{jN}\varphi_N$, where C_{ji} are the coefficients of the atomic orbitals φ_i in molecular orbital number ψ_j. Calculation of the coefficients and the energy levels of the molecular orbitals is accomplished by solving a secular determinant based upon these equations. This secular determinant is expressed in terms of two empirical energy parameters, the Coulomb and resonance integrals. The Coulomb integral (α) represents the effective energy of a bound electron in an atomic orbital and is related, but not equal, to the ionization energy. The resonance integral (β) applies to directly bonded atoms and is assumed to be zero otherwise. For a heteroatom such as the indole nitrogen the greater electronegativity relative to carbon is treated by defining a Coulomb integral α_N in terms of the Coulomb integral for carbon and the resonance integral β, that is $\alpha_N = \alpha_C + h\beta$. The principal difficulty then is selecting the proper value of constant h. Derivation of the secular determinant and its solution for energy levels of molecular orbitals and the coefficients of the atomic orbitals in various molecular orbitals are given in standard references.[152–154]

Energy levels of the molecular orbitals of indole and isoindole are shown in terms of the empirical energy parameters α and β in Figure 9. For both

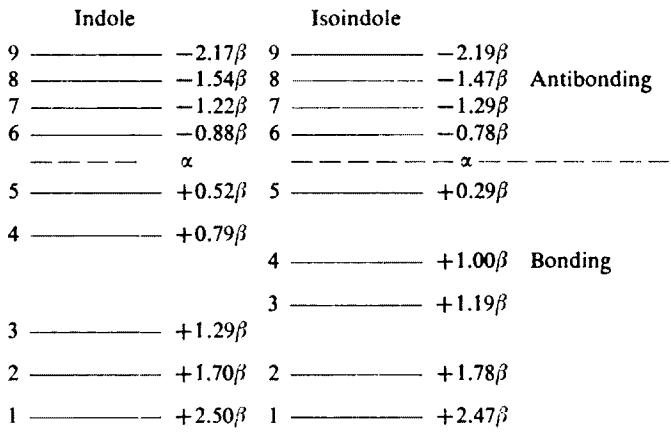


Figure 9. The energies of molecular orbitals of indole and isoindole.[155]

compounds, these levels fall into two groups, one of which is of lower energy than α (α and β are negative) and contains the bonding orbitals. The other group contains the antibonding orbitals. Distribution of the 10 π-electrons of these compounds according to the selection rules completely fills the bonding orbitals.[155]

Two properties immediately obvious from Figure 9 are that both indole and isoindole should be better electron donors and better electron acceptors than benzene. With respect to naphthalene and quinoline, indole and isoindole should be better electron donors, but poorer electron acceptors.

2. *Calculation of Properties*

Among the properties of indole which have been calculated by the application of molecular orbital theory are bond lengths and bond orders, resonance energies, charge densities, and uv absorption spectrum. Resonance energies and bond lengths were estimated by an advanced method in which both the σ and π electrons were included.[156] The resonance energy was 1.709 eV/mol or 1.807 eV/mol, depending upon the values used for repulsion integrals. Bond lengths were in good agreement with values obtained from X-ray analysis (Section II.A). Calculated bond orders for indole have been given by several authors.[68, 155, 157]

Total π-electron densities for indole, calculated by a variety of molecular orbital methods, are given in Table XV. Although there is considerable variation among these results, all methods predict a predominance of charge density at $C_{(3)}$. The greatest divergence of results is at $C_{(2)}$, where calculated

TABLE XV. Calculated π-Electron Densities for Indole

Position	Total π-electron density ϵ			
	LCAO-MO[a]	LCAO-MO with AIP[b]	SCF[c]	VESCF[d]
1	1.573	1.742	1.914	1.751
2	1.002	1.059	1.038	1.041
3	1.189	1.066	1.056	1.071
3*a*	1.068	—	1.032	1.031
4	1.025	1.009	0.984	1.008
5	1.044	1.015	1.020	1.018
6	1.035	1.013	0.992	1.014
7	1.041	1.010	1.034	1.032
7*a*	1.023	—	1.030	1.034

[a] Parameters $\alpha_N = \alpha_c + 1.0\beta$, $\beta_{CN} = \beta_{cc}$.[155]

[b] Parameters $\alpha_N = \alpha_c + 2.0\beta$, $\alpha_{c\,\text{adj.}} = \alpha_c - 0.25\beta$, $\beta_{cN} = \beta_{cc}$; *c* adj. is a carbon atom bonded to nitrogen; AIP stands for auxiliary inductive parameter (the *c* adj. correction).[158]

[c] Ref. 159.

[d] Ref. 160.

charge densities range all the way from second highest in the advanced SCF methods to lowest in the LCAO-MO calculations. This represents one of the more serious failures of the latter method; however, inclusion of suitable auxiliary parameters restores the charge density at $C_{(2)}$ for LCAO-MO calculations. The simpler MO calculations also predict a much greater delocalization of π-electrons from nitrogen to the carbon atoms (especially $C_{(3)}$) of indole.

Applications of molecular orbital calculations to the nmr and uv absorption spectra of indole are discussed in Sections II.F.4 and II.F.2, respectively.

The bond orders and total π-electron densities have also been calculated for isoindole by the LCAO-MO method.[155] Comparison of the total π-electron densities (Fig. 10), with those of indole determined by the same method (Table XV, Column 1) reveals that in isoindole a slightly greater delocalization of electrons from nitrogen to carbon occurs. Since most of this electron density builds up on the adjacent carbon atoms, the pyrrole ring of isoindole rather closely resembles pyrrole itself.[4]

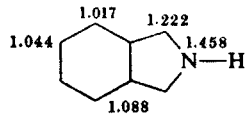
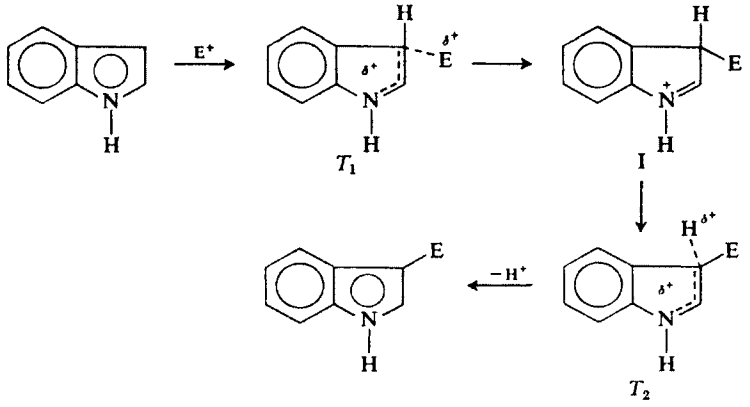


Figure 10. Total π-electron densities of isoindole.[155]

3. *Calculation of Reactivity*

A variety of theoretical reactivity indices, including total π-electron densities, localization energies, frontier electron densities, and superdelocalizabilities, have been applied to the interpretation of electrophilic substitutions in indoles. All of these indices successfully predict $C_{(3)}$ to be the preferred site of substitution and this prediction holds for LCAO-MO as well as SCF calculations.

The apparent success of the various indices does not mean that they are all equally acceptable in terms of transition state theory. There is controversy over the importance of total π-electron density in the starting material as a determining factor in orientation of substituents. It is possible that its success in predicting the site of electrophilic substitution of heterocyclic systems is merely fortuitous.[161] In certain other fields, such as the nucleophilic substitution of azines, total π-electron densities are of little predictive value.[162]



Scheme 15

A hypothetical pathway for the electrophilic substitution of indole at $C_{(3)}$ is shown in Scheme 15. In this pathway, metastable intermediate I is formed by way of transition state T_1, the point of highest energy in the reaction profile. Conversion of I to product occurs through a transition state T_2 which is probably of lower energy than T_1 since, at least in the case of diazo coupling at $C_{(3)}$, breaking of the $C_{(3)}$—H bond shows no isotope effect.[163] One of the main differences between intermediate σ-complex I and starting indole is the loss in total π-electron energy resulting from destruction of conjugation in the pyrrole ring. This kind of energy difference provides the basis for a readily obtained reaction index, the atom localization energy (L_E).[164] The localization energy for electrophilic substitution at $C_{(3)}$ is thus equal to the difference in

total π-electron energy between starting indole and intermediate I and is equivalent to the energy required to localize one pair of electrons on $C_{(3)}$. For electrophilic substitution at some other position, for example $C_{(2)}$, a similar relationship holds. Since aromaticity in the benzene ring would be destroyed in the intermediate σ-complex for $C_{(2)}$ substitution, it is anticipated that a higher L_E would be found at $C_{(2)}$ than at $C_{(3)}$. Benzene-ring aromaticity is not destroyed by electrophilic attack at $N_{(1)}$, hence a relatively low L_E might be expected for this position. In this context it may be recalled (Section II.E) that protonation of indole, a process in which a pair of electrons is effectively localized, appears to be favored at $C_{(3)}$ in solution, but certain indolium salts ($N_{(1)}$ protonation) could be isolated from these solutions by instantaneous precipitation.

Comparison of the localization energy at $C_{(3)}$ of indole (1.40β) with that of naphthalene (2.30β) helps explain why the former is more highly susceptible to electrophilic substitution.

The frontier electron theory predicts that the position most susceptible to electrophilic attack is the one that has the highest electron density, based upon calculations involving only the highest occupied molecule orbital in the ground state.[165] Since this frontier electron density is a property of the isolated molecule, its use as a reactivity index is based upon the assumption that the transition state resembles the starting material more than the intermediate σ-complex, or at least that there is no crossover in the energy profile curves. However, the frontier electron densities are associated with electron exchange rather than electrostatic interaction, and to the extent that electron exchange is important in stabilizing the transition state, they are important in determining the site of substitution. The frontier electron densities of indole, calculated by the LCAO-MO method, are shown in Figure 11.

Superdelocalizability, which has been derived from perturbation theory, probably reflects the relative energies of the various transition states more accurately than does frontier electron density. In superdelocalizability all of the molecular orbitals are considered to contribute to the ease of electron exchange at a given atom, but each contribution is weighted according to the reciprocal of the energy of the MO.[166] Values of superdelocalizability for electrophilic substitution at different carbon atoms of several indoles are

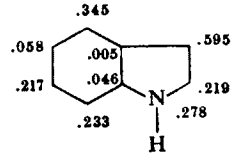


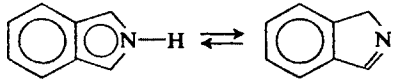
Figure 11. Frontier electron density of indole for electrophilic substitution.[165]

TABLE XVI. Calculated Superdelocalizabilities for Indoles[145]

Compound	Superdelocalizability at position					
	2	3	4	5	6	7
Indole	1.148	1.238	1.032	0.911	0.966	0.968
5-Methoxyindole	1.144	1.252	1.194	0.898	1.058	0.974
Tryptamine	1.298	1.256	1.040	0.908	0.974	0.974
5-Methoxytryptamine	1.300	1.273	1.254	0.888	1.089	0.981

given in Table XVI. The pronounced effects of substituents are apparent in this table.

Orientation in reactions between aromatic systems and free radicals is generally best correlated with the free valences of atoms in these systems. The free valence (Fr) of an atom is defined as the difference between the maximum value ($\sqrt{3}$) possible for the sum of all the bond orders between an atom and its neighbors and the actual sum for the particular atom under consideration. The larger the free-valence index of an atom, the smaller the change in π-electron energy upon substituting this atom, and the easier the reaction.[153] Free-valence indices for indole, calculated by the LCAO-MO method, are shown in Figure 12. In contrast to indices for electrophilic substitution, free valence does not simply predict the highest reactivity at $C_{(3)}$. Instead it suggests nearly equal free radical reactivity for $C_{(2)}$, $C_{(3)}$, and the four available positions in the benzene ring. This suggestion is consistent with the observed pattern of free radical substitution of indole wherein mixtures of products substituted at various positions in both rings are obtained (Section IV.K).



106 **107**

Molecular orbital theory has been applied to interpretation of the tautomerism and instability of isoindoles. According to LCAO-MO calculations, isoindole **106** should have a delocalization (resonance) energy 0.387β greater than that of isoindolenine **107**, and 1-phenylisoindole should be more stable

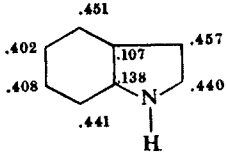


Figure 12. Free valences in indole.[153]

than 1-phenylisoindolenine by 0.440β. These calculations are consistent with the apparent predominance of isoindole-type tautomers in most compounds studied.[115] The main examples of favored isoindolenine tautomers occur where there are electron-releasing substituents at $C_{(1)}$. The instability of isoindole relative to indole and pyrrole cannot be explained by indices such as π-electron densities and delocalization energies, since there is little difference between the electron density patterns of pyrrole and the heterocyclic ring of isoindole, or between the delocalization energies of indole and isoindole. However, relatively high electron deficiencies at $C_{(1)}$ of the isoindolenine tautomers has been suggested as the cause of instability.[4] Those compounds in which the isoindolenine form makes a negligible contribution to the tautomeric equilibrium, for example 2-methylisoindole, appear to be relatively stable. The only stable compounds existing appreciably in the isoindolenine form are substituted at $C_{(1)}$ with electron-releasing groups which reduce electron deficiency at this position. Since isoindoles have an occupied molecular orbital of relatively high energy (Fig. 9), it is apparent why they can readily transfer an electron to oxygen in autoxidation processes (Section IV.F.1); however, such processes do not completely account for the instability of isoindoles, since the presence of electron-donating groups at $C_{(1)}$ appears to enhance stability.

A study on reduction of certain 1-methylindoles with lithium in ammonia (Section IV.G.2) revealed that formation of a radical anion by addition of one electron to the indole π system was rapid, whereas addition of a second electron was much slower. In both cases the equilibrium lay on the side of the starting indole. These observations are consistent with LCAO-MO calculations of the energy level for the lowest unoccupied molecular orbital in the indole π-electron system.[167] This level (0.87β) is intermediate between those of benzene (1.0β), which gives only a radical anion under the same conditions, and naphthalene (0.62β), which readily forms a dianion. Correlation of the sites of protonation in the indole radical anion and dianion with their total π-electron densities was attempted, based upon the supposition that in such highly exothermic processes the relative energies of transition states for reaction at the several carbon atoms would reflect the π-electron densities in their vicinities.[167]

IV. Reactions

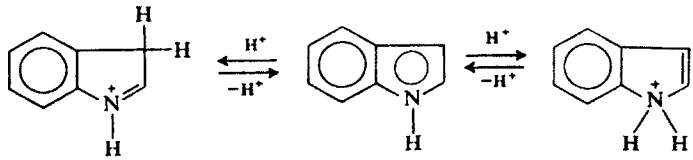
A. Protonation

Protonation is one of the most important processes in indole chemistry. A number of reactions including dimerization, trimerization, hydrogenation,

and cleavage of substituents of $C_{(3)}$ are initiated by protonation of the indole nucleus. Furthermore, the orientation and ease of electrophilic substitution (particularly nitration in sulfuric acid) is strongly influenced by nuclear protonation. In this section only the ease and position of protonation are discussed. The effect of protonation on other reactions is considered in the sections dealing with those reactions.

There exists some ambiguity in names given to the conjugate acids of indoles. In particular, both the 3- and 1-protonated species have been called indolium ions. Throughout the present treatment indolium ion will be reserved for *N*-protonated species, whereas the 3-protonated species, which possess the indolenine structure, will be designated indoleninium ions.

Many indoles dimerize in moderately strong acids, but in acids strong enough to afford complete protonation the monoprotonated species have appreciable stability. The pK_a's for protonation of various indoles are given in Section II.E They vary from -7.4 for 5-nitroindole to $+0.30$ for 1,2-dimethylindole. The protonation of indoles may be viewed as an equilibrium process in which the difference in energy in acidic medium between the neutral indole and the cations **108** and **109** determines the extent of protonation



108 **109** (2)

(Eq. 2). Contributions from protonation at $C_{(2)}$ are probably very small. The presence of electron-donating groups, particularly at $C_{(2)}$, stabilizes the cation and also decreases the π-electron energy of the neutral indole. In Section II.E the the dependence of pK_a upon structure is examined in detail.

Although the indole NH can be exchanged by deuterium in D_2O, rapid exchange of the proton at $C_{(3)}$ requires acid catalysis. A solution of indole in D_2O containing 5×10^{-3} *M* sulfuric acid at reflux temperature exchanges both the 1- and 3-protons.[57] Indole is more basic than 3-methylindole with respect to equilibrium protonation at $C_{(3)}$; however, the rate of exchange of the NH proton in 3-methylindole is faster than that of indole in dioxane solutions containing 10^{-4} *M* sulfuric acid. The enhanced rate of N-protonation may reflect a higher electron density on the nitrogen atom of 3-methylindole.[168] In somewhat stronger acid solutions all three pyrrole ring protons may be exchanged.[6]

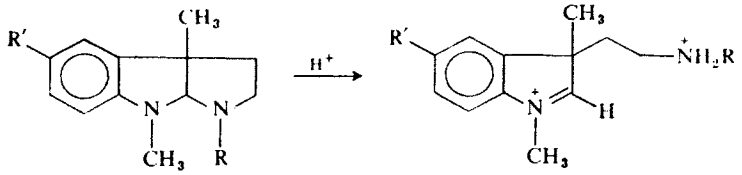
Most of the studies on the protonation of indoles in strongly acidic solutions have utilized sulfuric or perchloric acids,[35] although 85%

phosphoric acid was chosen for studies with 2-arylindoles.[169] Trifluoroacetic acid completely protonates indoles of high pK_a such as 2-methylindole, but it is not strong enough to fully protonate indole or 3-methylindole.[170]

In strong sulfuric or perchloric acid solutions where complete protonation occurs, the proton added appears to be largely at $C_{(3)}$. The uv and nmr evidence for the structure of the resulting indoleninium cation (**108**) is given in Sections II.F.2 and II.F.4. Deuterium exchange experiments indicated that in strong acid the deuterium adds to $C_{(3)}$ and the indoleninium cation then loses a proton from either $C_{(3)}$ or nitrogen. The $C_{(2)}$ position also exchanges by a competitive deuteration at this site. The $C_{(2)}$ deuteration is much slower than $C_{(3)}$ deuteration in indole or 1-methylindole, but is relatively accelerated in 3-methylindole.[6]

Instantaneous precipitation of acid salts of indole from solutions in sulfuric acid or perchloric acid of high concentration gave products in which the position of protonation depended upon both the nature of the acid and the structure of the indole. Thus all perchlorates studied were 3-protonated. The acid sulfates of 1,2-dimethylindole and of 1,2,3-trimethylindole showed N-protonation, whereas the acid sulfate of 2-methylindole showed both 1- and 3-protonated species. These variations in site of protonation were explained by assuming an equilibrium between 1- and 3-protonated forms in solution, with the 1-protonated form preferentially precipitating in some cases because of its lower solubility in ether.[6, 57] The ir evidence for the structures of these salts is given in Section II.F.1.

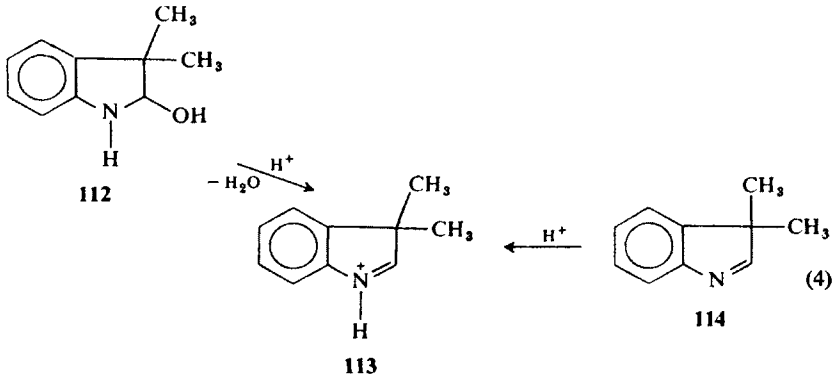
Tryptamines protonate completely at $C_{(3)}$ in 18 *N* sulfuric acid and these protonations are reversible.[170] In strong hydrochloric acid solutions the uv absorption spectra of certain physostigmine derivatives (**110**) change to spectra of indolenines and tryptamines. Acid catalyzed ring opening of the physostigmine system begins at 1 *M* acid, and by 5 *M* acid the indoleninium salt (**111**) (Eq. 3) is completely formed.[170] Indoleninium salts (**113**) are also



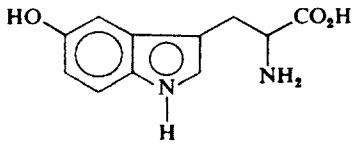
110 **111** (3)

obtained upon treatment of 2-hydroxy-3,3-dimethylindoline (**112**) or 3,3-dimethylindolenine (**114**) with strong acids (Eq. 4).

In 5-hydroxytryptophan (**115**) the hydroxyl group increases electron density in the benzene ring, especially at the 4- and 6-positions, to a level at which acid catalyzed deuterium exchange can readily occur. Solutions of **114** in



D_2O containing 1 *M* DCl gave complete exchange of the 4-proton after 45 min at room temperature and complete exchange of the other nuclear

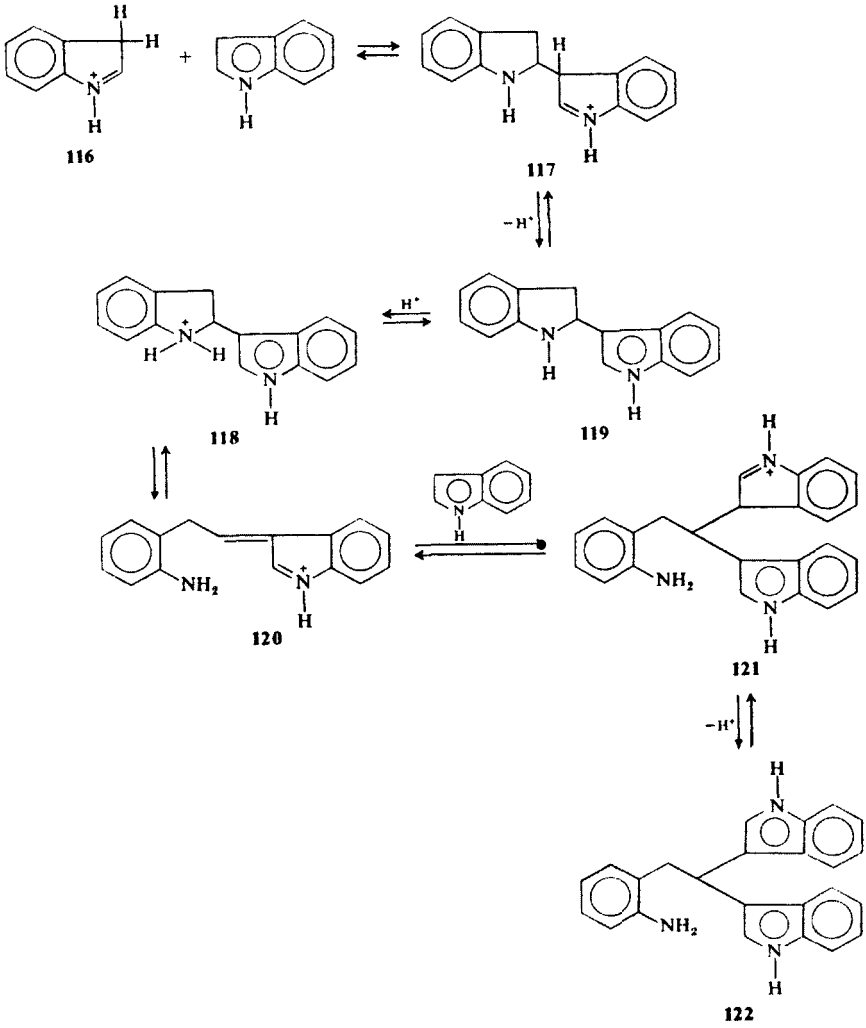


protons at 100° at the following times: C-6, 3 mins; C-2, 19 mins; C-7, 1 hr. No exchange of aliphatic protons occurred.[105]

B. Dimerization and Trimerization

Indole forms the hydrochloride salt of dimer **119** when treated with dry hydrogen chloride in aprotic solvents.[171] In aqueous acids a more complicated situation is encountered, for an equilibrium is established among indole, dimer **119**, trimer **122**, and their salts.[172] The product composition is then determined by the relative solubilities of the dimer and trimer salts.[173] Both the dimerization and trimerization are catalyzed by acid and their rates depend upon the acid concentration.

Scheme 16 shows the generally accepted pathway[172] for the formation of indole dimer and trimer. Protonation of indole at $C_{(3)}$ initiates the sequence of reactions, affording indoleninium cation **116**. This cation is a good electrophile and it accepts electrons at $C_{(2)}$ which bears a substantial portion of the positive charge (Section III.13). The electrophilic attack by this cation occurs at $C_{(3)}$ of an unprotonated indole molecule. Loss of a proton from intermediate **117** then affords indole dimer **119**. Reprotonation at the more

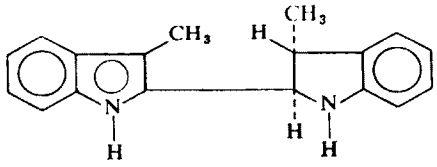


Scheme 16

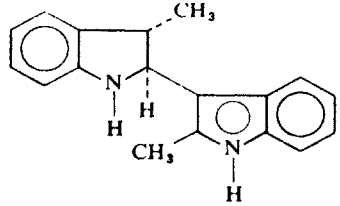
basic indoline nitrogen gives dimer salt **118**. This salt is in equilibrium with **120** in which the indoline ring has opened and the positive charge is borne by the indole nitrogen. Electrophilic attack of **120** on another unprotonated indole molecule then furnishes **121**, which loses a proton in going to trimer **122**. Salts of trimer **122** result from protonation of the anilino nitrogen. All steps in this scheme are reversible. The structure of the dimer was established by degradition studies,[174] whereas the trimer structure was suggested by degradation[175] and confirmed by synthesis.[176]

Acid catalyzed dimerization of 3-methylindole occurs readily, but the resulting dimer (**123**) has both moieties joined at their 2-positions.[177] Electrophilic substitution by the 3-methylindoleninium ion at the 2-position of unprotonated 3-methylindole has evidently occurred, which is consistent with the generalization that large electrophiles attack 3-methylindole at the 2-position because of steric factors.[178] It has also been suggested[128] that the 3-methylindoleninium ion attacks at the 3-position and then rearranges to the 2-position, analogous to the rearrangements of 3,3-dialkylindolenines. However, experimental evidence has not been adduced in the case of this dimerization. The structure of this dimer was determined by careful analysis of its nmr spectrum.[177]

2-Methylindole does not dimerize, presumably because the anticipated dimer has appreciable steric crowding. This dimer has been synthesized by another route. It is relatively unstable, as indicated by reversion to monomer upon distillation.[172] A crossed dimer (**124**) between 2-methylindole and 3-methylindole has been prepared in the presence of hydrogen chloride in benzene.[177] Since 2-methylindole is the more basic molecule (Section II.E), it is protonated to a greater extent and is largely unavailable for reaction with protonated 3-methylindole, hence the major product is 3-methylindole dimer (**123**).[177] However 2-methylindole is highly reactive toward electrophiles and evidently is present in sufficient concentration to give an appreciable amount of **124**.

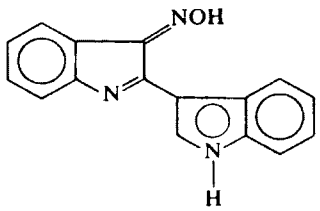


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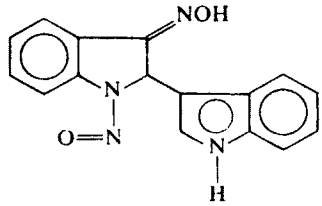


124

Dimerization of indole accompanies certain reactions involving electrophilic substitution. For example, nitrosation in aqueous acetic acid gives both "indole red" (**125**) and "dinitrosoindole" (**126**).[179] Condensation of indole

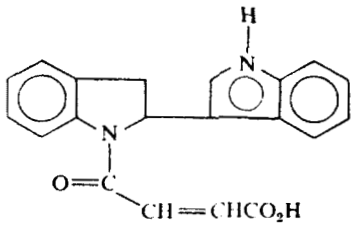


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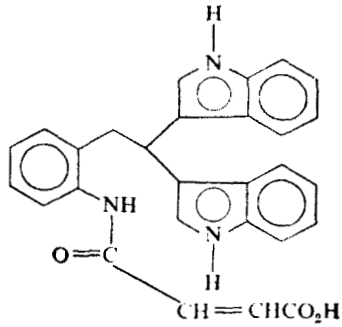


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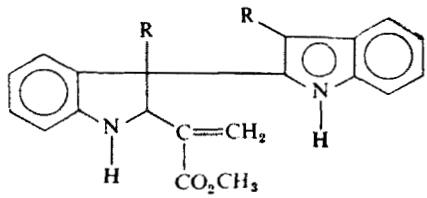
with maleic anhydride in ethyl acetate at low temperature yields acylated indole dimer **127** whereas at room temperature the same system affords acylated indole trimer **128**.[180] Treatment of 3-[2-(4-oxopiperidino)ethyl]indole with pyruvic acid in methanolic hydrogen chloride gave dimer **129**.[181]



127

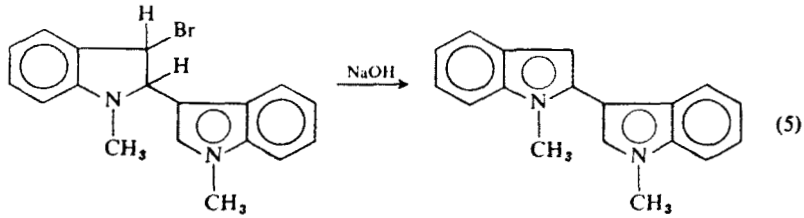


128



129; R = 2-(4-oxopiperidino)ethyl

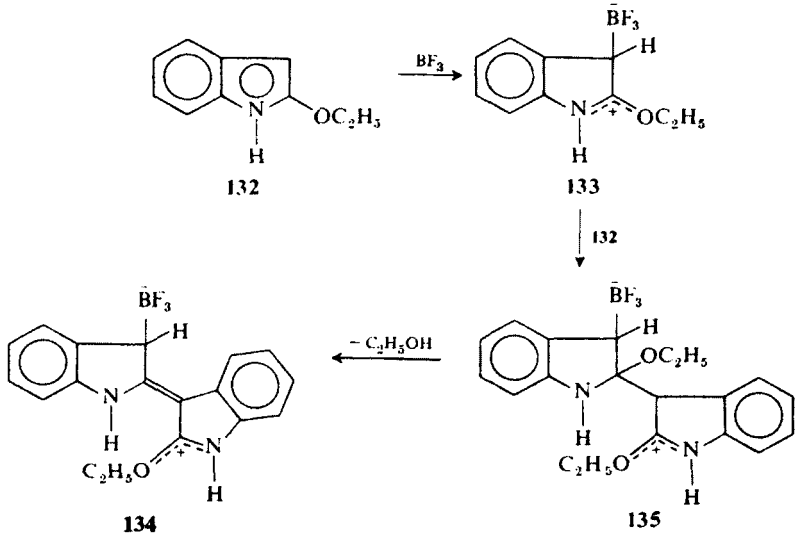
Bromination of 1-methylindole with dioxane dibromide in tetrahydrofuran furnished monobrominated dimer **130**, which was converted by aqueous sodium hydroxide to 1,1′-dimethyl-2,3′-diindolyl (**131**)[182] (Eq. 5). A parallel route to **131** was afforded by chlorination with sulfuryl chloride followed by treatment of the monochlorodimer with sodium bicarbonate.[183]



(5)

130 **131**

2-Ethoxyindole (**132**) dimerizes when treated with boron trifluoride etherate. The reaction is initiated by addition of BF_3 to the 3-position, after which the relatively electropositive 2-carbon of the resulting intermediate **133**



Scheme 17

attacks a neutral molecule of **132** to give dimer **135**. Loss of ethanol from **135** finally affords the isolated boron-containing dimer **134**[184] (Scheme 17).

C. Electrophilic Substitution

1. *General Considerations*

Electrophilic substitutions constitute by far the largest and most important group of indole reactions. The high electron density and low localization energy for electrophilic substitution (Section III.B) render indoles susceptible to attack by a wide variety of electrophiles, including such weak ones as alkyl halides, α,β-unsaturated carbonyl compounds, and α-carbonylcarbenes.

If the indole is unsubstituted at $C_{(3)}$, this atom is generally the preferred site of substitution. The $N_{(1)}$ position is next most active, but many of the reactions on this nitrogen are reversible. Consequently products of N-substitution are isolated in only a few cases. If the indole already bears a substituent at $C_{(3)}$, then products of electrophilic substitution at $C_{(2)}$ are generally found. In some cases it has been demonstrated that the $C_{(2)}$ substituent was formed by rearrangement of a 3,3-disubstituted indolenine, whereas in certain other instances it is supposed that substitution at $C_{(3)}$ is rapid, but reversible, whereas substitution at $C_{(2)}$ is practically irreversible. Most of the electrophilic substitutions of indole can be correlated with the supposition that its $N_{(1)}$, $C_{(2)}$, $C_{(3)}$ system behaves as an enamine triad.[185]

This approach represents an oversimplification of the problem, since the triad is contained within a heterocyclic ring. However, observations that the 2,3-bond has considerable double-bond character and that disruption of aromaticity in its benzene ring is not a favorable process suggest that indole can be viewed with some confidence as an enamine fused at both ends to adjacent positions on a benzene ring.

Mannich reactions of indoles bearing hydroxyl groups in the benzene ring represent a special case wherein the aminomethyl group is introduced next to the hydroxyl group, even if $C_{(3)}$ is unsubstituted.

Many of the electrophilic substitution reactions are acid catalyzed, which means that their application to indoles may lead to dimerization or polymerization (Section IV.B). Therefore careful control of acidity is required, as in nitration and bromination of simple indoles. Electron-withdrawing substituents in the pyrrole ring retard protonation and polymerization of indoles, but they also decrease reactivity toward the electrophile and may prevent reaction or direct it into the benzene ring. Indoles are reasonably stable in concentrated sulfuric acid, which completely protonates them. The resulting indoleninium ions then are substituted at $C_{(5)}$ in the benzene ring.

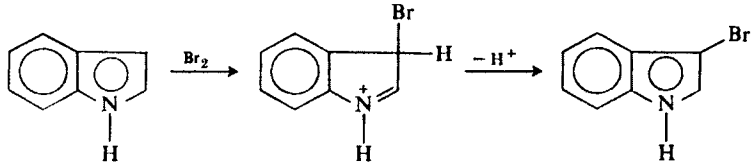
Anions and Grignard reagents of indole, which are highly reactive toward electrophiles, are considered in a separate Section (IV.E).

2. *Halogenation*

a. BROMINATION. The bromination of indole presents difficulties in that indole, as well as certain of its bromo derivatives, is unstable in the presence of hydrobromic acid. For a number of years the best method for the preparation of 3-bromoindole (**137**) was bromination of *N*-benzoylindole with bromine[186] or *N*-bromosuccinimide (NBS)[187] followed by hydrolysis of the benzoyl group. More recently it has been found that mild brominating agents such as dioxane dibromide or pyridinium bromide perbromide in the presence of an acid scavenger such as pyridine at 0–2° afford 3-bromoindole directly in moderate yields.[188]

Several mechanisms have been proposed for the bromination of indoles,[189, 190] but there is not sufficient experimental evidence to support any of them in detail. Mechanisms in which the indole is treated as an enamine or an aromatic system seem preferable to those in which the 2,3-double bond is considered to participate in forming a cyclic bromonium ion as do isolated double bonds. However, bromine (and nitric acid) appears to add to the 2,3-bond of 2,3-dimethylindole.[191]

For indole the bromination can be viewed as involving 3-bromoindoleninium ion **136**, without specifying exactly how this ion is formed. Loss of a proton



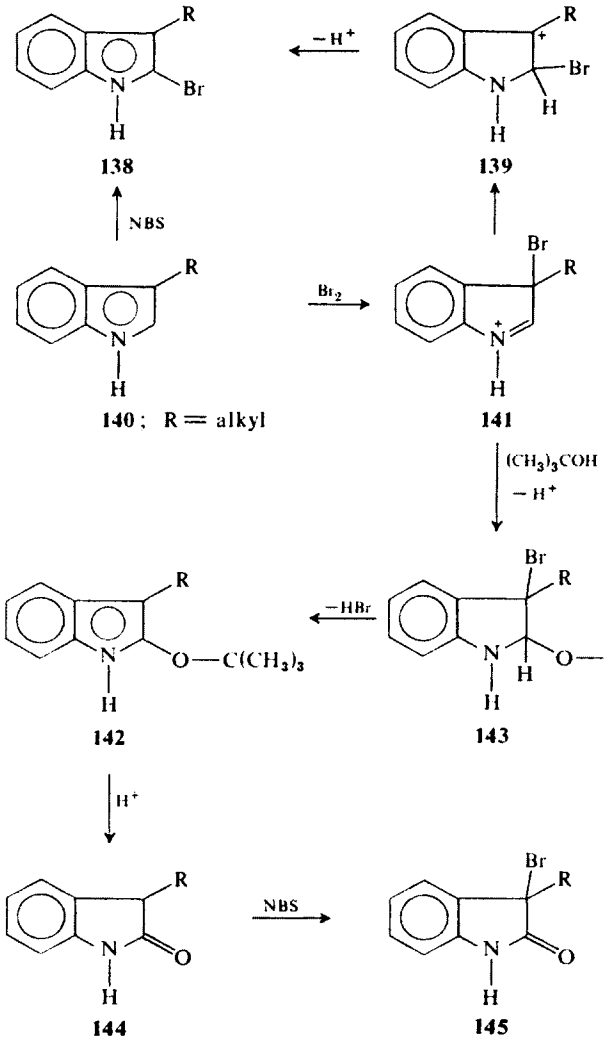
136 137 (6)

from $C_{(3)}$ of **136** then affords 3-bromoindole (**137**) (Eq. 6). A variety of products, mostly resulting from reactions at $C_{(2)}$, is obtained from bromination of 3-methylindole and other 3-substituted indoles. Thus in glacial acetic acid, 3-alkylindoles **140** gave with NBS the corresponding 2-bromo compounds (**138**) plus 2,6-dibromo derivatives[57] (Eq. 7). Treatment of the same 3-substituted indoles in dry *t*-butyl alcohol with one equivalent of NBS afforded oxindoles (**144**). A second equivalent of NBS converted these oxindoles to the corresponding 3-bromooxindoles (**145**)[57] (Eq. 8). Bromination of 3-indolepropionic acid (**146a**) and 3-indolebutyric acid (**146b**) with two equivalents of NBS in aqueous solution gave the oxindole lactones **150a** and **150b**, respectively. These lactones were also obtained by treatment of 3-bromooxindoles **149** with sodium acetate or water.[57, 192]

The formation of these products may be explained by a scheme based upon initial bromination at $C_{(3)}$, followed in certain cases by migration of the bromine to $C_{(2)}$ in the intermediate bromoindoleninium ions (**141** → **139**)[190] however, direct bromination at $C_{(2)}$ is not ruled out by the experimental evidence in at least one instance. In the absence of nucleophiles this migration takes place and loss of a proton from **139** then affords the 2-bromo-3-alkylindole **138**. When a nucleophile such as *t*-butyl alcohol is present, the 3-bromoindoleninium ions **141** might be intercepted before they undergo rearrangement. Bromo ethers **143** would then be formed. These bromo ethers would first give 2-*t*-butoxyindoles **142**, which would afford oxindoles **144** upon acid-catalyzed ether cleavage. For the 3-indolealkanoic acids, bromination in water or *t*-butyl alcohol might initially give oxindoles **147**, which would undergo further bromination at $C_{(3)}$ in the presence of excess NBS. In a nonpolar medium such as *t*-butyl alcohol, dissociation of the carboxylic acid groups might be suppressed allowing the isolation of 3-bromooxindoles **149**; however, in aqueous solution the carboxylate anions **148** could be present in sufficient concentration to cause displacement of bromide ion, affording oxindole lactones **150**[57] (Scheme 18).

Bromination at the 3-position of oxindoles **144** requires catalysis by HBr and apparently proceeds through the enol tautomer.[57] The benzene ring is brominated rather than the 3-position only in relatively polar media under acidic or neutral conditions. Thus 3-methylindole gave 5-bromo-3-methyloxindole when treated with 2.5 equivalents of NBS in aqueous acetic acid.

When 3-methyl-2-phenylindole was treated with bromine in acetic acid a thermally unstable yellow precipitate was obtained. This precipitate was

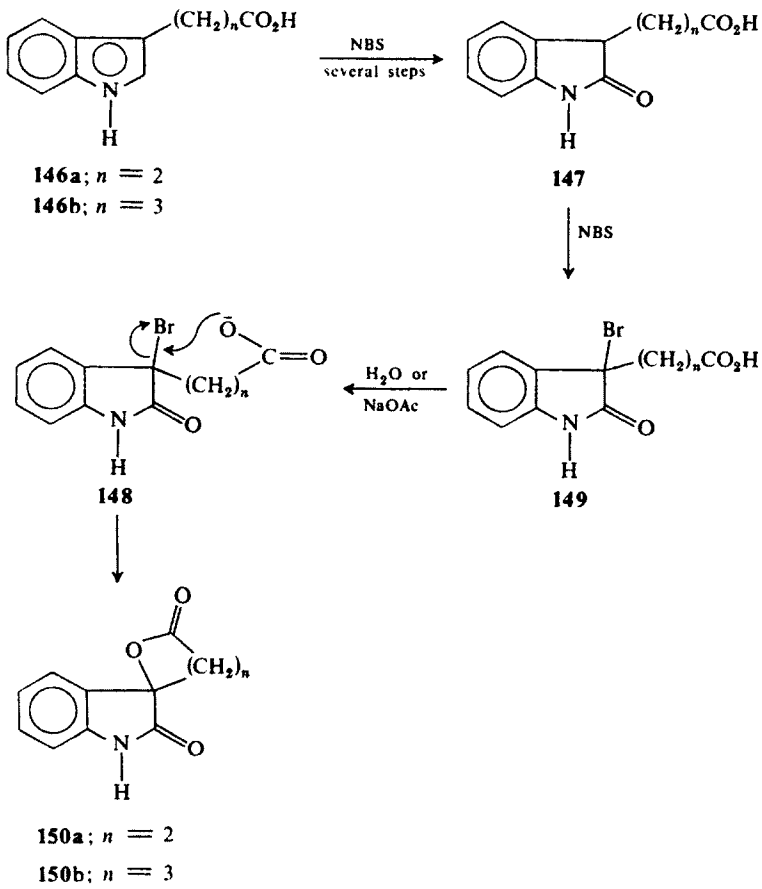


(7)

(8)

found to be the dibromide complex **151**, and was an intermediate in the formation of the final product, 6-bromo-3-methyl-2-phenylindole.[192]

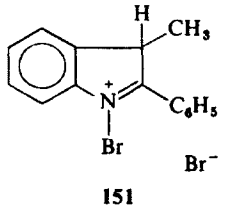
An unstable yellow precipitate was also obtained in the bromination of 3-methylindole with bromine in ether at $-60°$. Treatment of this precipitate with piperidine or with 10% sodium hydroxide gave good yields of 2-bromo-3-methylindole, (**138**, R = CH_3), whereas with 10% hydrochloric acid 78% of 3-methyloxindole (**144**, R = CH_3) was obtained.[193] When pyridine was



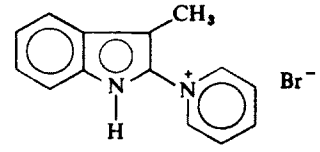
Scheme 18

used as the base, bromination of 3-methylindole with NBS or with dioxane dibromide gave the 2-pyridinium salt **152**.[193–195] Hydrolysis of this salt with hydrochloric acid gave 3-methyloxindole in high yield.[195]

Indoles substituted at $C_{(3)}$ with strong electron-withdrawing groups have the 2-position sufficiently deactivated that bromination occurs in the benzene ring. Thus bromine in acetic acid converted ethyl indole-3-carboxylate to



151



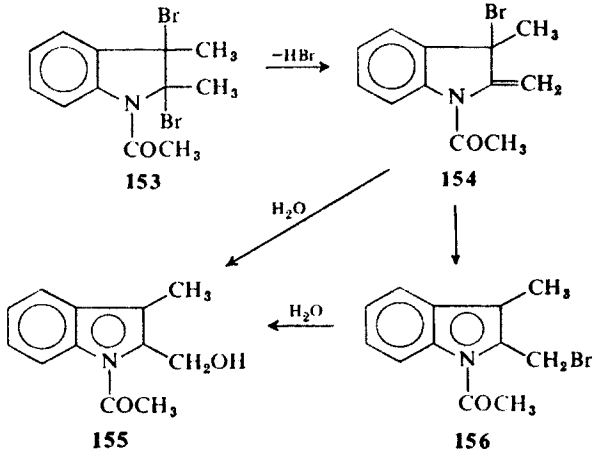
152

the 6-bromo derivative and gave low yields of the 5- and 6-bromo derivatives with indole-3-carboxaldehyde.[196] Further bromination of these indole-3-carboxaldehyde derivatives gave the 5,6-dibromide and some 2,3,5,6-tetrabromide. In the last compound the aldehyde group was cleaved.[196]

In contrast to the 3-carboxylate, ethyl indole-2-carboxylate first gave bromination in the pyrrole ring. The resulting 3-bromo compound was converted to the 3,5-dibromide with a second equivalent of bromine. Excess bromine in carbon tetrachloride gave the 1,3,4,5,6,7-hexabromo derivative.[197]

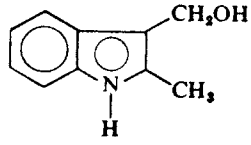
Bromination of 2,3-dimethylindole in sulfuric acid containing silver sulfate gave the 5-bromo derivative as did similar bromination of 1-acetyl-2,3-dimethylindole.[198] The indole nucleus is evidently protonated before bromination under these conditions. With the same conditions 2,3-dimethylindoline gave the corresponding 6-bromo compound.

A different set of results was reported for the bromination of 2,3-dimethylindole and 1-acetyl-2,3-dimethylindole with bromine in acetic acid.[191] The latter compound afforded the 2-bromomethyl derivative (**156**) in the absence of water and the corresponding 2-hydroxymethyl compound (**155**) when water was added. These products have been rationalized in terms of addition of bromine to the 2,3-double bond, followed by elimination of HBr from the dibromide **153** to give either 3-bromo-2-methylene derivative **154** or its allylic rearrangement product **156** (Scheme 19). Replacement of bromine



153 154 155 156

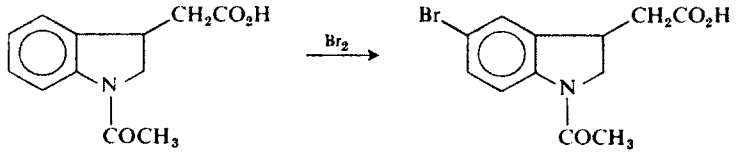
Scheme 19



157

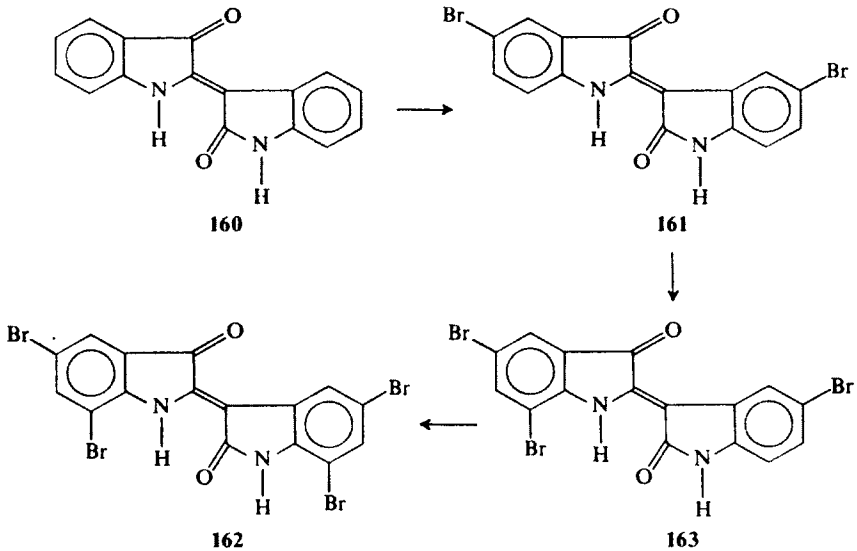
by hydroxyl then occurs in water, accompanied by an allylic rearrangement if this step has not already taken place. From 2,3-dimethylindole the product was considered to be the 3-hydroxymethyl derivative (**157**). It has been pointed out, however, that this structure should be unstable with respect to diindolylmethane formation.[199]

The preferred site for bromination in indolines appears to be $C_{(5)}$, which is *para* to the nitrogen atom. Thus 1-acetylindoline-3-acetic acid (**158**) gave its 5-bromo derivative **159** in 98% yield when treated with bromine in acetic acid[200] (Eq. 9).



158 **159** (9)

Oxindole and its *N*-alkyl derivatives are dibrominated at $C_{(3)}$ by bromine in carbon tetrachloride; however, aqueous bromine gives bromination first at $C_{(5)}$, followed by $C_{(7)}$, and finally $C_{(3)}$.[201] The pattern of bromination first at $C_{(5)}$ and next at $C_{(7)}$ was also observed with isatin[202] and dioxindole.[203] Indigo (**160**) first gives the 5,5′-dibromo derivative (**161**), followed by stepwise bromination of the 7 and 7′ positions to give **162** and **163** (Scheme 20). Vigorous conditions, such as bromine in boiling nitrobenzene or in cold concentrated sulfuric acid, are required for bromination of indigo.[204]

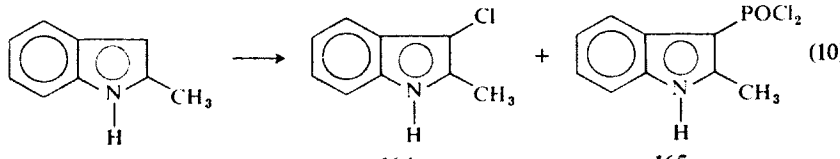


160 **161** **162** **163**

Scheme 20

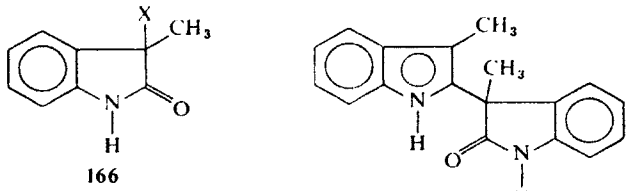
b. CHLORINATION. The products obtained from chlorination of indole and its simple derivatives are closely related to products from the analogous brominations, suggesting that similar mechanisms operate in the two cases. Thus treatment of indole with sulfuryl chloride afforded 3-chloroindole.[205] No 2-chloroindole was obtained, despite a previous claim that both isomers were produced.[206] Chlorination of 2-methylindole with *N*-chlorosuccinimide or phosphorus pentachloride gave 3-chloro-2-methylindole (**164**) plus a little 3-dichlorophosphoryl derivative **165** (Eq. 10). With chlorine or sulfuryl chloride, 2-methylindole polymerized.[207]

The chlorination of 3-methylindole was complex and inconsistent in yields of various products. However, the products isolated closely resembled those obtained from brominations. For example, sulfuryl chloride or phosphorus pentachloride in chlorocarbon solvents afforded 3-chloro-3-methyloxindole (**166**, X = Cl), whereas chlorine gave 3,5-dichloro-3-methyloxindole. With *N*-chlorosuccinimide in methanol a mixture of 3-methoxy-3-methyloxindole (**166**, X = OCH_3) and dimer **167** was obtained.[205]



(10)

164 **165**

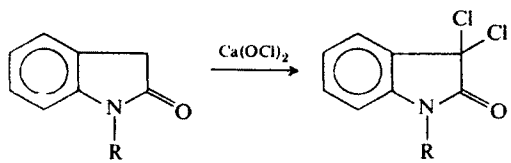


166

167

Ethyl 2-indolecarboxylate gave the 3-chloro derivative when treated with phosphorus pentachloride or sulfuryl chloride at room temperature. The 3,6-dichloro derivative was obtained by heating this 3-chloro product with powdered phosphorus pentachloride at 105–110°.[207]

N-Alkyl oxindoles were converted into 3,3-dichloro derivatives (**168**) when



(11)

168

treated with calcium hypochlorite[208] (Eq. 11). Chlorination of isatin gave 5-chloroisatin, which afforded 5,7-dichloroisatin with excess chlorine.[209]

c. IODINATION. Indole and 2-methylindole were converted by dilute aqueous iodine[210–213] and by potassium triiodide[189] to their 3-iodo derivatives. Oxidation of indole to indigo has also been effected by aqueous iodine.[210] The solid complexes formed between iodine and indole, which display an esr signal, have been suggested as intermediates (radical cations) in the iodination reaction[189]; however, there is not sufficient evidence to confirm this suggestion.

Isatin is iodinated at $C_{(5)}$ by iodine monochloride, but diiodination has not been effected.[209]

3. *Nitration*

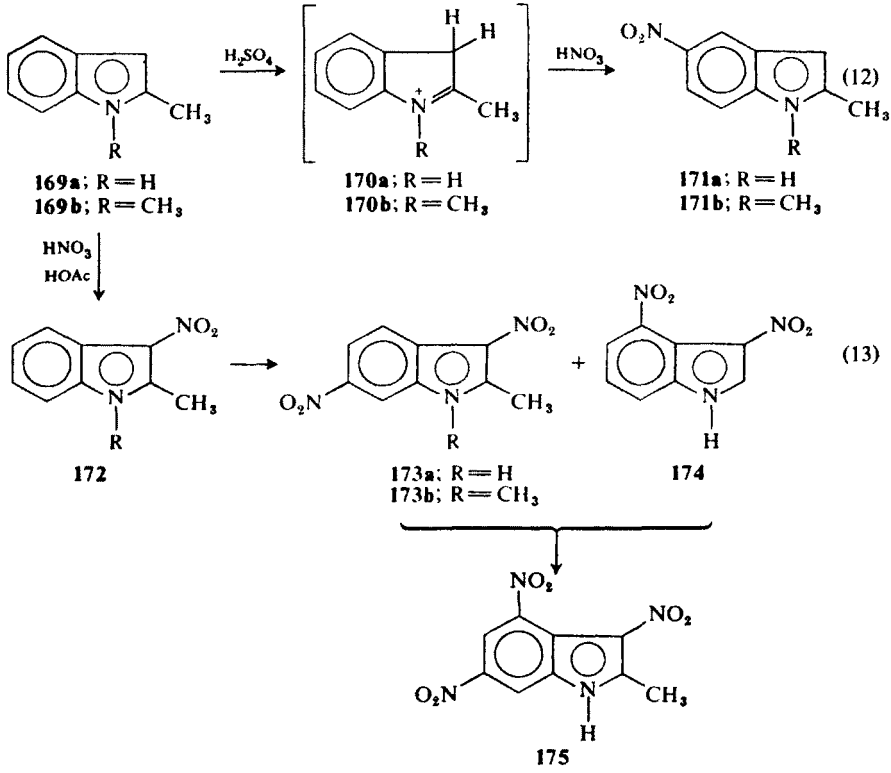
The position and ease of nitration depends upon the nitrating agent and the structure of the indole. Indole and alkyl derivatives unsubstituted at the 2-position afforded only polymeric products when nitration was attempted in sulfuric or acetic acid solutions[214]; however, treatment of indole with preformed benzoyl nitrate in acetonitrile gave a 35% yield of 3-nitroindole.[215] This product has also been prepared from indolyl sodium and amyl nitrate (Section IV.D). Benzoyl nitrate has also been effective for nitrating 1-methylindole and 3-methylindole. The former compound gave a 25% yield of 1-methyl-3-nitroindole and the latter compound gave 4.5% of 3-methyl-2-nitroindole, the first 2-nitroindole isolated.[215]

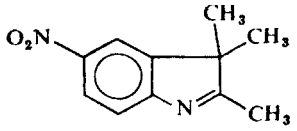
Indoles bearing a substituent at $C_{(2)}$ are stable to nitration in strongly acidic media, possibly because the acid-catalyzed dimerization is suppressed by the steric effect of substituents at this position (Section IV.B). The position and extent of nitration of 2-methylindoles is different in sulfuric acid than it is in acetic acid.[216] Concentrated sulfuric acid completely protonates these indoles at $C_{(3)}$, which deactivates the pyrrole ring and allows nitration of the benzene ring by nitronium ion (present in relatively high concentration). This nitration occurs at the 5-position, indicating that the immonium group on a benzene ring (as in **170**) is predominantly *para* directing. Substantiation of this explanation was obtained by nitration in sulfuric acid of 2,3,3-trimethylindolenine[217] and nitration in nitric acid of 2-phenylisatogen,[218] both of which involve immonium type nitrogens and give 5-nitro derivatives (**176** and **177**, respectively). Thus concentrated nitric acid in sulfuric acid at 0–5° gave high yields of 5-nitro derivatives (**171a** and **171b**) of 2-methylindole and 1,2-dimethylindole (Eq. 12). 2-Methylindole also underwent nitration at $C_{(5)}$.[214]

In concentrated nitric acid or nitric acid in acetic acid there is a very low

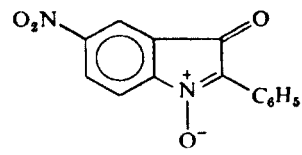
concentration of the nitrating agent as well as a low concentration of unprotonated indole; hence nitration does not occur at low temperatures. It is necessary to heat the reaction mixtures at steam-bath temperature, whereupon vigorous reactions ensue with evolution of nitrogen oxides. Under these conditions oxidation reactions compete with nitration and the yields of nitroindoles are low.[216] If the 3-position is free, 3,6-dinitro derivatives are isolated. Since no mononitroindoles are found, it is presumed that the product of the first nitration (probably the 3-nitro derivative **172**) is not sufficiently basic to undergo protonation. Therefore it is less deactivated than the starting 2-alkylindole and reacts preferentially. 3,6-Dinitration in low yields was observed with 2-methylindole and 1,2-dimethylindole (affording **173a** and **173b**, respectively). A small amount of 3,4-dinitro derivative **174** was also obtained from 2-methylindole. Dinitroindoles **173a** and **174** could be further nitrated to 2-methyl-3,4,6-trinitroindole (**175**) (Eq. 13). 2-Methyl-3,5-dinitroindole is nitrated at $C_{(6)}$ rather than at $C_{(4)}$ because the 4-position is sterically hindered. No tetranitration or 7-nitration has been observed.[216]

Mononitration at the 3-position of 2-methylindole and 1,2-dimethylindole





176

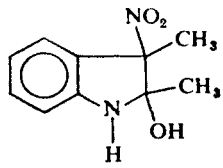


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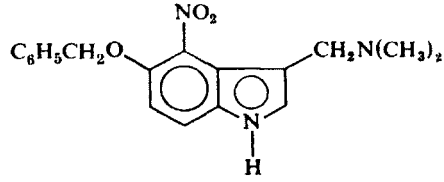
was obtained with benzoyl nitrate. In these cases better yields (33 and 60%, respectively) resulted if the benzoyl nitrate was generated in the presence of the indoles.[218]

Electron-withdrawing substituents, particularly in the pyrrole ring, protect the indole nucleus from oxidative attack, allowing nitration to be effected. The nitro group has already been mentioned as an example. Acetylation of the 1-position of 2,3-dimethylindole permitted the preparation of some 4- and 6-nitro derivatives by nitric acid in acetic acid, although oxidation also occurred. However, the product (**178**) obtained from similar treatment of 1-benzoyl-2,3-dimethylindole was the result of addition of nitric acid to the 2,3-double bond.[191]

A positively charged group in a side chain at $C_{(3)}$ also protects the indole nucleus, apparently by an electrostatic effect.[214] Thus tryptophan nitrate was nitrated in the 6-position by nitric acid in acetic acid, and gramine or 1-methylgramine gave mainly 6-nitration plus some 4-nitration. 5-Benzyloxygramine afforded exclusively the 4-nitro derivative (**179**), which indicates the powerful directing effect of the oxygen at $C_{(5)}$.[219]



178

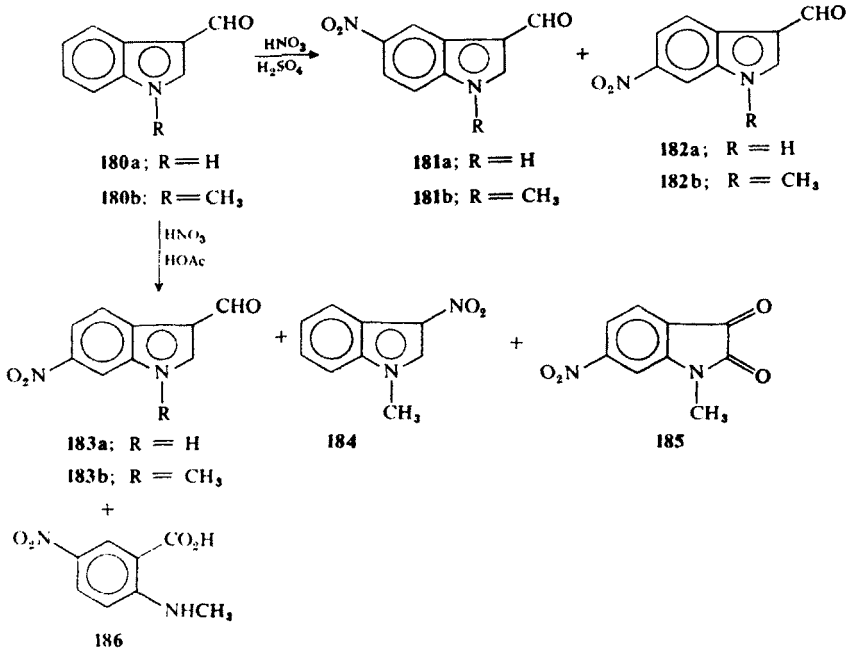


179

Indole-3-carboxaldehyde (**180a**) gave upon nitration in sulfuric acid at 10° a high yield of a mixture containing 66% 5-nitro derivative **181a** and 34% 6-nitro derivative **182a**.[220, 221] The extent and site of protonation of **180a** under these conditions is not known, although protonation of the carbonyl oxygen, with delocalization of the charge onto the nitrogen, should be relatively facile. Nitration of the 1- and 2-methyl and 1,2-dimethyl homologs of **180a** gave over 90% yields of mononitration products with similar ratios of 5- and 6-isomers (**181b** and **182b** for 1-methylindole-2-carboxaldehyde).[222]

When these same indole-3-carboxaldehydes were nitrated with nitric acid in acetic acid at 80°, the yields of mononitro derivatives were low and side

reactions were prevalent. One of the principal side reactions was nitration at $C_{(3)}$ accompanied by cleavage of the carboxaldehyde group.[223] Nitroisatins and nitroanthranilic acids were isolated in several cases. Thus indole-3-carboxaldehyde (**180a**) gave 22–28° of its 6-nitro derivative **183a**[220, 221] whereas 1-methylindole-3-carboxaldehyde afforded 20% of the corresponding 6-nitro compound **183b**, plus small amounts of 1-methyl-3-nitroindole (**184**), 1-methyl-6-nitroisatin (**185**), and *N*-methyl-5-nitroanthranilic acid (**186**)[223] (Scheme 21). 2-Methylindole-3-carboxaldehyde gave a low yield of its 6-nitro

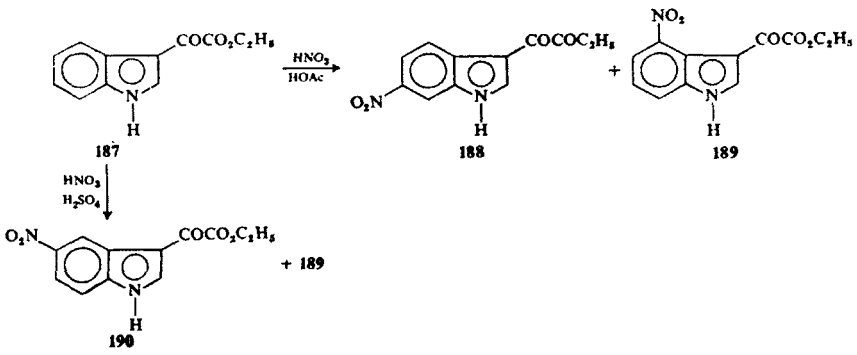


Scheme 21

derivative plus traces of 2-methyl-3-nitroindole and 3,6-dinitro-2-methylindole.[223] From 1,2-dimethylindole-3-carboxaldehyde were obtained 30% of 1,2-dimethyl-3-nitroindole, some 1,2-dimethyl-3,6-dinitroindole, and anthranilic acid derivatives.[223]

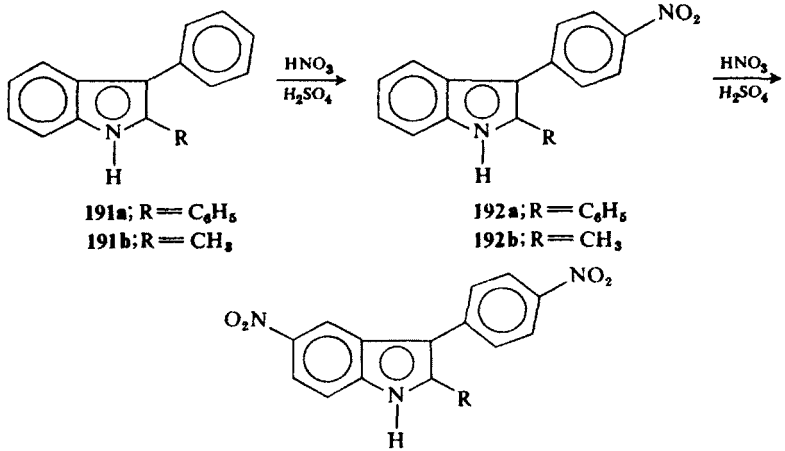
Ethyl indole-3-glyoxylate (**187**) did not undergo cleavage when nitrated in acetic acid. It gave nearly 50% of a mixture containing its 6- and 4-nitro derivatives **188** and **189** in a 4:1 ratio. Nitration of **187** in sulfuric acid afforded a good yield of the 5- and 6-nitro derivatives **190** and **189** in a 66:44 ratio[221] (Scheme 22). Similar nitration of ethyl 5-benzyloxyindole-3-glyoxylate gave only the 4-nitro derivative due to the directing effect of oxygen at $C_{(5)}$.[224]

Indoles substituted at the 2- and 3-positions with phenyl groups present an interesting test of the relative abilities of the various benzene rings to undergo



Scheme 22

nitration. Since protonation of the indole at $C_{(3)}$ puts a relatively high positive charge on $C_{(2)}$, the 2-phenyl substituent is not nitrated in sulfuric acid.[225] 2,3-Diphenylindole (**191a**) and 2-methyl-3-phenylindole (**191b**) gave nitration in the 3-phenyl group (**192**), with nitration of the 5-position occurring subsequently to give **193a** and **193b** (Eq. 14). 3-Methyl-2-phenylindole underwent



191a; R = C_6H_5
191b; R = CH_3

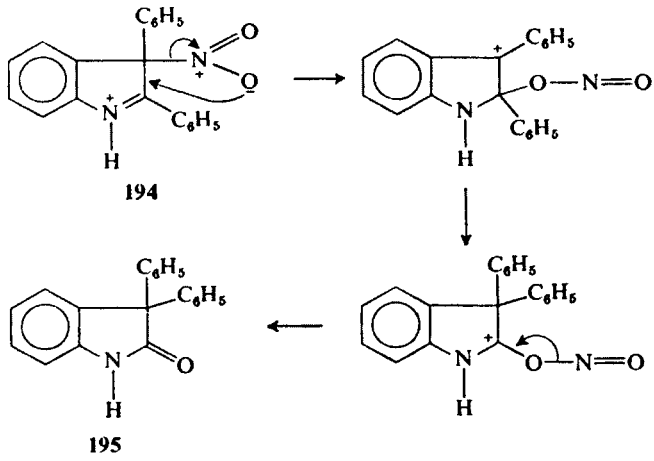
192a; R = C_6H_5
192b; R = CH_3

193a; R = C_6H_5
193b; R = CH_3

(14)

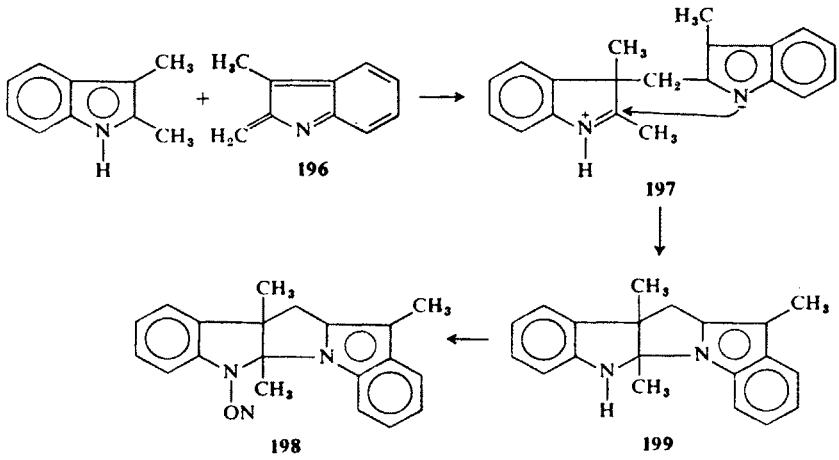
only 5-nitration in sulfuric acid.[225] Cupric nitrate in acetic acid afforded 21% of the 6-nitro derivative of **191a**, whereas preformed benzoyl nitrate converted it mainly to 3,3-diphenyloxindole (**195**). The mechanism suggested[215] for the formation of **195** (Scheme 23) involves a rearrangement (**194–195**) related to the Plancher rearrangement (Section IV.C).

Addition of 2,3-dimethylindole to preformed benzoyl nitrate afforded an



Scheme 23

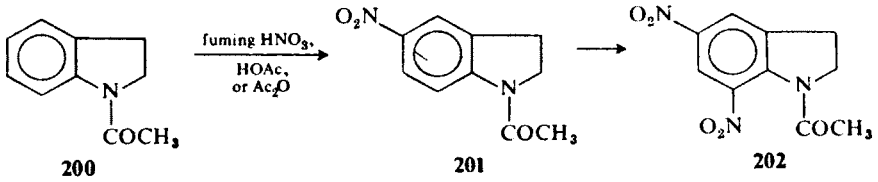
unusual oxidative coupling reaction in which a 20% total yield of **199** and its nitroso derivative **198** were formed. The proposed mechanism[215] for this coupling involves intermediates **196** and **197** (Scheme 24).



Scheme 24

Indoline may be considered as a substituted aniline, hence the preferred sites of nitration would be *para* and *ortho* to the nitrogen. When the nitrogen is protonated by strong acids, the nitro group should be introduced at a *meta* position. These expectations have been realized experimentally. Thus treatment of indoline with nitric acid in sulfuric acid below 0° afforded 95% of 6-nitroindoline.[226, 227] 1-Acetylindoline (**200**) gave the corresponding 5-nitro derivative **201** in yields of 68–80% when treated with fuming nitric

acid in acetic acid or acetic anhydride.[200, 226, 228] A small amount of 1-acetyl-5,7-dinitroindoline (**202**) was also obtained from the reaction in acetic anhydride. Direct nitration of **201** furnished **202** in 42% yield[228] (Eq. 15).



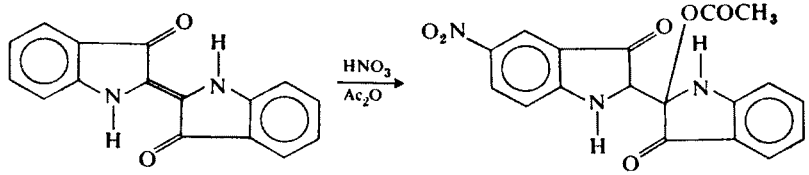
200 **201** **202**

(15)

Nitration of 5-bromoindoline-3-acetic acid also afforded a 7-nitro derivative.[200] It may be recalled that indoles could not be nitrated in the 7-position.

Oxindole and isatin also behave like substituted anilines in nitration, affording 5-nitro and 5,7-dinitro derivatives.[229, 230]

Oxidative cleavage of the 2,2'-double bond precludes nitration of indigo by most procedures. However, nitric acid in acetic anhydride gives a product (**203**) in which 5-nitration is accompanied by addition of the elements of acetic



203

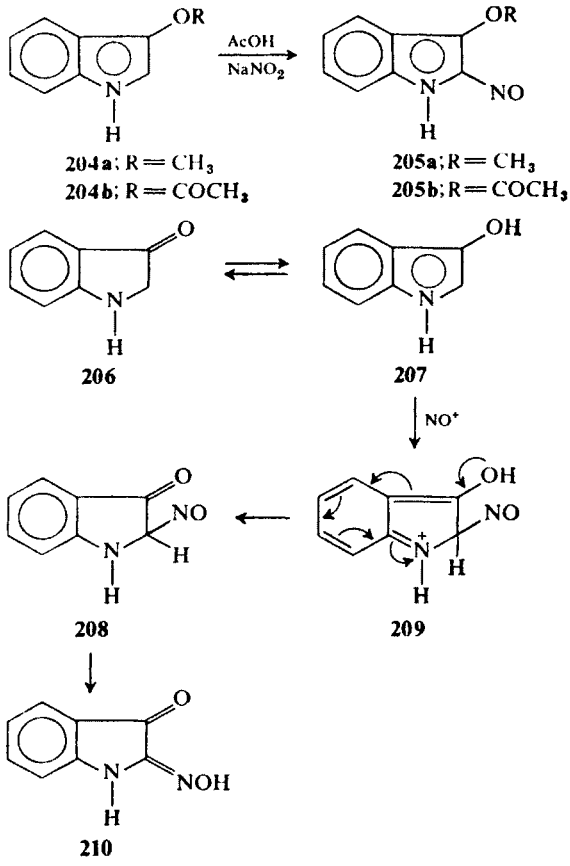
(16)

acid across this double bond. Increasing the amount of nitric acid results in stepwise formation of the 5,5'-dinitro and 5,5',7-trinitro analogs of **203**[202] (Eq. 16).

4. *Nitrosation*

Only a few examples of the nitrosation of indoles have been reported, and these were with indoles bearing oxygen at $C_{(3)}$. Thus sodium nitrite and acetic acid converted 3-methoxyindole (**204a**) and 3-acetoxyindole (**204b**) into their 2-nitroso derivatives **205a** and **205b**, respectively (Eq. 17). Indoxyl (**206**) was also nitrosated, presumably by way of its 3-hydroxyindole tautomer (**207**), with the product assuming the oximino form (**210**)[231] (Scheme 25). Electrophilic substitution at $C_{(2)}$ should be more facile in structures such as **204a**, **204b**, and **207** than in most other indoles due to supply of electrons into the π-system from the oxygen atom at $C_{(3)}$.

Indolines are converted into their *N*-nitroso derivatives by nitrous acid.

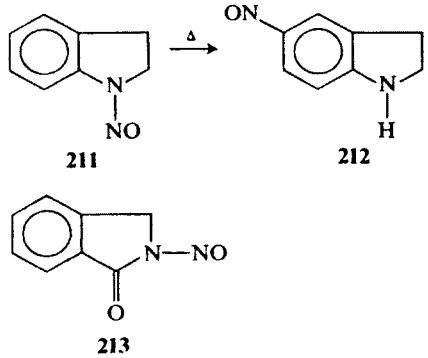


(17)

Scheme 25

These derivatives are relatively unstable and readily rearrange to the corresponding 5-nitrosoindolines (**211** → **212**)[232] (Eq. 18).

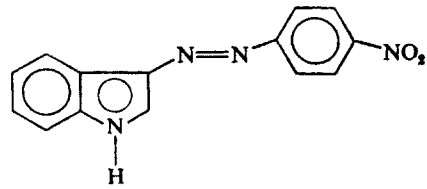
Nitrosation of phthalimidine affords a stable *N*-nitroso derivative (**213**).[233]



(18)

5. *Diazo Coupling*

The coupling between indole and *p*-nitrobenzenediazonium chloride is the only electrophilic substitution of indole for which kinetic studies have been made.[163] Between pH 4 and 6 at 0° this reaction is first order with respect to both indole and the diazonium ion and it is independent of pH in this region. A nearly quantitative yield of 3-*p*-nitrophenylazoindole (**214**) is obtained.



214

The coupling reaction is not appreciably slowed if 3-deuteroindole is used which indicates that the attack of the diazonium ion on indole is rate determining and deprotonation is a faster step. Reaction below pH 6 involves the neutral indole molecule, but above this pH its conjugate base is thought to compete for diazonium ion and the kinetics become complicated.

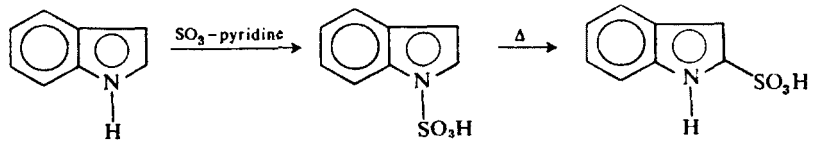
The coupling at pH 4 to 6 thus appears to represent a typical electrophilic substitution of an aromatic nucleus, and it is unnecessary to invoke addition to the double bond as was done for certain bromination reactions of indoles (Section IV.C.2).

Several other diazo couplings have been reported for indole. These include reactions with benzenediazonium chloride,[234] diazotized arsanilic acid,[235] and *p*-bromophenylazoxycarboxamide in alkaline solution.[236] A color test for indole is based upon its coupling with diazotized sulfanilic acid.[237]

Typical aniline type behavior is shown by indolines upon treatment with benzenediazonium ion. *N*-Azo derivatives are formed, but they readily rearrange to the corresponding 5-azo derivatives.[238]

6. *Electrophilic Sulfur and Selenium Reagents*

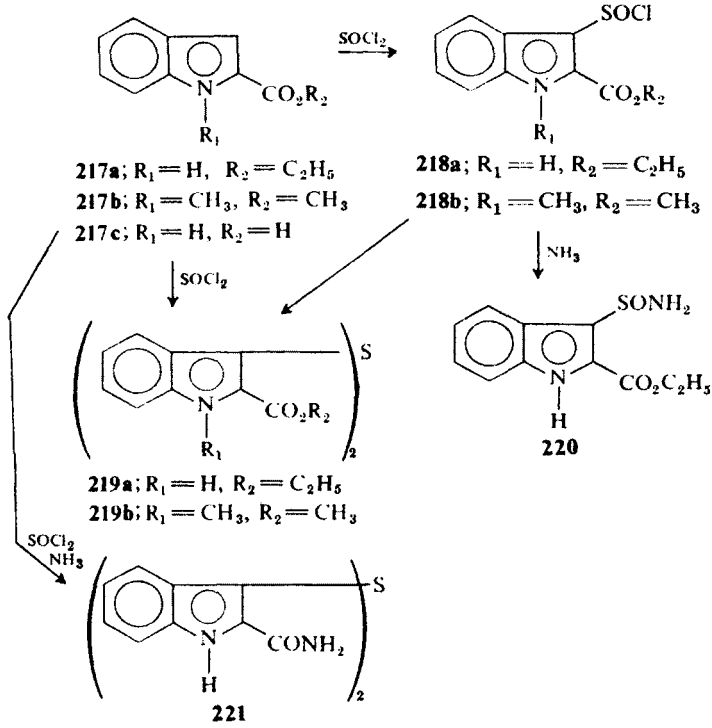
a. SULFUR TRIOXIDE. Sulfonation of indole with pyridine–sulfur trioxide complex below 50° affords indole-1-sulfonic acid (**215**). At higher temperature indole-2-sulfonic acid (**216**) is obtained (Eq. 19). Since the 2-position of indole is not normally the preferred site of electrophilic substitution, it seems probable that **216** is formed from **215** by intramolecular rearrangement of the sulfonyl group. Additional evidence for this supposition is provided by the



(19)

failure of 2-methylindole to undergo sulfonation, whereas 3-methylindole (usually much less reactive toward electrophilic substitution than 2-methylindole) is sulfonated at $C_{(2)}$.[239]

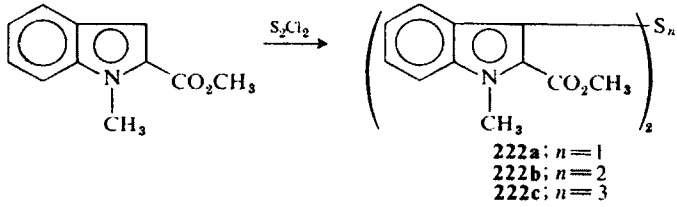
b. THIONYL CHLORIDE. Indoles that are stabilized by an electron-withdrawing group such as carboxyl at $C_{(2)}$ undergo normal electrophilic substitution at $C_{(3)}$ when treated with thionyl chloride. The initial products are apparently chlorosulfinyl derivatives (e.g., **218**), but in some instances two of these molecules lose sulfur dioxide and chlorine to form bis(indolyl)-sulfides (e.g., **219**). Thus under virtually the same conditions (thionyl chloride in refluxing benzene) one investigator obtained from ethyl indole-2-carboxylate the 3-sulfinyl chloride (**218a**),[240] whereas another investigator obtained



Scheme 26

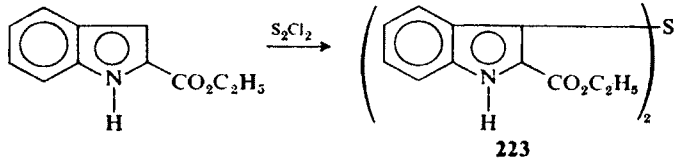
bis(2-ethoxycarbonyl-3-indolyl)sulfide (**219a**).[241] Methyl 1-methylindole-2-carboxylate (**217b**) gave its 3-chlorosulfinyl derivative (**218b**) under these conditions. This compound was stable enough to be isolated and converted into a variety of sulfinamides, but upon drying in vacuum it formed bis(indolyl)sulfide (**219b**).[240] Treatment of indole-2-carboxylic acid (**217c**) with thionyl chloride in benzene followed by ammonia afforded bis(2-aminocarbonyl-3-indolyl)sulfide (**221**),[239] whereas with the corresponding ester the 3-sulfinamide (**220**) was obtained[242] (Scheme 26). These examples further illustrate the subtle variations in indole structure and experimental conditions which determine the type of product isolated from the thionyl chloride reactions.

c. Sulfur Monochloride. Sulfur monochloride introduces sulfur into indoles in a rather complex manner. Bisindolyl compounds joined by a varying number of sulfur atoms are obtained. Thus methyl 1-methylindole-2-carboxylate afforded a mixture of mono (**222a**), di (**222b**), and tri (**222c**) sulfides[240] (Eq. 20). Only the monosulfide **223** was isolated from the reaction of ethyl indole-2-carboxylate with sulfur monochloride[243] (Eq. 21). 3-Methylindole afforded 2,2′-diindolyl compounds (**224**) joined by one, two,



(20)

222a; $n=1$
222b; $n=2$
222c; $n=3$



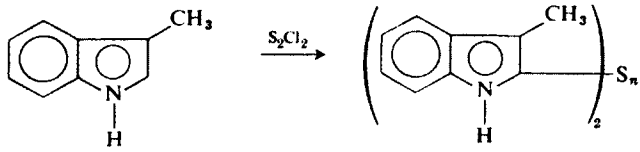
(21)

223

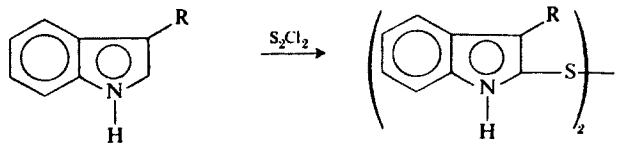
and three sulfur atoms (Eq. 22), whereas 3-phenylindole and indole-3-acetic acid gave the corresponding 2,2′-diindolyl disulfides **225a** and **225b**, respectively[244] (Eq. 23).

d. Thiocyanogen and Selenocyanogen. Thiocyanogen, generated from potassium thiocyanate and bromine in methanol, reacted with indole at −70° to form 3-thiocyanoindole (**226**) in 89% yield. Cupric thiocyanate also converted indole to **226**. Some 3,3′-diindolyl disulfide (**227**) was obtained from the latter method, presumably by way of **226**, since the conversion of **226** to **227** was found to be very facile. Indole-2-carboxylic acid gave its 3-thiocyano derivative in 92% yield when treated with thiocyanogen.[245]

The reaction of selenocyanogen with indole closely paralleled that of

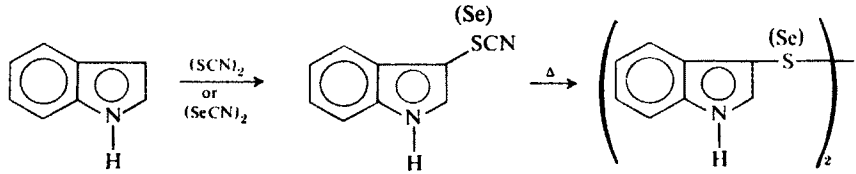


224; $n = 1, 2, 3$ (22)



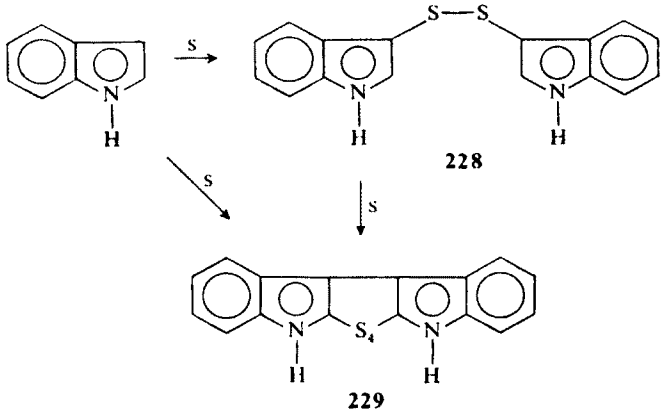
225a; R = C_6H_5
225b; R = CH_2CO_2H (23)

thiocyanogen, affording a 70% yield of 3-selenocyanoindole (**226**). Some 3,3′-diindolyl diselinide (**227**) was formed during recrystallization of **226**[216] (Eq. 24).



226 **227** (24)

e. SULFUR. When indole was heated at 124° with a limited amount (one-half equivalent) of sulfur 3,3′-diindolyl disulfide (**228**) was obtained. With excess sulfur, especially in dimethylformamide solution, the product was 3,3′-diindolyl-2,2′-tetrasulfide (**229**) (Eq. 19). Surprisingly, **229** could



228 **229** (25)

be prepared readily from **228** and additional sulfur, but not from 3,3′-diindolyl and sulfur.[247]

f. FUMING SULFURIC ACID. Fuming sulfuric acid sulfonates isatin at $C_{(5)}$.[248] It converts indigo into its 5,5′-disulfonic acid derivative, "indigo carmine," which may be further sulfonated to the corresponding 5,5′,7,7′-tetrasulfonic acid.[249]

7. *Alkylation and Arylation*

a. ALKYLATION. In this section only alkylation of indoles under neutral or acidic conditions is described. Alkylations of alkali metal salts and Grignard reagents of indoles are considered in Section IV.D.

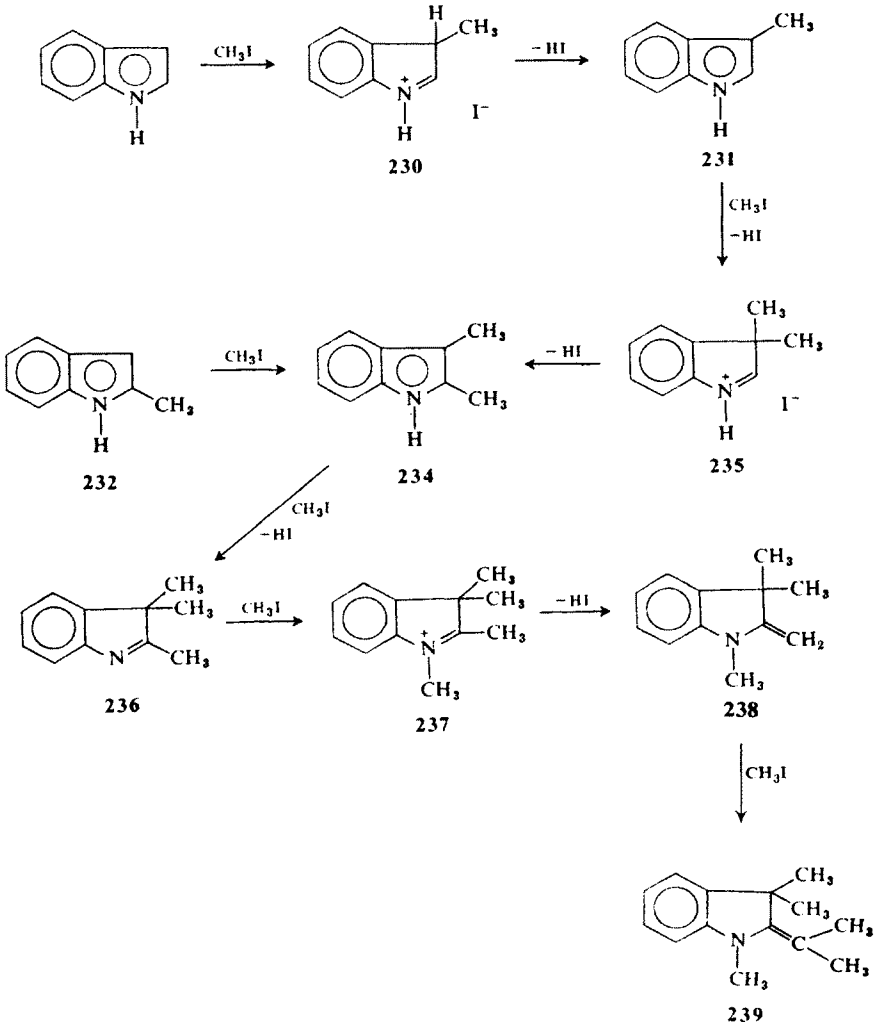
Indole is a sufficiently strong nucleophile that it will react with such weak electrophiles as alkyl halides and alkyl esters of toluenesulfonic acid. However, relatively vigorous conditions, such as heating the indole with an alkyl iodide and methanol in a pressure vessel at 110°, are required to effect its alkylation. Under these conditions the products of kinetic control are not obtained[190]; instead the alkylation often proceeds through several stages and involves rearrangement of substituents between the 2- and 3-positions before the equilibrium-controlled product is formed.

For example, when either indole or 2-methylindole is heated with methyl iodide in methanol at 110° the product isolated is 2,3,3-trimethylindolenine (**236**).[250] In the case of indole the reaction course has been interpreted[190] as beginning with methylation at $C_{(3)}$, possibly by way of a π-complex and then a σ-complex (**230**). A second methylation at $C_{(3)}$ then affords protonated 3,3-dimethylindolenine (**235**), which is unstable under the experimental conditions and rearranges to 2,3-dimethylindole (**234**). This type of rearrangement is discussed in detail in Section IV.E. The 2,3-dimethylindole thus formed is subject to further methylation and affords the isolated indolenine **236**. If the same mixture is heated for a prolonged time **236** is not isolated, but is *N*-methylated to methiodide **237**.[250]

From 2-methylindole the first step is formation of 2,3-dimethylindole (**234**) and the alkylation sequence is then identical with the indole case.[251]

Treatment of 2-methylindole **232** with methyl *p*-toluenesulfonate at 150–155° followed by potassium iodide also afforded tetramethylindoleninium iodide **237**.[252] This quaternary salt readily loses a proton from the 2-methyl group when treated with aqueous alkali, furnishing 2-methyleneindoline **238**. The exocyclic methylene carbon atom of **238** may be dimethylated with methyl iodide (**238** → **239**)[251] (Scheme 27).

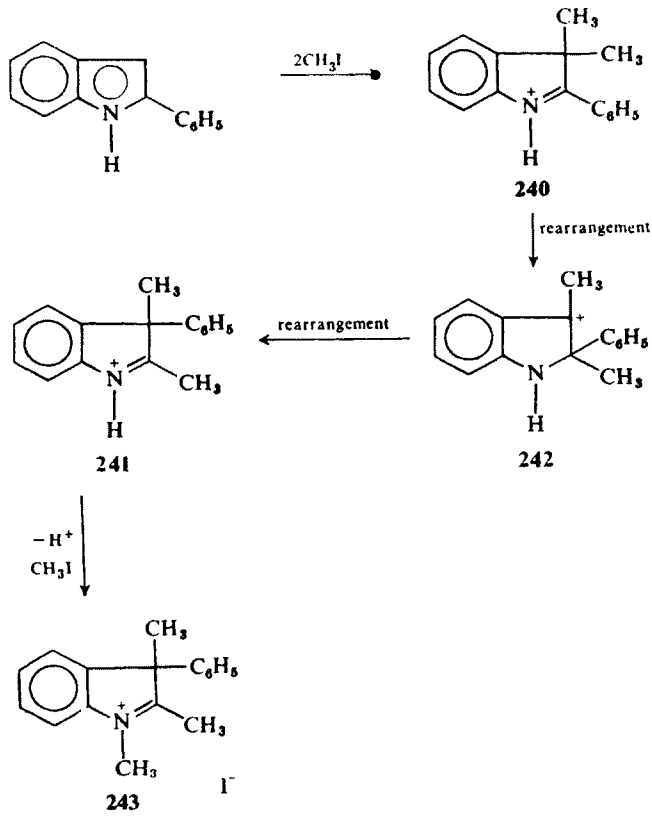
When 2-phenylindole was alkylated with methyl iodide the equilibrium-controlled product (**243**) resulted from migration of the phenyl group to $C_{(3)}$



Scheme 27

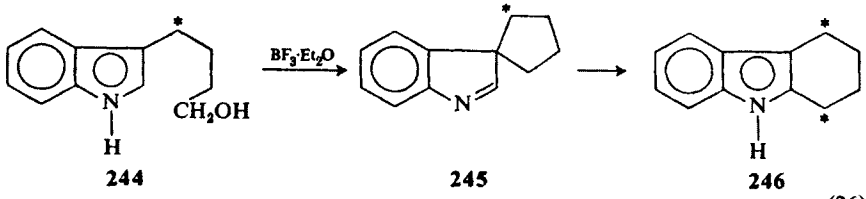
during the course of the reaction sequence.[250] It seems likely that this migration occurred after formation of protonated 3,3-dimethyl-2-phenylindolenine (**240**), since in this molecule the shift of a methyl group to $C_{(2)}$ gives a highly stabilized tertiary benzylic carbonium ion at $C_{(3)}$ (**242**), and the phenyl group may then readily shift to $C_{(3)}$, forming the rearranged indolenine **241** (Scheme 28).

It has been generalized that 3-substituted indoles are preferentially substituted at $C_{(2)}$ if the attacking species is large.[178] However, a recent study[190]



Scheme 28

with tritiated 4-(3-indolyl)butanol (**244**) demonstrated that the tetrahydrocarbazole (**246**) formed by its cyclization must have resulted from rearrangement of the intermediate spiroindolenine (**245**) (Eq. 26). Thus treatment of **244** with boron trifluoride etherate afforded **246** in which the tritium label was

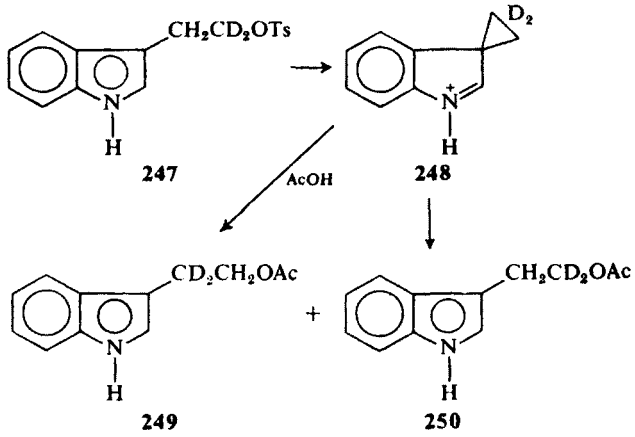


(26)

distributed in roughly equal amounts between the 1- and 4-positions. Direct substitution into $C_{(2)}$ would have left all of the tritium at $C_{(4)}$, but

rearrangement from a symmetrical intermediate such as **245** accounts for the observed distribution of tritium.

The propensity of $C_{(3)}$ of 3-substituted indoles to participate in alkylation reactions may also be inferred from the results of studies on the acetolysis of α,α-dideuteriotryptophol tosylate (**247**) in acetic acid. This reaction afforded products (**249** and **250**) in which the two carbon atoms in the side chain were completely equilibrated by equal amounts of deuterium in the α and β carbons[253] (Scheme 29). Furthermore, the rate of acetolysis was greatly



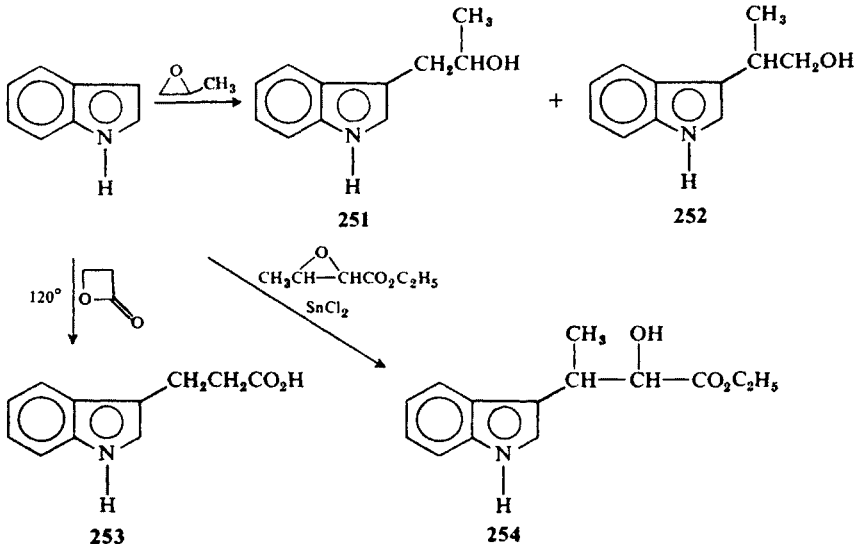
Scheme 29

enhanced over acetolysis rates for 2-ethyl tosylates of aromatic carbocycles.[253, 254]

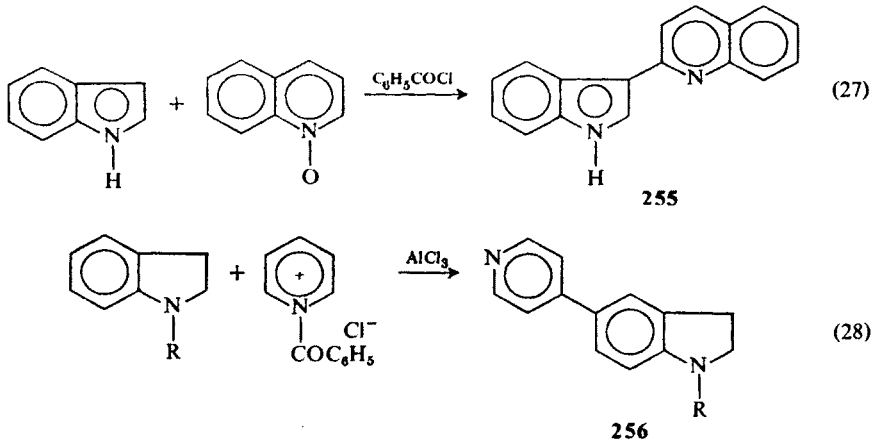
Alkylation of indole and 3-methylindole with *p*-hydroxybenzyl halides under halide solvolysis conditions (aqueous dioxane at pH 3.5) afforded monosubstitution products. Indole was substituted at $C_{(3)}$ and 3-methylindole was substituted at $C_{(2)}$. These reactions evidently involved electrophilic attack by benzyl carbonium ions, since very mild conditions afforded good yields of the products.[255]

Indole has been alkylated by propylene oxide in ether to furnish a mixture containing predominantly α-methyltryptophol (**251**). Some β-methyltryptophol (**252**) was also formed.[256] Treatment of indole with ethyl 2,3-epoxybutyrate in the presence of stannous chloride gave ethyl 2-hydroxy-3-(3-indolyl)butyrate (**254**).[257] When pripiolactone and indole were heated together at 120 for 6 hr, indole-3-propionic acid (**253**) was formed in 40–45% yield. Several 2-substituted indoles gave similar reactions with propiolactone, but 3-substituted indoles afforded no pure products.[258]

b. ARYLATION. Indole may be condensed with quinoline and pyridine *N*-oxides in the presence of acid chlorides to give 3-arylindoles.[259] For



example, with quinoline *N*-oxide and benzoyl chloride, 3-(2-quinolyl)indole (**255**) is obtained (Eq. 27). If the quinoline 2-position is blocked with a chlorine

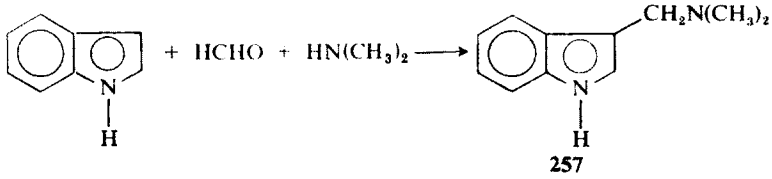


substituent, a 4-quinolyl derivative of indole is formed. 2-Substituted indoles also give related 3-aryl derivatives.

The 5-position of 1-alkylindolines has been arylated with 1-benzoylpyridinium chloride and Lewis acids such as aluminum chloride and titanium tetrachloride. 1-Alkyl-5-(4-pyridyl)indolines (**256**) were obtained in moderate yields[260] (Eq. 28).

8. *Mannich and Related Reactions*

The Mannich reaction, which involves condensation of active methylene or other electron-rich compounds with an aldehyde and a secondary amine, has been widely used in indole chemistry.[261] Preparation of gramine (**257**)

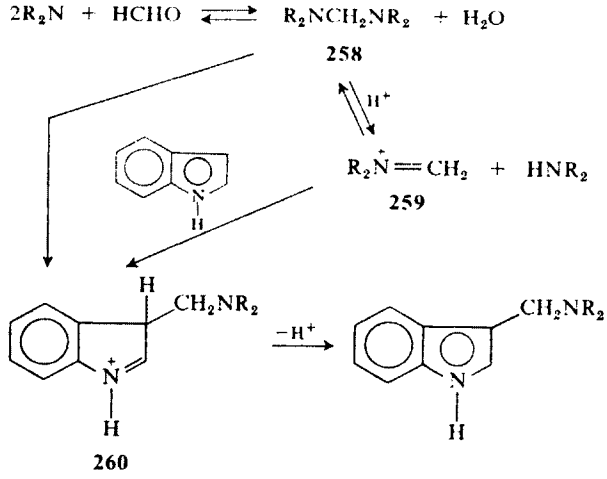


(29)

257

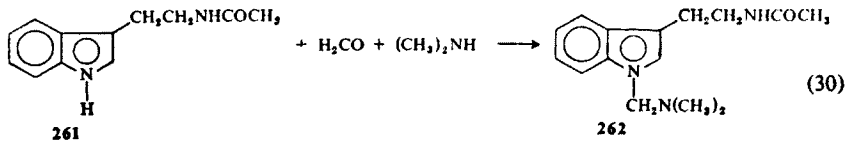
from indole, formaldehyde, and dimethylamine is one of the most important examples of this reaction[262] (Eq. 29).

Mild conditions, such as warming the reactants in ethanol, usually suffice to effect the aminomethylation of indoles. Where the reaction is slow it may be promoted by acetic acid. The mechanism of the Mannich condensation with indoles is not certain. For some time it has been thought that electrophilic attack by an immonium ion (**259**) is involved,[243] and this is probably the case when acetic acid is present.[264] However, a recent study with 2,4-dimethylphenol, formaldehyde, and morpholine disclosed that at higher pH the rate-determining intermediate was *N*,*N*′-methylenebismorpholine.[265] In the aminomethylation of indole this would involve a displacement by an electron pair from the π-system of indole on the activated methylene carbon of the gem diamine (**258** → **260**) (Scheme 30). The preferred site of reaction,



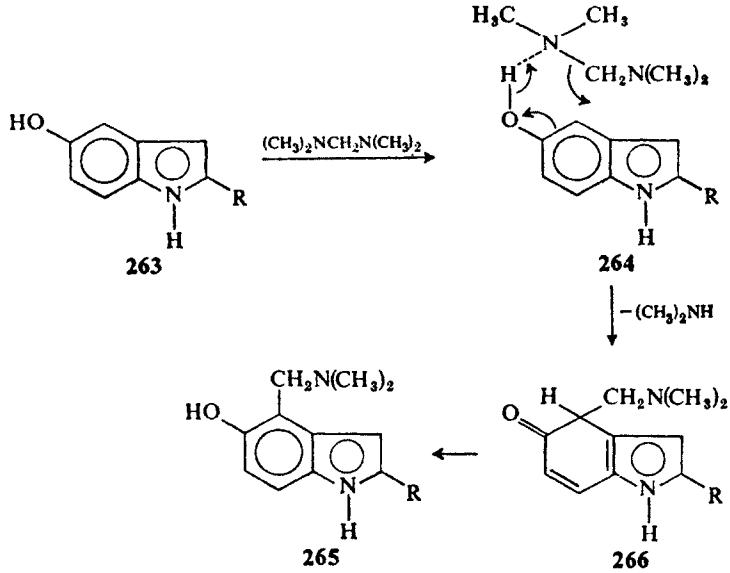
Scheme 30

in the absence of free hydroxyl groups, is $C_{(3)}$. If this position is substituted, as in acetyltryptamine (**261**), the aminomethylation occurs at $N_{(1)}$[266] to give **226** (Eq. 30).



(30)

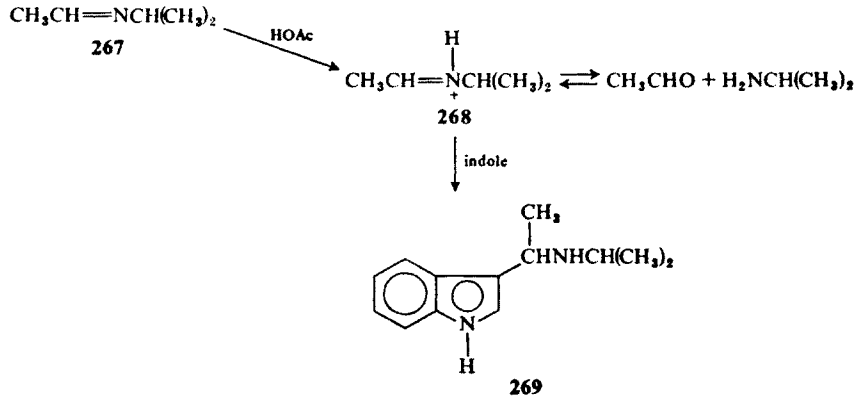
Indoles bearing hydroxyl groups in the benzene ring afford aminomethylation adjacent to the hydroxyl group even if $C_{(3)}$ is unsubstituted. Thus 4-, 5-, 6-, and 7-hydroxyindoles gave the corresponding 5-, 4-, 7-, and 6-dimethylaminomethyl derivatives with dimethylamine and formaldehyde.[267] Since 4-, 5-, and 6-benzyloxyindoles all react at $C_{(3)}$ under the same conditions,[268] the powerful directing effect of the hydroxyl group cannot be explained simply by its ability to donate electrons by mesomerism. Rather, the intermediacy of a six-membered ring (**264**) involving hydrogen bonding between the indole hydroxyl group and aldehyde amine has been invoked to account for this phenomenon[269] (Scheme 31). Here the intermediacy of a



Scheme 31

methylenebisamine would be of particular importance. This reaction would then closely parallel the model reaction with 2,4-dimethylphenol.[265]

Other aldehydes have been utilized in the Mannich reaction of indoles. For example, indole, acetaldehyde, and isopropylamine gave 3-(isopropylaminoethylidene) indole (**269**).[270] Condensation of indole with ethylideneisopropylamine (**267**) in the presence of acid also afforded **269**,[270] which

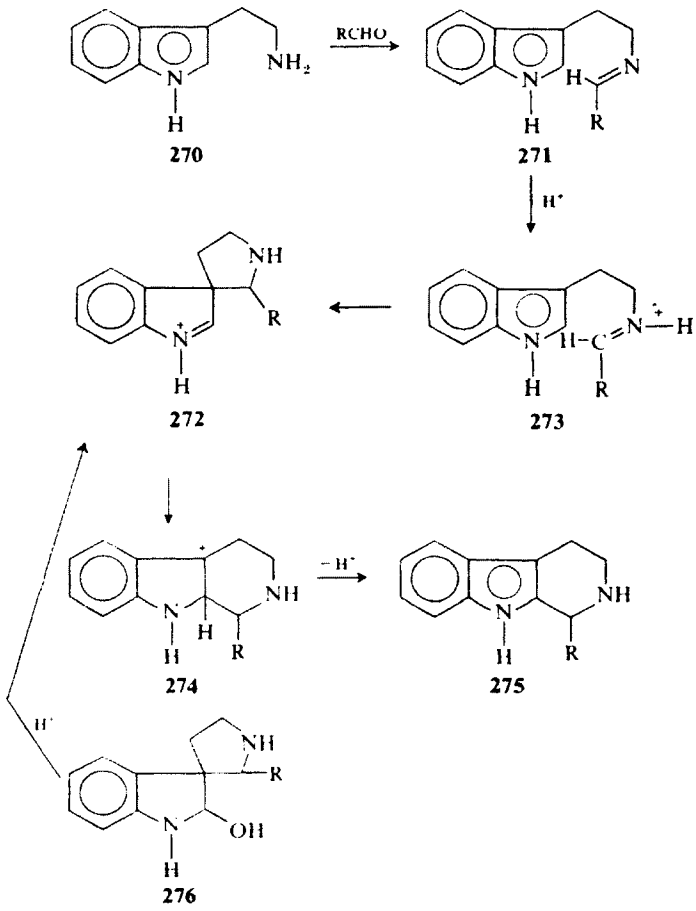


suggests that both reactions proceed through a common mechanism, namely electrophilic attack of immonium ion **268** on the indole (Eq. 31).

The synthesis of 1-alkyl-1,2,3,4-tetrahydro-β-carbolines (**275**) from tryptamines (**270**) and aldehydes in the presence of acid is an example of the Mannich reaction in which the tryptamine supplies both the nucleophilic and the basic centers[271] (Scheme 32). This synthesis proceeds by way of a Schiff's base (**271**), which upon protonation affords an immonium ion (**273**). It is not certain whether the tetrahydro-β-carboline **275** results from electrophilic substitution directly at $C_{(2)}$, or from electrophilic substitution at $C_{(3)}$ followed by rearrangement to $C_{(2)}$. The latter course is reasonable since the indolenines (**272**) formed by substitution at $C_{(3)}$ are of a type that readily rearrange under acidic conditions to give 2,3-disubstituted indoles. Furthermore, the carbinolamine **276** underwent an extremely facile acid-catalyzed rearrangement to the corresponding 1,2,3,4-tetrahydro-β-carboline (**275**).

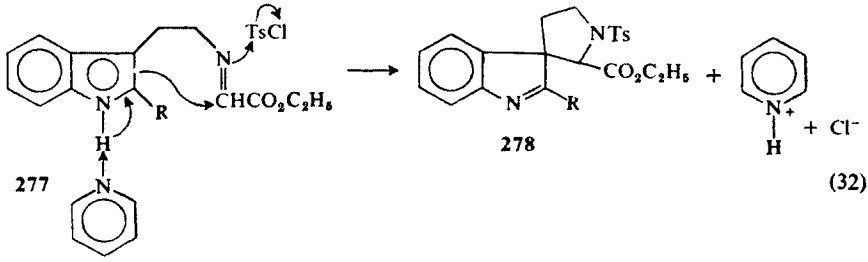
In a related reaction, Schiff's base **277** underwent cyclization into the indole 3-position when treated with pyridine and *p*-toluenesulfonyl chloride to give **278** (Eq. 32). Simple acid catalysis had been ineffective in promoting this cyclization.[273]

Tryptophans also react readily with aldehydes, affording 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids.[271]



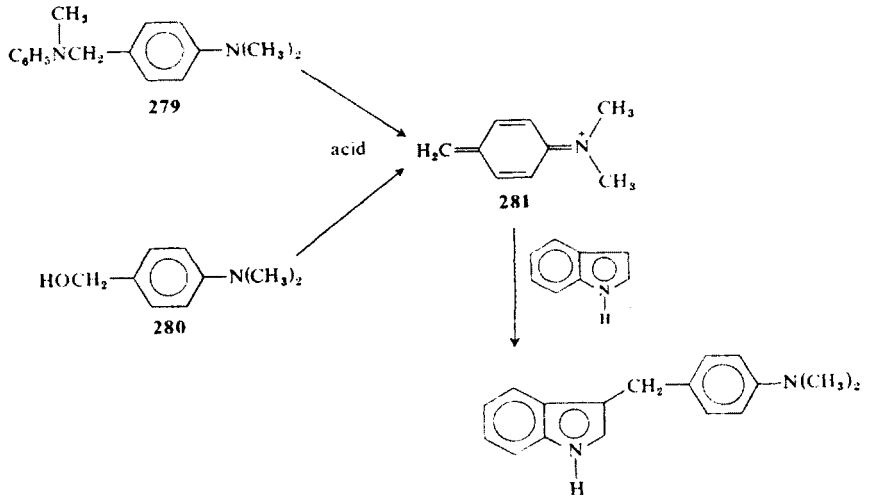
Scheme 32

Indole condensed with *p*-dimethylaminobenzyl alcohol (**280**) or with benzylamine derivative **279** in the presence of acid catalysts to give Com-



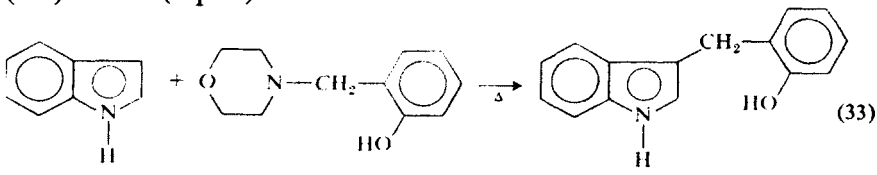
(32)

pound **282** which is closely related to typical Mannich products.[274, 275] Mesomeric cation **281** is the presumed agent of electrophilic attack on the



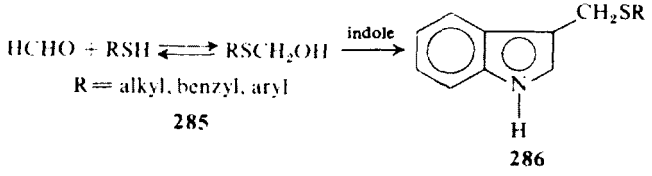
Scheme 33

indole under these conditions (Scheme 33). A series of substituted hydroxymethylphenols and products of Mannich condensations of morpholine with phenols were also condensed with indole and its 3-methyl and 2,3-dimethyl homologs by heating (90–155°) or by boron trifluoride catalysis.[274] In the case of indole the products (30–80% yields) resulted from substitution at $C_{(3)}$, whereas 2,3-dimethylindole was substituted in low yield on $N_{(1)}$. 3-Methylindole gave mixtures of $C_{(2)}$ and $N_{(1)}$ substituted products. A representative example of these reactions might be the formation of 3-(2-hydroxybenzyl)-indole (**284**) in 70% yield from indole and *N*-(2-hydroxybenzyl)morpholine (**283**) at 119° (Eq. 33).



(33)

Treatment of indole with formaldehyde and various thiols afforded 3-indolythioethers **286** in an analogy to the Mannich reaction (Eq. 34).



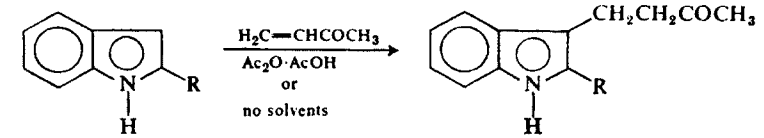
(34)

Catalysis by acetic acid was required for this reaction and the yields were low. It was suggested that thiomethanol compounds **285** are the reactive intermediates; however, by analogy to aminomethylation, dialkylsulfide or sulfonium ion intermediates might also be considered.

9. *Michael-type Reactions*

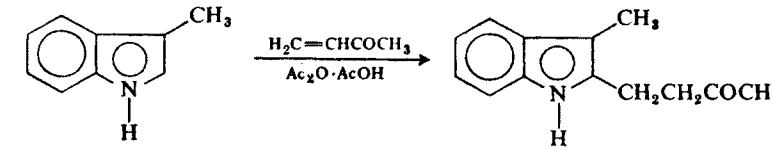
Compounds that have an olefinic linkage in conjugation with an electron-withdrawing group such as carboxyl, cyano, or nitro (sometimes referred to as dienophiles) are sufficiently strong electrophiles to react with indoles. A Michael-type reaction occurs in which the carbon atom β to the electron-withdrawing group of the electrophile is bonded to the indole nucleus. Under neutral or acidic conditions this bond is usually made to C_3 of the indole, whereas the base-catalyzed Michael reaction occurs at $N_{(1)}$.[277] The latter reaction is discussed in Section IV.D.

Thus treatment of indole, 2-methylindole, or 2-phenylindole with methyl vinyl ketone in the presence of acetic acid and acetic anhydride gave the corresponding 1-(3′-indolyl)-butanone-3-derivatives (**287**) in good yields (60–84%)[277, 278] (Eq. 35). These reactions also occurred in the absence of solvents at 160°, but then the yields were much lower. 3-Methylindole (**288**) and methyl vinyl ketone gave 1-[2′-(3-methylindolyl)]-butanone-3 (**289**) in the presence of acetic acid and acetic anhydride[277] (Eq. 36).



(35)

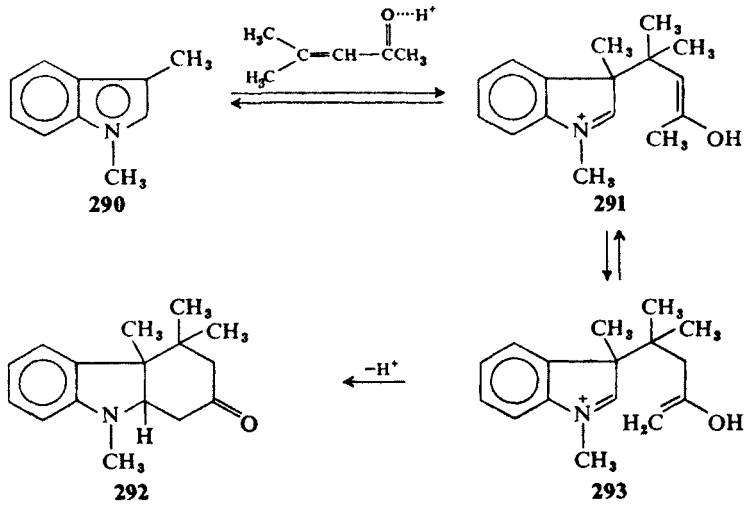
R = H, CH_3, C_6H_5 **287**



(36)

288 **289**

Condensation of 1,3-dimethylindole (**290**) with mesityl oxide in the presence of acid afforded a carbazole product (**292**) in which the initial electrophilic substitution apparently occurred at $C_{(3)}$. An explanation[279] for this process was that electrophilic attack at $C_{(3)}$ gave an intermediate enol (**291**) which could readily isomerize to the terminal enol (**293**) via ketonization, and that this terminal enol afforded cyclization into $C_{(2)}$ (Scheme 34).



Scheme 34

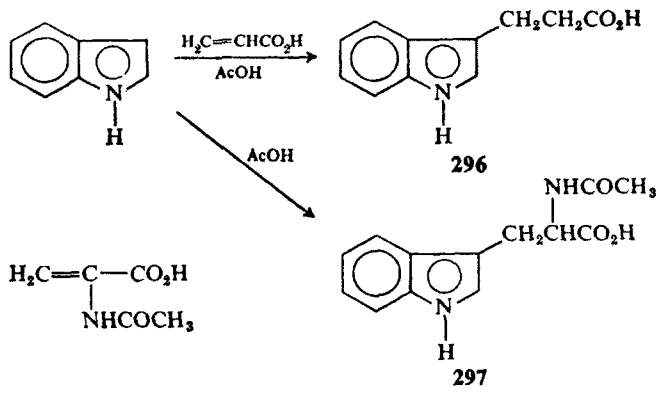
In the normal case, as with the reaction of 3-methylindole with methyl vinyl ketone described above, electrophilic substitution at $C_{(3)}$ of an indole already substituted at this position gives a cation (**294**) which can only regain



aromaticity by losing the electrophile, hence this relatively rapid reaction is reversible. However, the slower electrophilic substitution at $C_{(2)}$ affords a cation (**295**) which can rearomatize by losing a proton. This process leads to a 2,3-disubstituted indole.[279]

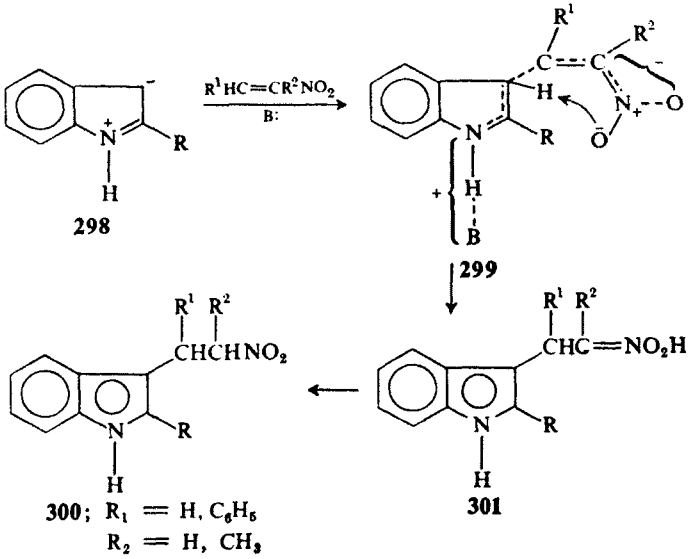
The reactions of indoles under conditions wherein acetone, mesityl oxide, and isophorone appeared to be in acid-mediated equilibrium are treated in the following section. Other reactions of indoles with α,β-unsaturated ketones include condensations with chalcones in the presence of acetic acid and acetic anhydride.[280]

Indole is readily substituted at $C_{(3)}$ by acrylic acid in the presence of acetic acid. A good yield of indole-3-propionic acid (**296**) is obtained. The process is thought to involve addition of acetic acid to the acrylic acid prior to attack of the indole.[281] If acetamidoacrylic acid is used in place of the acrylic acid, the product is *N*-acetyltryptophan (**297**) (Eq. 37).



(37)

The condensations of a number of indole derivatives with nitroolefins have been studied.[282–286] A reactivity order obtained for the indoles was as follows: 2-methyl > 1,2-dimethyl > 2-phenyl > no substituents > 1-methyl > 3-methyl (unreactive). Equimolar portions of the indoles and nitroolefins were reacted without solvents, except that excess nitroethylene was used to moderate its reaction with 2-methylindole. This reaction, and also the reactions of 1,2-dimethylindole with nitroethylene, were performed at room temperature. 1-Methylindole failed to react with nitroethylene under these conditions.[283]

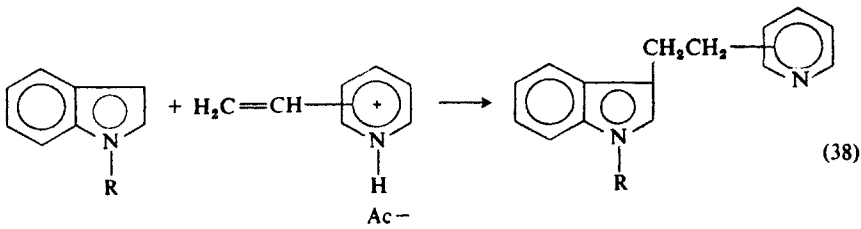


Scheme 35

2-Nitrostyrene is less reactive than nitroethylene toward indoles, but it also has less tendency to polymerize. Hence it has been used successfully for the preparation of 3-(1-phenyl-2-nitroethyl)indoles at higher temperatures. Still higher temperatures (up to 130°) were used for substitutions involving the more stable but slow reacting 2-methyl-2-nitrostyrene.[283] The 2-nitroethyl derivatives **300** of indoles obtained from these reactions were useful intermediates for tryptamine syntheses[283, 284] (Scheme 35).

Any mechanism proposed for the nitroethylation of indoles under neutral conditions must account for the diminished reactivity of 1-methylindoles. The 1-methyl group should enhance the rate of electrophilic substitution by donating electrons to the nitrogen; however, some other effect must predominate over this one with the NH indoles. It has been suggested[283] that partial bonding to the NH hydrogen in the transition state (**299**) helps spread the positive charge and thus stablize this state for the NH compounds.

3-Pyridethylations of indole and 1-methylindole have been effected with either 2- or 4-vinylpyridine in acetic acid at reflux[287] to give **303** (Eq. 38). The



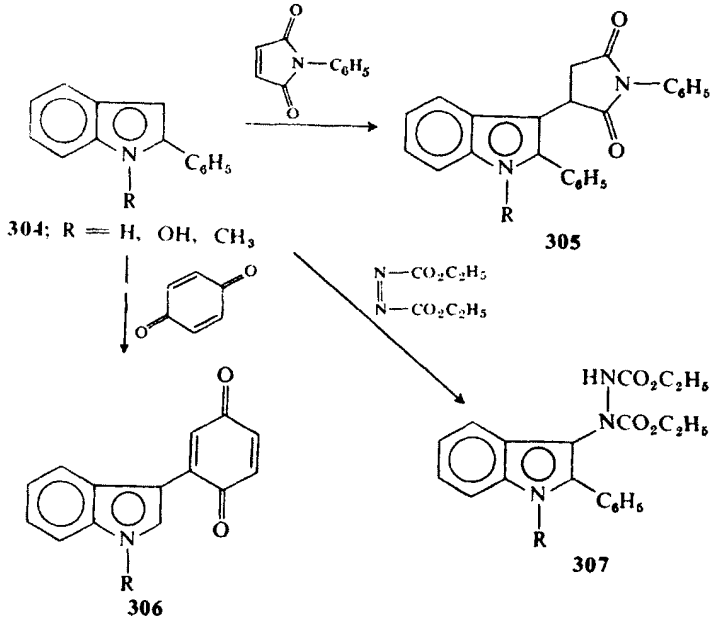
(38)

302 **303**

electrophile in this case is presumably the vinylpyridinium ion (**302**) which should bear a partial positive charge in the vinyl group.

2-Phenylindole and its *N*-hydroxyl and *N*-methyl derivatives (**304**) underwent 3-substitution with typical dienophiles such as *N*-phenylmaleimide, ethyl azodicarboxylate, and *p*-benzoquinone[288] (Scheme 36). No Diels-Alder type cycloadducts were obtained from these reactions. This behavior contrasts that of the isoindoles, which normally give the cycloadducts (Section IV.H).

Treatment of 2-ethoxyindole (**308**) with maleic anhydride or ethyl azodicarboxylate also gave 3-substitution.[289] 2-Ethoxyindole (**308**) was sufficiently reactive to condense with dimethyl acetylenedicarboxylate, and a complex mixture of products resulted.[290] This mixture was composed of various 3-(2-ethoxyindolyl)fumaric and -maleic esters (**309–311**), plus the interesting benzazepine (**312**) (Eq. 39). The related benzazepine (**315**) formed from 2-ethoxy-1-methylindole (**313**) had a different conjugation of olefinic and



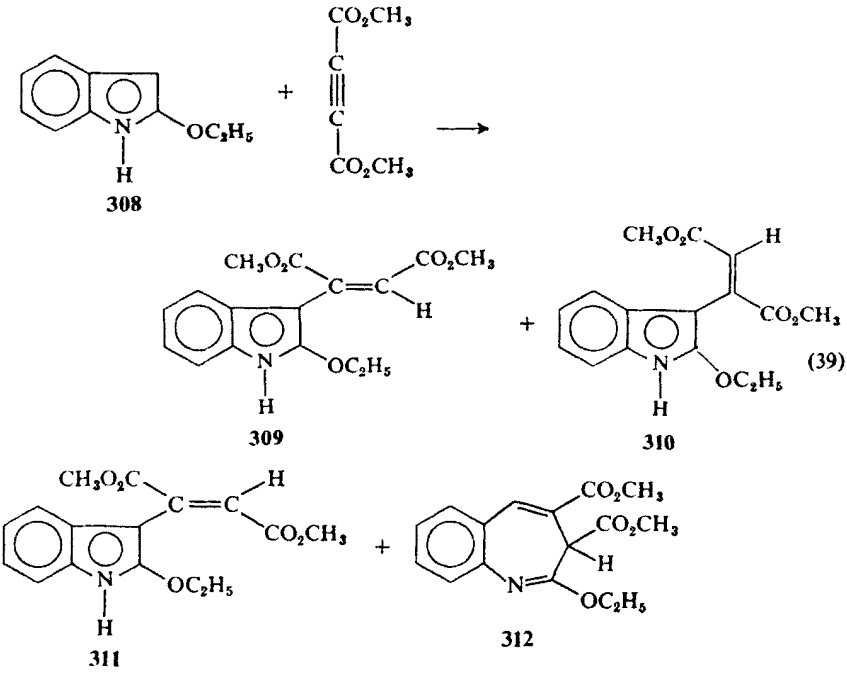
304: R = H, OH, CH_3

305

306

307

Scheme 36



308

309

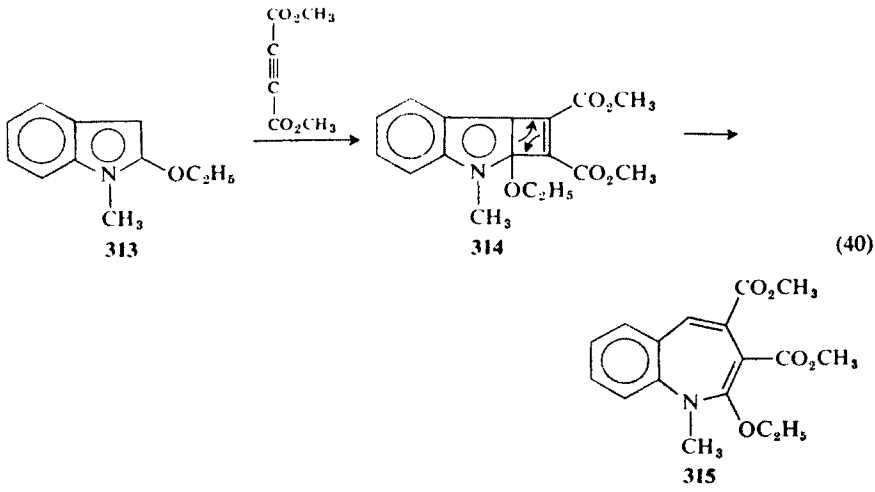
310

311

312

(39)

aromatic bonds. A suggested pathway for its formation involved an intermediate (**314**) with a cyclobutene ring[290] (Eq. 40).

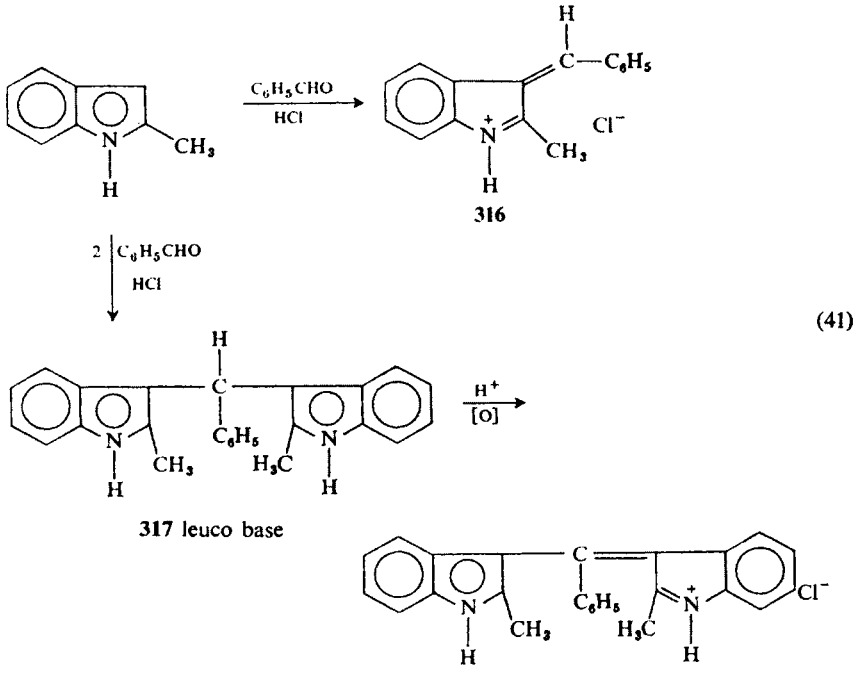


(40)

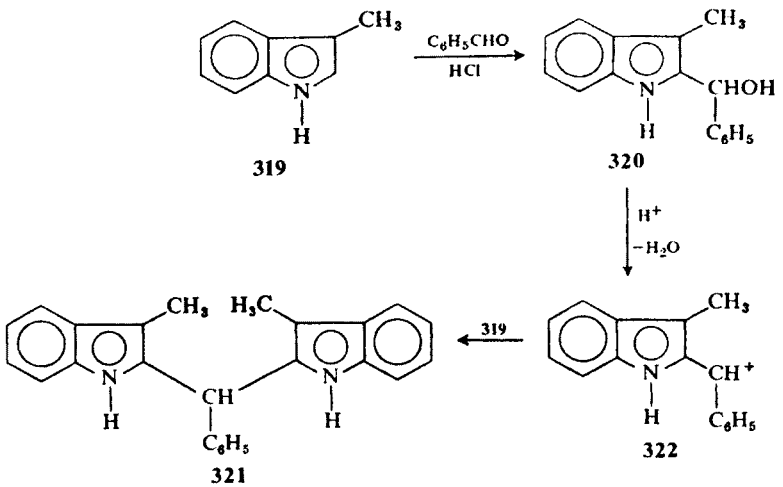
10. *Reactions with Aldehydes and Ketones*

Indoles react with a variety of aldehydes and ketones in the presence of acid, affording products derived from either one or two molecules of the indole and one or two molecules of the carbonyl compound. The initial reaction involves electrophilic attack by the carbonyl carbon, which bears a substantial partial positive charge due to protonation of the carbonyl by the acid, on the indole nucleus. The 3-position of the indole is favored for substitution, but if this site is already occupied the 1-position is next favored, followed by the 2-position.[291, 292] Substituents on $N_{(1)}$ are usually less stable than those at $C_{(2)}$ and where a mobile equilibrium exists the products of $C_{(2)}$ substitution are obtained.[292] However, in several instances the products of $N_{(1)}$ substitution have been isolated.[291, 293]

a. ALDEHYDES. Treatment of 2-methylindole with one equivalent of benzaldehyde in the presence of hydrochloric or sulfuric acid afforded crystalline salts of the 3-benzylidineindolenine (**316**). With excess 2-methylindole present the corresponding 3,3′-diindolylphenylmethane (**317**, leuco base) formed initially, but was readily converted by acid and oxygen to rosindole **318**[294, 295] (Eq. 41). Treatment of 3-methylindole (**319**) with benzaldehyde in ethanolic hydrochloric acid gave the 2,2′-diindolylphenylmethane (**321**). Formation of such diindolylmethanes presumably involves initial formation of the carbinol (**320**), followed by conversion to the highly stabilized


C6H5CHO
HCl
CH3
N
H
Cl⁻
316
2 C6H5CHO
HCl
C6H5
H3C
H+
[O]
317 leuco base
318 rosindole

(41)


CH3
C6H5CHO
HCl
CHOH
319
320
H+
−H2O
319
CH
322
321

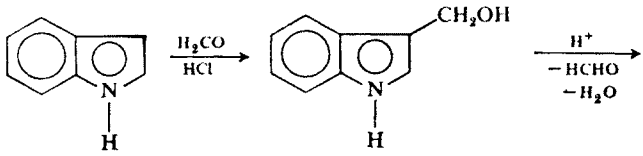
Scheme 37

carbonium ion (**322**), which then attacks another molecule of 3-methylindole (Scheme 37).

The formation of a rosindole-type dye provides the basis for the Ehrlich test. This test involves treating an indole with *p*-dimethylaminobenzaldehyde in hydrochloric acid. A recent study shows rosindole formation to be fast for indoles with no substituent at $C_{(3)}$ and no electron-withdrawing groups on the nucleus; slow for indoles substituted at $C_{(3)}$ but containing no free amine in the 3-substituent, and having no electron-withdrawing group on the nucleus; negative for a 3-substituent containing a free amine, for substitution at both $C_{(2)}$ and $C_{(3)}$, and for an electron-withdrawing group in the nucleus.[296]

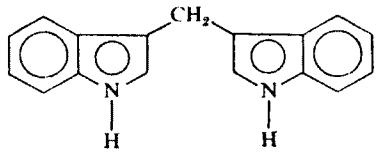
Isoindoles also give a color test with *p*-dimethylaminobenzaldehyde and acid. The structure of the dye that is formed has not been elucidated.

Indoles and formaldehyde readily combine in the presence of acid to give 3,3′-diindolylmethanes (**324**)[199, 274] (Eq. 42). 3-Hydroxymethylindoles (**323**)



323

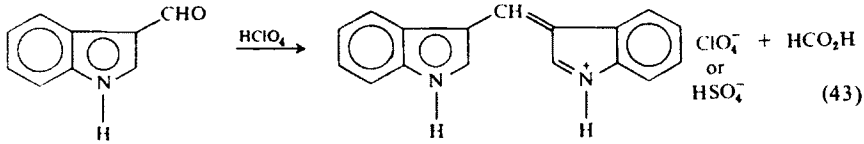
(42)



324

are apparently intermediates in these reactions; however, these intermediates are unstable in the presence of acid, forming the diindolylmethanes with loss of formaldehyde and water (Section V.A.3).

An acid-catalyzed cleavage reaction also occurs when indole-3-carboxaldehyde (**325**) is treated with perchloric acid or sulfuric acid. In this case formic acid is eliminated and the product is urorosein (**326**) (Eq. 43).

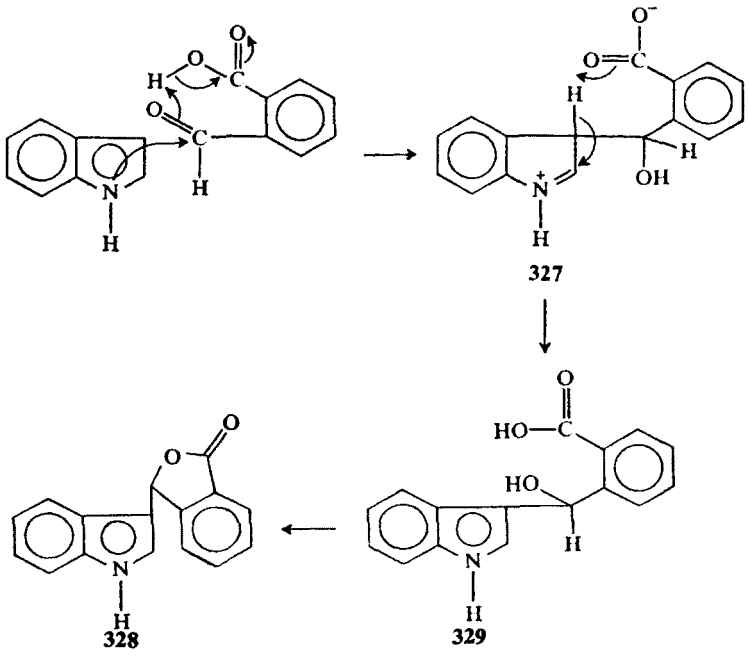


(43)

325 **326**

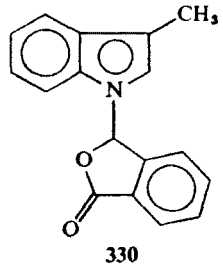
Urorosein may also be prepared from indole and ethyl orthoformate in the presence of hydrochloric and perchloric acids, or by treating indole with formic acid and sulfuric acid.[297]

The order of preference 3 > 1 > 2 for electrophilic substitution of indoles was clearly evident in the reactions of indoles with phthalaldehydic acid.[291] Thus indole gave 3-phthalidylindole **328** at room temperature in benzene.[291] This reaction, which was faster than the corresponding reaction with benzaldehyde, has been interpreted as involving intramolecular acid catalysis and trapping of the intermediate alcohol (**329**), which prevented diindolylmethane formation[291] (Scheme 38). 3-Methylindole required more vigorous

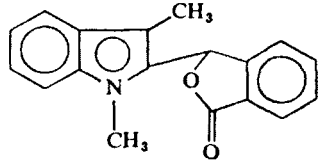


Scheme 38

conditions (fusion) to promote reaction and then the 1-phthalidyl derivative (**330**) was formed. Similar conditions converted 1,3-dimethylindole to the corresponding 2-phthalidyl compound (**331**).

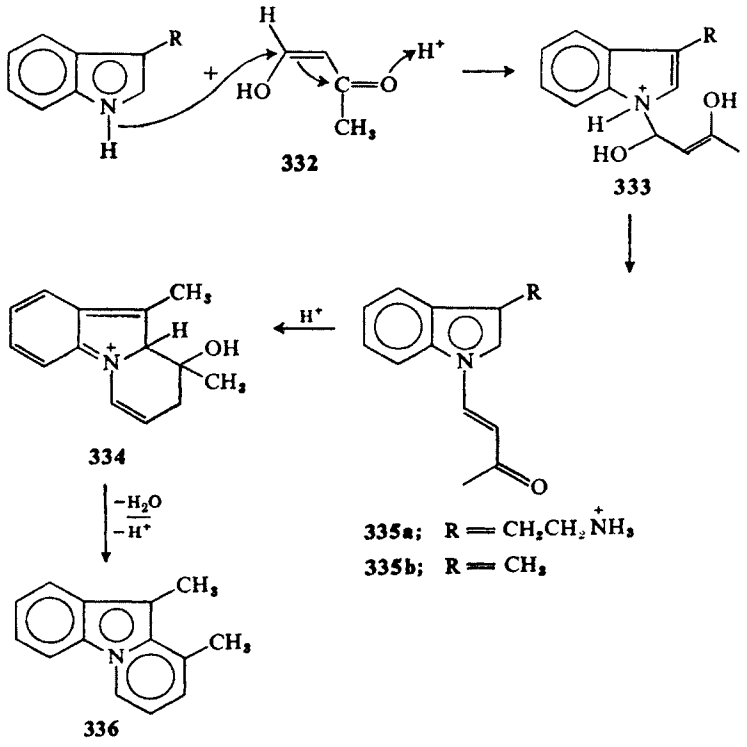


330



331

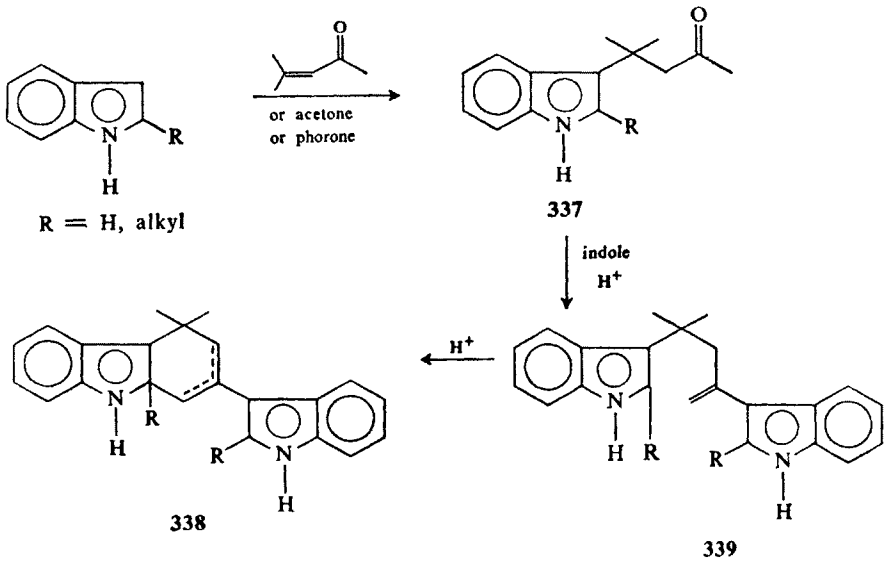
Condensation of tryptamine with acetoacetaldehyde (**332**) furnished the product (**335a**) of substitution on $N_{(1)}$.[293] A similar product was obtained in good yield from 2,3-dimethylindole and **332**; however, 3-methylindole gave only a small amount of its $N_{(1)}$ substitution product (**335b**). Under somewhat more vigorous conditions 3-methylindole condensed with **332** to afford 1,8-dimethyl-2,3-benzopyrrocoline (**336**), presumably by way of substitution of the ketonic carbonyl carbon into the indole 2-position of **335a**[297] (Scheme 39). Treatment of 3-methylindole with acetonylacetone and hydrochloric acid furnished 1,5,8-trimethyl-2,3-benzopyrrocoline.[300]



Scheme 39

b. KETONES. Treatment of indole or 2-alkylindoles with acetone, mesityl oxide, or phorone in strong acid gave diindolylalkenes **339** and hexahydrocarbazoles **338**. Presumably **338** are formed by acid-catalyzed cyclization of **339**[298] (Scheme 40). Analogous products were obtained with a variety of ketones such as benzalacetone and methyl vinyl ketone.[299]

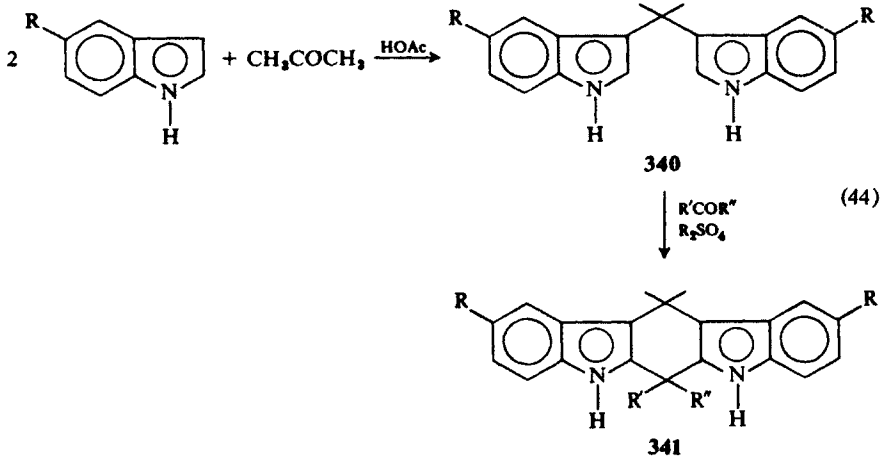
Condensation of certain indoles with acetone in acetic acid gave diindolylalkanes **340**. With stronger acids, such as maleic or hydrochloric, diindolylalkanes with open 2-positions became vulnerable to attack by



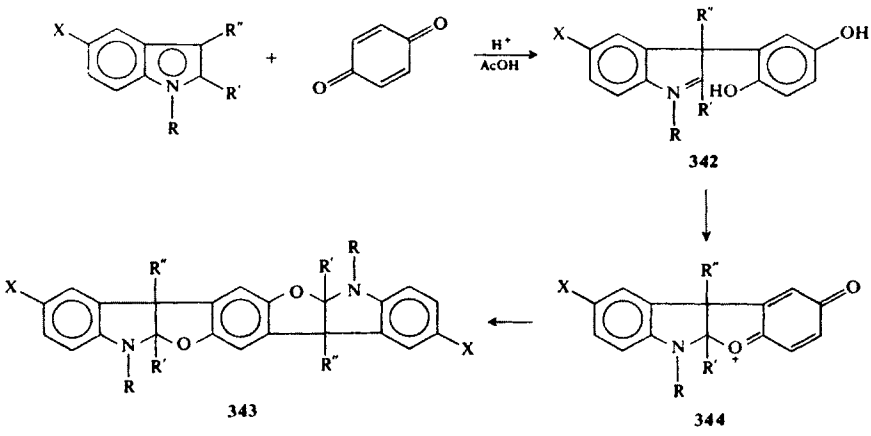
Scheme 40

acetone at these positions, and they underwent cyclizative condensation to indolo[2,3-*b*]carbazoles **341** (Eq. 44). Other carbonyl compounds, including formaldehyde, acetone, and acetophenone, also reacted with diindolylalkanes **340** to give the corresponding indolo[2,3-*b*]carbazoles.[301]

A variety of 3-alkylindoles reacted with *p*-benzoquinone in acetic acid at 25° to give 2:1 cycloadducts of type **343**. The initial adduct in these transformations is probably the result of substitution of a quinone carbon at $C_{(3)}$



(44)

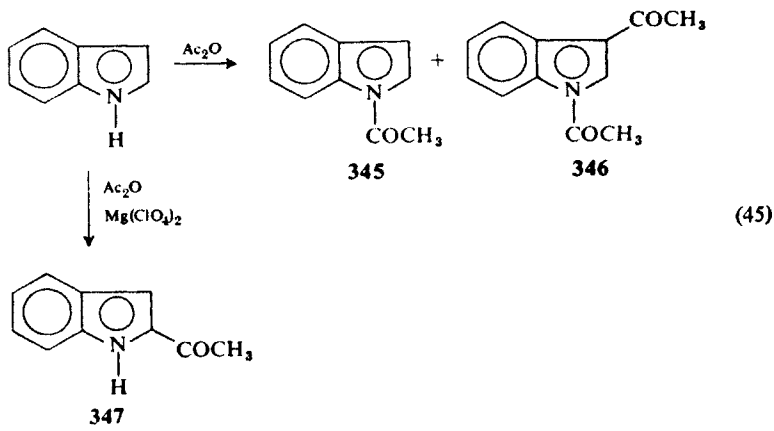


Scheme 41

of the indole. This adduct (**342**) then undergoes cyclization, either before or after reoxidation to a quinone, and the resulting intermediate **344** reacts with a second molecule of indole to furnish **343**[302–304] (Scheme 41).

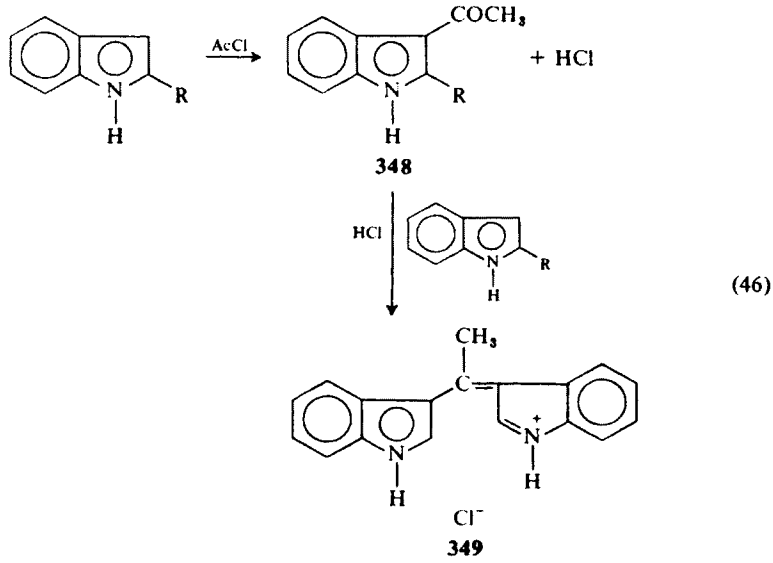
11. *Acylation*

a. Acid Chlorides and Anhydrides. Heating a mixture of indole and acetic anhydride at 180–200° affords a mixture of 1-acetylindole (**345**) and 1,3-diacetylindole (**346**) (Eq. 45). This mixture may be separated by utilizing the steam volatility of 1-actylindole.[305] 2-Methylindole, 2-phenylindole, and 1,2-dimethylindole react more readily, furnishing their 3-acetyl derivatives in high yields when heated with acetic anhydride and sodium acetate.[306]



(45)

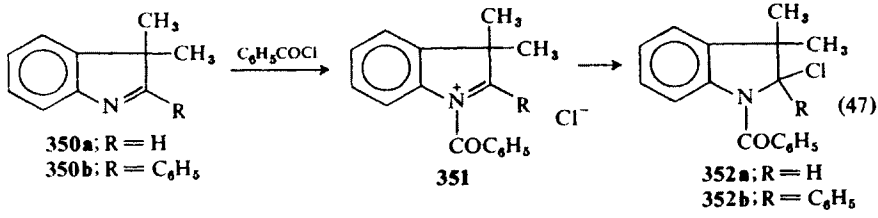
However, treatment of 2-methylindole and 2-phenylindole with acetyl chloride causes formation of rosindoles (**349**)[307] (Eq. 46). Evidently the HCl



(46)

liberated by acetylation catalyzes the condensation of the 3-acetyl derivatives (**348**) with starting material to give these rosindoles (see Section IV.C.10).

The reaction of 3-methylindole with acetyl chloride to give 2-acetyl-3-methylindole is promoted by zinc chloride.[305] Treatment of indole with acetic anhydride and a catalytic amount of magnesium perchlorate at room temperature gave 2-acetylindole (**347**) in 50% yield.[308] The important role of the

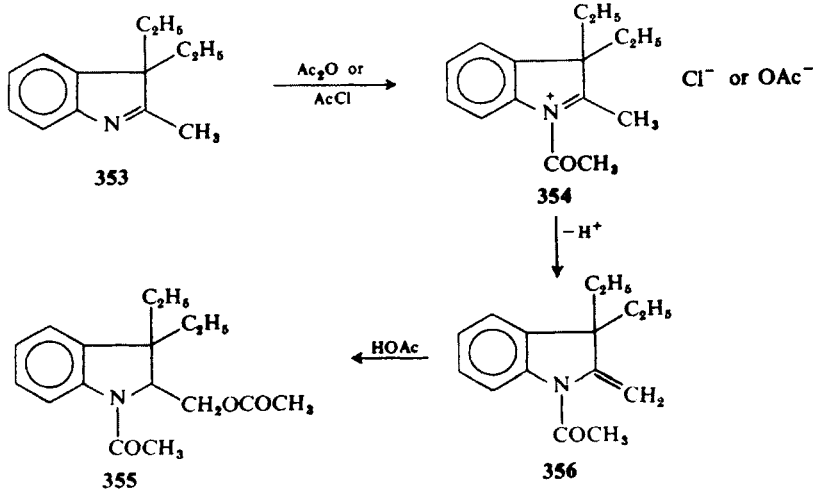


(47)

catalyst is possibly to effect rearrangement of an acetyl group from $N_{(1)}$ to $C_{(2)}$.

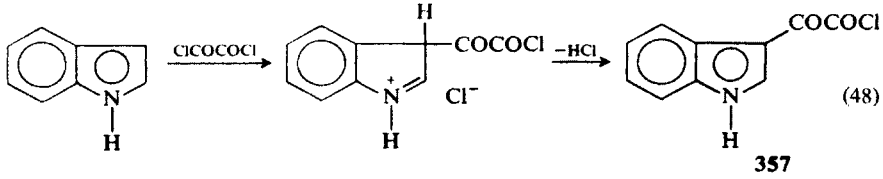
Certain indolenines, such as 3,3-dimethylindolenine (**350a**) and 3,3-dimethyl-2-phenylindolenine (**350b**) react with benzoyl chloride to furnish 1-benzoyl-2-chloroindolines (**352a** and **352b**)[305] (Eq. 47). Iminium ions **351** are presumed to be intermediates in these reactions. The 2-chloroindolines have highly reactive halogens and they proved useful in the preparation of other 2-substituted indolines (Section IV.O).[309]

Acylation of the nitrogen of 3,3-diethyl-2-methylindolenine (**353**) with acetic anhydride or acetyl chloride afforded the corresponding 1-acetyl-2-methyleneindoline (**356**), apparently by loss of a proton from the methyl group of intermediate immonium ion (**354**). This methyleneindoline further added the elements of acetic acid (in the reaction with acetic anhydride) to give 2-acetoxymethylindoline **355**[305] (Scheme 42).



Scheme 42

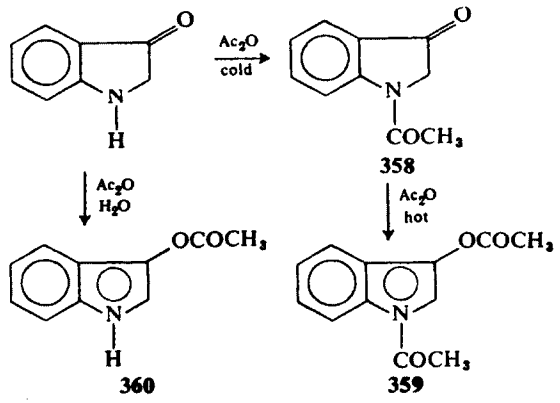
Oxalyl chloride reacts with many indoles at room temperature in ether to give crystalline 3-glyoxalyl chloride derivatives (**357**) in excellent yields[310] (Eq. 48). These derivatives have become very important in syntheses of



(48)

tryptamines. A chloro substituent at $C_{(4)}$ of indole renders the reaction with oxalyl chloride more difficult, whereas bromine completely inhibits it (at least in refluxing ether) due to steric hindrance.[311] A strong electron-withdrawing group such as carbethoxy at $C_{(2)}$ also prevents reaction with oxalyl chloride.[310]

Indoxyl may be acylated either on oxygen or nitrogen depending upon the experimental conditions. Thus the *O*-acetyl derivative (**360**) is obtained in a mixture of water and acetic anhydride, whereas in cold neat acetic anhydride the *N*-acetyl derivative (**358**) is formed.[312, 313] Treatment of indoxyl with hot

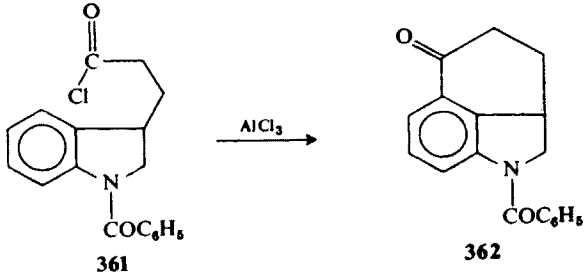


(49)

acetic anhydride affords 1,3-diacetylindoxyl (**359**) (Eq. 49). The facile tautomerism of indoxyl to 3-hydroxyindole is apparent from these reactions.

b. FRIEDEL-CRAFTS. Indolines and certain 2,3-disubstituted indoles acylate only on nitrogen when treated with acyl halides. However, if the acyl halide is activated by complexing with aluminum chloride it becomes a sufficiently strong electrophile to substitute the benzene rings of their *N*-acyl derivatives. The 2,3-disubstituted *N*-acylindoles are then acylated at the 6-position, whereas the *N*-acylindolines acylate at $C_{(5)}$, *para* to the nitrogen.[305]

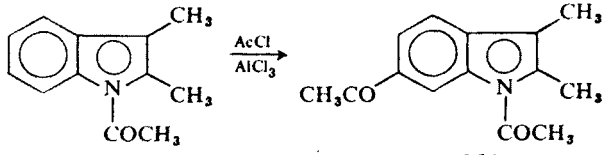
Thus the *N*-acetyl derivatives of indoline and 2-methylindoline gave 5-acylation with aluminum chloride and acetyl chloride, propionyl chloride, or chloroacetyl chloride.[314] 1-Benzoyl-3-chloropropionylindole (**361**) underwent cyclization into the 4-position to give **362** when treated with aluminum chloride in carbon disulfide[315] (Eq. 50).



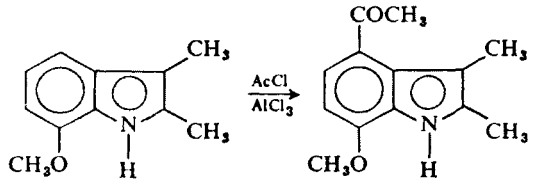
(50)

Treatment of 1-acetyl-2,3-dimethylindole (**363**) with acetyl chloride and aluminum chloride afforded the 6-acetyl derivative (**364**) (Eq. 51). The strong directive effect of its methoxyl group caused 2,3-dimethyl-7-methoxyindole (**365**) to acylate at $C_{(4)}$ under similar conditions[307] (Eq. 52).

c. DIKETENE. Condensation of indole with diketene in acetic anhydride at 90°, or in a mixture of benzene, toluene, and a tertiary amine, afforded

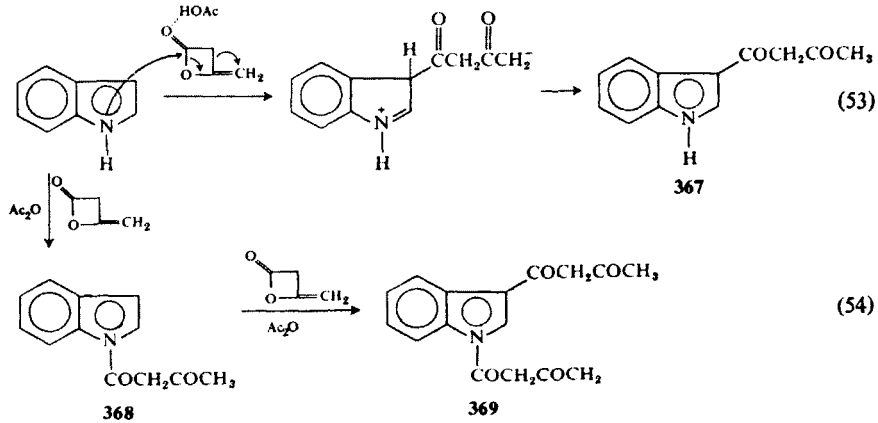


363 364 (51)



365 366 (52)

1-acetoacetylindole (**368**). Prolonged treatment of **368** with acetic anydride converted it to 1,3-diacetoacetylindole (**369**) (Eq. 54). In comparison, when



(53)

367

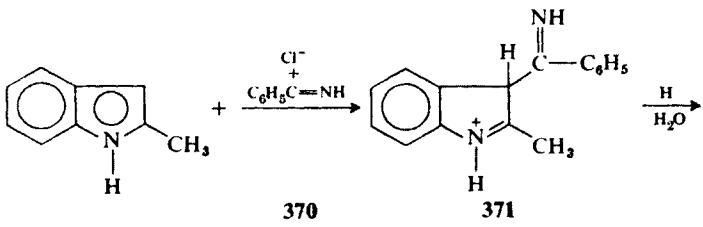
(54)

368 369

indole and diketene were heated in acetic acid, 3-acetoacetylindole (**367**) was obtained[316] (Eq. 53).

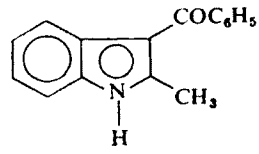
d. Reactions With Nitriles. The Gatterman reaction, involving hydrocyanic acid and hydrochloric acid, has been useful in the preparation of indole-3-carboxaldehydes in those cases where the strongly acidic medium does not cause dimerization of the indole. Thus 2-methylindole (stabilized by steric hindrance to dimerization) and ethyl 5-methoxyindole-2-carboxylate afforded the corresponding 3-carboxaldehydes in good yields.[306] Indoles sensitive to acid are better formylated by the Vilsmeier-Haack method.

2-Methylindole has also been converted into 3-alkanoyl and 3-aroyl derivatives with appropriate nitriles and hydrochloric acid (Houben-Hoesch reaction).[306] For example, condensation with benzonitrile under these conditions gave 3-benzoyl-2-methylindole (**372**).[317] This reaction involves



370 371

(55)



372

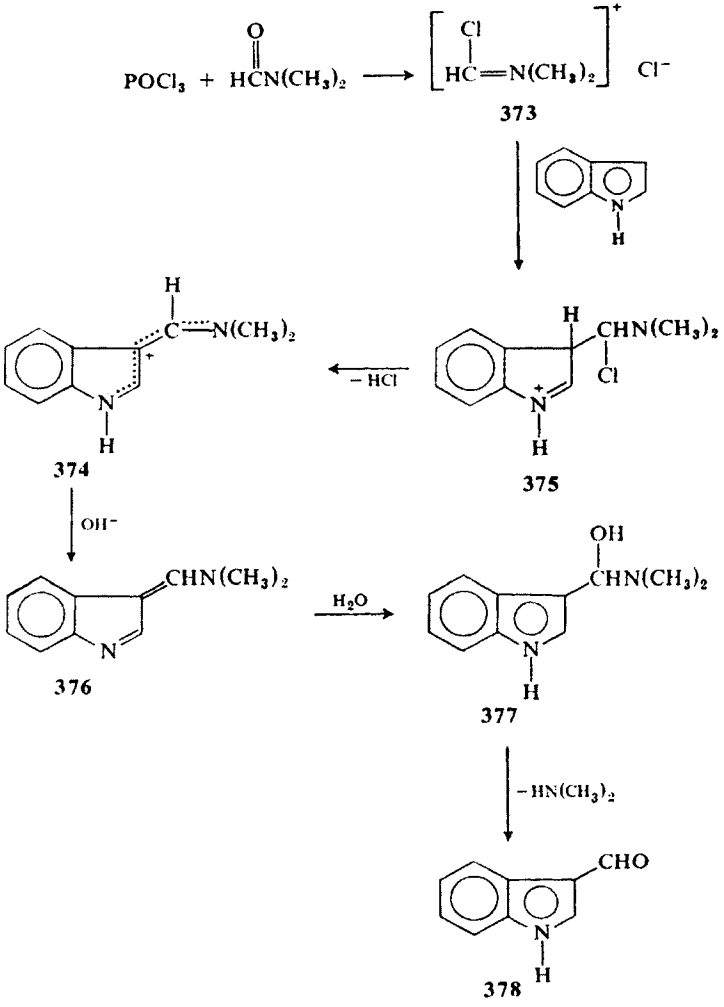
electrophilic attack of the indole by the protonated nitrile **370**. The intermediate imine **371** is then hydrolyzed to a ketone in the aqueous acid (Eq. 55).

e. VILSMEIER-HAACK FORMYLATION. The Vilsmeier-Haack reaction[318] has been important in the preparation of indole-3-carboxaldehydes and 3-acylindoles. In this reaction a complex, considered to be chloroimmonium salt **373**,[319] is prepared from phosphorus oxychloride and a tertiary amide such as dimethylformamide or *N*-methylformanilide. The indole is then added to this complex and electrophilic attack by the chloroimmonium ion at the indole 3-position initiates the reaction. Loss of HCl from the resulting intermediate **375** then affords a relatively stable mesomeric cation (**374**). This cation has been identified spectroscopically in the case where indole was treated with phosphorus oxychloride in excess dimethylformamide,[320] and upon careful neutralization it gave the crystalline free base **376**. The free base was readily hydrolyzed to indole-3-carboxaldehyde (**378**) by boiling water[320] (Scheme 43).

In general the free base is not isolated, but the cation **374** is converted directly to the aldehyde by making the solution distinctly alkaline and heating if necessary. This hydrolysis, presumably involving aminohydrin **377**, affords the aldehyde in high yield.[320, 321]

Indoles which are substituted at $N_{(1)}$, $C_{(2)}$, or in the benzene ring are also readily formylated or acylated at $C_{(3)}$ by the same method.[322–324]

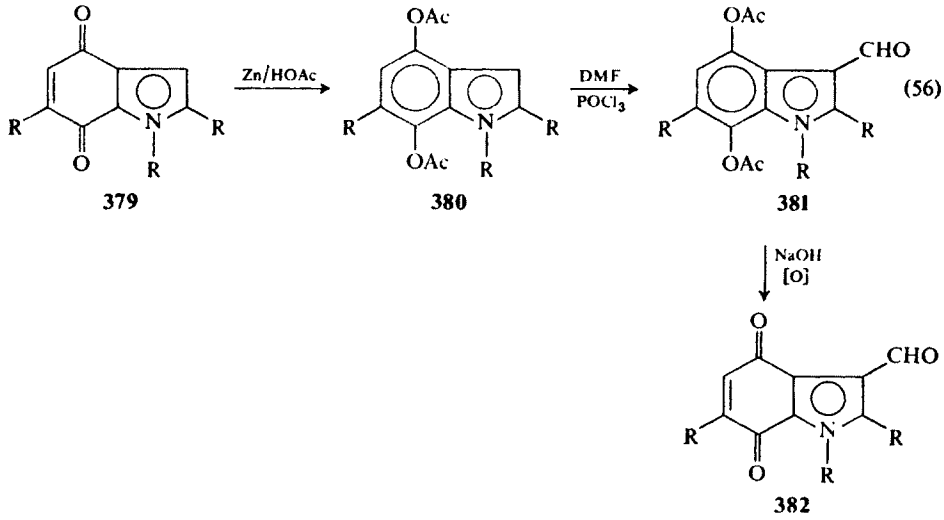
Electron-withdrawing substituents such as phenyl and carbethoxy at $C_{(2)}$ permit formation of the 3-carboxaldehydes in high yields[322, 325]; however, a 2-acetyl group prevents reaction, even under vigorous conditions.[326] In one instance a 2-acylindole-3-carboxaldehyde was prepared from the corresponding 2-acylindole by reduction of the 2-acetyl group to the secondary



Scheme 43

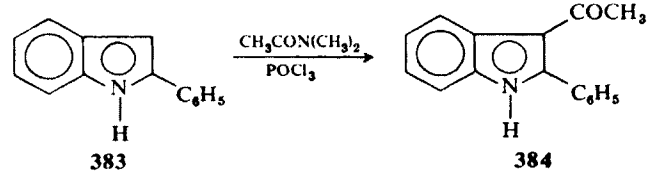
alcohol, protection of this alcohol as the acetate, formylation at $C_{(3)}$, and regeneration of the 2-acyl group.[326] Indole-4,7-diones (**379**) are also deactivated toward electrophilic substitution, but their 3-carboxaldehyde derivatives (**382**) could be prepared by way of the hydroquinone acetates (**380**)[327] (Eq. 56).

3-Acylindoles such as 2-phenyl-3-acetylindole (**384**) may be conveniently prepared by the use of dimethylacetamide and phosphorus oxychloride[324]

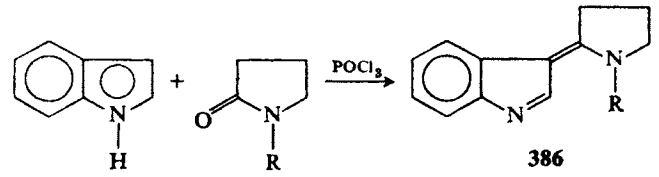


(56)

(Eq. 57). When a variety of indoles were treated with phosphorus oxychloride and 1-alkyl-2-pyrrolidinones (**385**), no amino ketones were produced. Instead, the products were 3-(2-pyrrolidinylidene)3*H* indoles (**386**)[328] (Eq. 58).

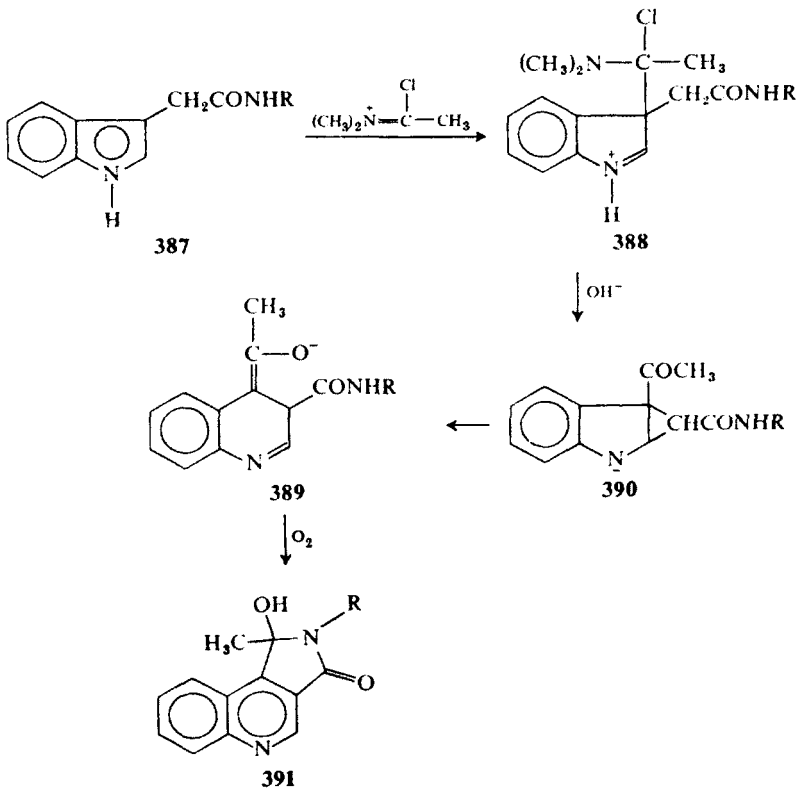


(57)



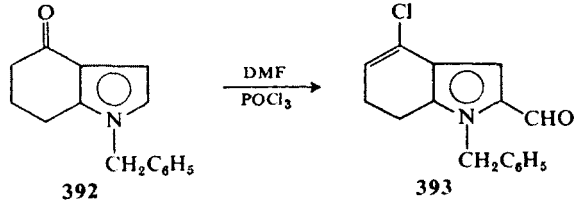
(58)

Substitution of *N*-(3-indoleacetyl)benzylamine (**387**) with the complex formed by dimethylacetamide and phosphorus oxychloride, followed by alkaline hydrolysis, afforded 3-oxopyrrolo[3,4-*c*]quinoline **391**. It was postulated that this unusual transformation occurred by initial formation of the anticipated indoleninium ion **388**, followed by base-catalyzed rearrangement and air oxidation[329] (Scheme 44).



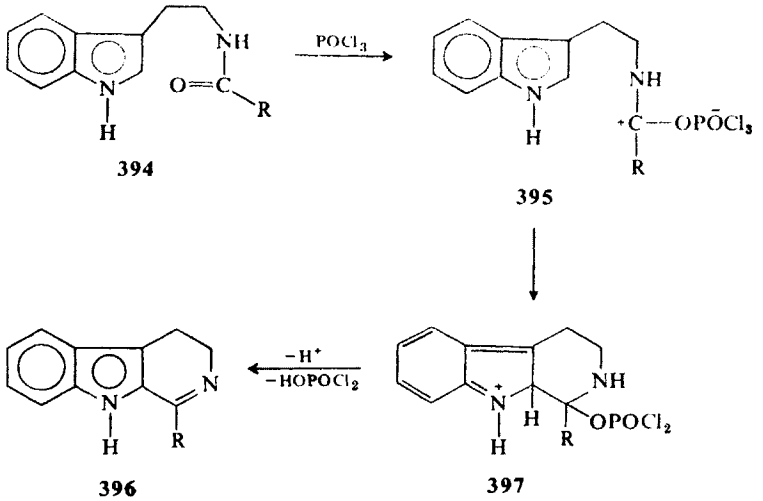
Scheme 44

1-Benzyl-4-oxo-4,5,6,7-tetrahydroindole (**392**) undergoes formylation at $C_{(2)}$ in the pyrrole ring when treated under Vilsmeier-Haack conditions. The product isolated (**393**) also has the carbonyl group transformed into a vinyl chloride[330] (Eq. 59).



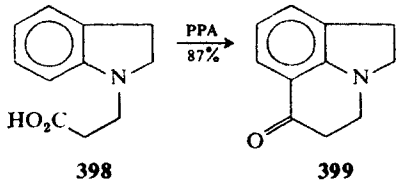
(59)

f. CYCLODEHYDRATION. The preparation of 3,4-dihydro-β-carbolines (**396**) from acetyltryptamines (**394**) in the presence of phosphorus oxychloride or polyphosphoric acid (Bischler-Napieralski reaction) represents the most important cyclodehydration reaction of indoles (Scheme 45). Several reviews describe this method in detail.[331, 332]



Scheme 45

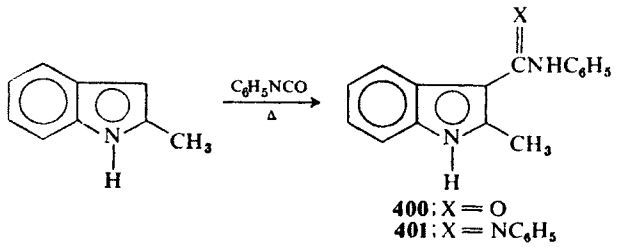
Another example of cyclodehydration is the conversion of 1-indolinepropionic acid (**398**) to 1-ketolilolidine (**399**) by polyphosphoric acid[333] (Eq. 60).



(60)

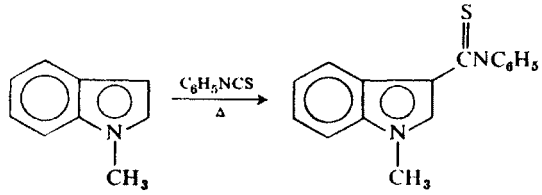
g. Other Methods of Acylation. The Reimer-Tiemann reaction is discussed under the general heading of electrophilic substitution of indoles by carbenes (Section IV.C.12). Acylations of indole alkali metal salts and indole Grignard reagents are described in Section IV.D.

In several cases, highly reactive indoles were acylated at $C_{(3)}$ by heating with phenylisocyanate and phenylisothiocyanate. Thus 2-methylindole and the former reagent afforded a mixture of 3-carboxanilide **400** and its amidine



(61)

derivative **401** (Eq. 61), whereas the latter reagent gave thiocarboxanilide **402** with 1-methylindole[334] (Eq. 62).



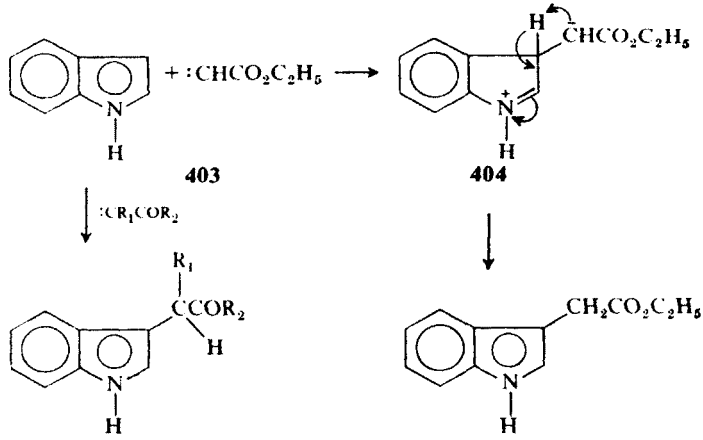
(62)

402

12. *Reactions with Carbenes*

a. α-CARBONYLCARBENES. The products normally expected for electrophilic substitution are obtained when indoles are heated in the presence of copper powder with diazo compounds which contain α-carbonyl groups.[335] Thus indole afforded the ethyl esters of indole-3-acetate (**406**), indole-3-pyruvate (**405a**), indole-3-levulinate (**405b**), and indole-3-succinate (**405c**) when treated with the corresponding diazoesters and diazoketoesters.[336, 337] 1-Methylindole also was substituted at $C_{(3)}$ by ethyl diazoacetate,[338] but 2,3-dimethylindole was unreactive.[335]

These electrophilic substitutions are considered to involve attack of the indole by the α-carbonylcarbenes; for example, carbethoxycarbene (**403**) in the case of ethyl diazoacetate.[335] Rearrangement of hydrogen from $C_{(3)}$ to the negatively charged carbon atom in the side chain of the resulting intermediate (**404**) then affords the product **406** (Scheme 46).



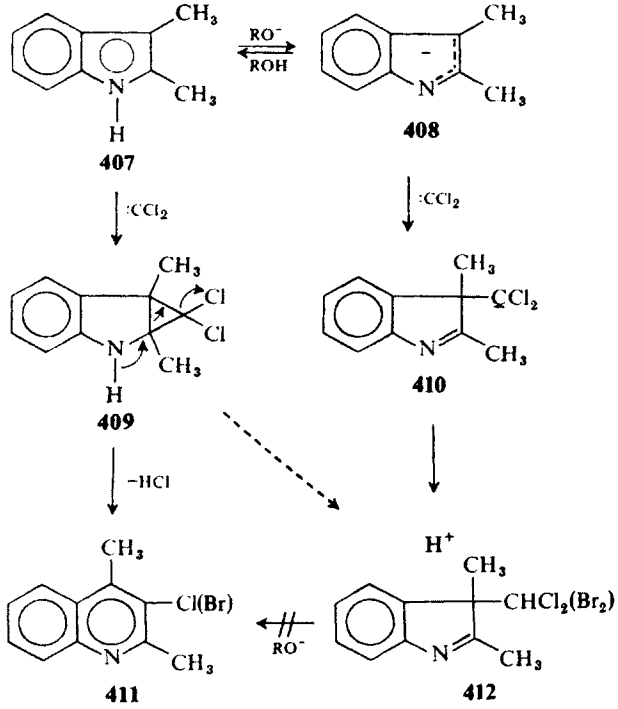
405a; $R_1 = H$, $R_2 = CO_2C_2H_5$
405b; $R_1 = H$, $R_2 = CH_2CH_2CO_2C_2H_5$
405c; $R_1 = CH_2CO_2C_2H_5$, $R_2 = OC_2H_5$

Scheme 46

b. HALOCARBENES. In contrast to the simple products obtained from α-carbonyl carbenes and indoles, treatment of indoles with halocarbenes affords quinolines in addition to compounds derived from 3-halomethylindoles or 3-halomethylindolenines. These products are of little preparative value, but the reactions by which they are formed have received considerable attention.[335]

When 3-unsubstituted indoles are treated with chloroform and alkali or ethoxide (Reimer-Tiemann conditions) the corresponding indole-3-carboxaldehydes are obtained in low yields. Small amounts of haloquinolines are also formed. These reactions are generally considered to involve interaction of dichlorocarbene with the indoles.[335, 339]

The reactions of dihalocarbenes with 2,3-dimethylindole (**407**) have been carefully studied.[340–342] That the dihalocarbenes are more reactive than α-carbonylcarbenes is apparent, since examples of the latter type fail to react with this indole.[336] From the dihalocarbenes, mixtures of 3-halo-2,4-dimethylquinolines (**411**) and 3-dihalomethyl-2,3-dimethylindolenines (**412**) are obtained. Their relative proportions depend upon the mode of carbene formation.[340] Thus with chloroform and sodium ethoxide in ethanol 11% of

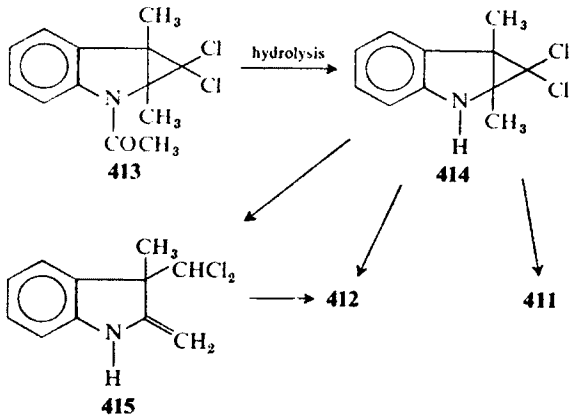


Scheme 47

411 and 13% of **412** were obtained, indicating a quinoline/indolenine ratio of 0.9, whereas ratios of 0.4 and 2.6 were found when the dichlorocarbene was generated from ethyl trichloroacetate and potassium *t*-butoxide and from sodium trichloroacetate in refluxing 1,2-dimethoxyethane, respectively. When the corresponding tribromoacetates were used under the last two sets of conditions, the ratios of quinoline to indolenine were 1.15 and 6.4, respectively. Only the indolenine (**412**) was obtained from the reaction of **407** with potassium *t*-butoxide and ethyl chlorodifluoroacetate[340] (Scheme 47.)

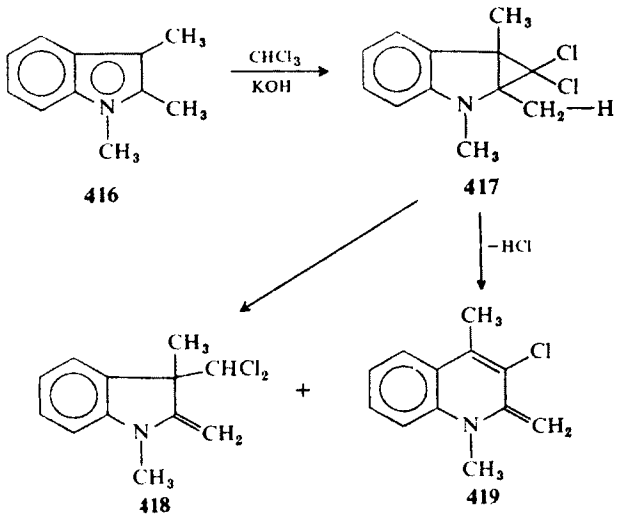
The above-described product ratios are accounted for by the following possible mechanism.[335] In neutral solutions the dihalocarbene adds to the 2,3-double bond of 2,3-dimethylindole, forming an intermediate (**409**) which has a cyclopropyl ring. This intermediate is unstable and opens to give the quinoline **411** and possibly a small amount of the indolenine **412**. In the presence of strong bases the ambident anion **408** is formed from the indole and it is attacked at $C_{(3)}$ by the dihalocarbene. Protonation of the resulting carbanion (**410**) then affords the indolenine **412**. That the indolenine is not converted into the quinoline has been established in several investigations.[340, 341]

An alternative mechanism was based upon studies in which the dichlorocarbene was generated by interaction of chloroform-^{14}C and methyl lithium.[342] Acetyl chloride was added to the mixture in order to trap any intermediates. In addition to **411** and **412** this mixture afforded, after washing and purging with carriers, a solution from which both **411** and **412** could be obtained by alkaline hydrolysis. It was proposed that this solution contained a labile cyclopropane intermediate (e.g., **413**) which upon hydrolysis gave **414**, the precursor common to **411** and **412**. Formation of the indolenine **412** by way of 2-methyleneindoline **415** was also considered possible[342] (Scheme 48).



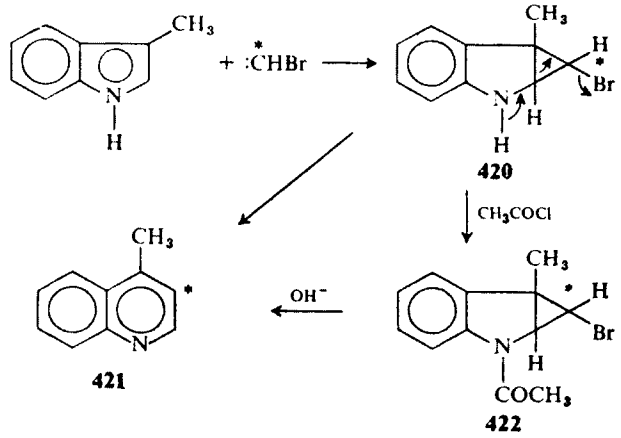
Scheme 48

1,2,3-Trimethylindole (**416**) is unable to lose a proton from nitrogen following the addition of dichlorocarbene. Instead it gives up a proton from the 2-methyl group, affording methyleneindoline **418** and 2-methylene-1,2-dihydroquinoline **419**[340] (Scheme 49).



Scheme 49

In contrast to the usual observations that 3-methylindole reacts more slowly than indole in electrophilic substitution, a radiotracer technique revealed that the former reacted 1.8 times as rapidly as the latter with bromocarbene (generated from methyl lithium and methylene bromide).[343] Addition of acetyl chloride to the mixture led to the isolation of a neutral



Scheme 50

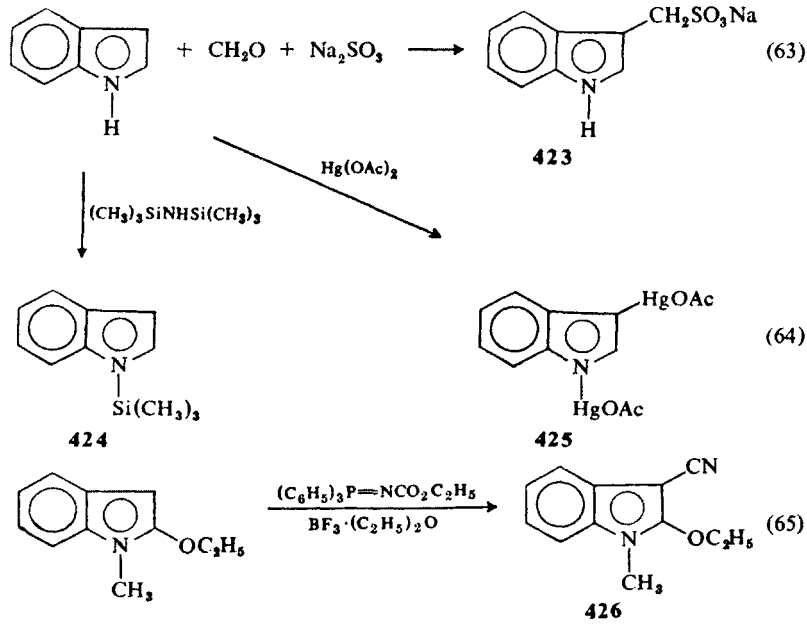
compound which was thought to be cyclopropane derivative **422** on the basis of its ir absorption. Upon alkaline hydrolysis this intermediate gave 4-methylquinoline (**421**) labeled at $C_{(3)}$[343] (Scheme 50).

Treatment of indole with chlorocarbene afforded 13% of quinoline, the only product isolated.[344, 345] It is conceivable that some 3-chloromethylindolenine was formed initially, but this compound would readily lose HCl and polymerize.[345]

13. *Miscellaneous Electrophilic Substitutions*

a. SULFOMETHYLATION. Treatment of indole with formaldehyde and sodium sulfite in aqueous solution at reflux temperature gave sodium 3-indolemethanesulfonate (**423**) in 52% yield (Eq. 63). This salt was converted to the relatively unstable free acid by passage through an acid resin column.[346]

b. REACTION WITH ETHOXYCARBONYLIMINOTRIPHENYLPHOSPHORANE. A 96% yield of 2-ethoxy-1-methylindole-3-carbonitrile (**426**) was obtained upon



(63) (64) (65)

heating a solution of 2-ethoxy-1-methylindole, ethoxycarbonyliminotriphenylphosphorane, and BF_3-ether in tetrahydrofuran[347] (Eq. 65).

c. HEXAMETHYLDISILAZANE. *N*-Trimethylsilylindole (**424**) was formed upon heating indole with hexamethyldisilazane[348] (Eq. 64).

d. MERCURATION. Treatment of indole with 2 moles of mercuric acetate in water or ethanol afforded in high yield a diacetoxymercuri derivative, which appeared to be 1,3-diacetoxymercuriindole (**425**) on the basis of labeling experiments with deuterium and tritium (Eq. 64). Thus tritium at $C_{(2)}$ of indole was not lost by mercuration and demercuration, whereas reduction of unlabeled **425** with lithium aluminum incorporated deuterium only at $C_{(3)}$. A 3,3-diacetoxymercuri derivative could not be rigorously excluded.[349]

D. Indolyl Anions

1. *Introduction*

In neutral indoles $C_{(3)}$ has the highest electron density and is the preferred site of electrophilic substitution according to theoretical reactivity indices. Protonation occurs mainly at $C_{(3)}$ in solution, although certain salts of *N*-protonated indoles have been isolated (Section IV.B). Alkylation of neutral indoles can be effected only under vigorous conditions, and then mixtures of polyalkylated indoles and indolenines are obtained. The initial alkylation is at $C_{(3)}$ if this position is unsubstituted (Section IV.C).

Since indoles are relatively acidic, varying in pK_a from 12 for indole-3-carboxaldehyde to 18 for tryptamine (Section II.E), they may be readily converted into the corresponding indolyl anions by treatment with bases. Nearly all indoles give potassium salts with potassium *t*-butoxide, and the more acidic indoles form salts when treated with sodium methoxide or even aqueous sodium hydroxide. These indolyl anions bear a formal negative charge on the nitrogen, which causes this atom to become the most nucleophilic in the molecule. Electron density at $C_{(3)}$ and other carbon atoms is enhanced due to delocalization of charge from nitrogen, but this effect is apparently insufficient to keep $C_{(3)}$ more nucleophilic than $N_{(1)}$. The transition states for reactions such as alkylation and acylation are probably lower at $N_{(1)}$ than at $C_{(3)}$ since the π-electron system of the indole nucleus is not interrupted by bond making at $N_{(1)}$, whereas it is at $C_{(3)}$. Indolenines would be initially formed by reaction at $C_{(3)}$, but they could readily rearrange to the corresponding indoles if no other substituent is present at this position.

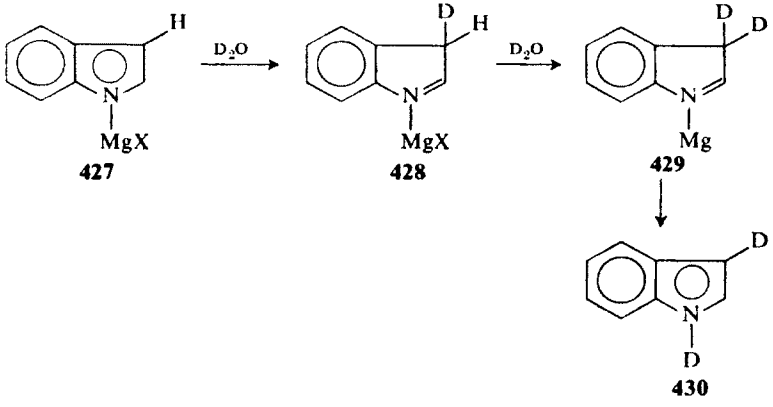
It is thus anticipated that indolyl anions should preferentially react on nitrogen when treated with electrophiles. This is generally true under conditions where the free anions exist. However, conditions are frequently encountered in which intimate ion pairs or even higher aggregates of ions are present.[350] Furthermore, certain divalent metals tend to form partially covalent bonds with the indolyl nitrogen. This is particularly true for

indolylmagnesium halides in ether. In these circumstances the metal may decrease the nucleophilicity of $N_{(1)}$ to such an extent that it is less reactive than $C_{(3)}$.

Reversibility of substitution is also an important factor with indolyl anions. Carboxyl and carbonyl substituents on $N_{(1)}$ are particularly prone to rearrange to $C_{(3)}$ at higher reaction temperatures.

2. *Structure and Protonation*

In tetrahydrofuran solution both indolyl sodium and indolylmagnesium bromide appeared to exist largely as the free anions. Their nmr and ir spectra showed striking similarities and no NH was observed in either case.[102, 351] Addition of D_2O afforded rapid exchange on nitrogen for the magnesium salt as well as for the sodium salt in tetrahydrofuran. When D_2O was added to the sodium and lithium salts of indole in ether, the deuteration was again entirely on nitrogen; however, the magnesium salt in ether gave up to 75% exchange at $C_{(3)}$ with a moderate excess of D_2O, and the zinc salt gave a small amount of exchange at $C_{(3)}$.[352] A large excess of D_2O gave almost complete deuteration on nitrogen with the magnesium salt. These results have been explained in the following manner.[352] In both media the alkali metal salts are largely ionic. The magnesium salt is largely ionic in tetrahydrofuran, but in ether the N—Mg bond has substantial covalent character. Addition of D_2O to the magnesium salt (**427**) in ether forms indolenine **428** which remains coordinated to magnesium. This complex has a sufficient lifetime for the hydrogen atom on $C_{(3)}$ to be displaced by a second deuterium before collapse to 1,3-dideuterioindole (**430**) occurs (Eq. 66). When a large excess of D_2O is added the N—Mg bond is dissociated to ionic species which give N-deuteration before there is time for exchange by way of indolenine **428**.



(66)

3. *Alkylation*

In contrast to the alkylation of neutral indoles, the alkylation of indolyl anions takes place at low temperatures (usually room or ice-bath temperatures) and generally the main product results from introduction of a single alkyl group. Sometimes small yields of 1,3-dialkyl derivatives are obtained, since the indolenines that result from 3-alkylation can react with excess alkyl halide. The ratio of $N_{(1)}$ to $C_{(3)}$ alkylation is influenced most strongly by the degree of dissociation of the nitrogen-metal bond of the indolyl salt.[350, 353] Thus $N_{(1)}$ alkylation is increased by more polar solvents, especially those of high cationic solvation power such as hexamethylphosphorotriamide (HMPT). It is also increased by dilution and improved solubility. In one study treatment of indolyl potassium with allyl bromide gave the following $N_{(1)}/C_{(3)}$ ratios in various solvents: heptane 1.1; toluene 1.4; dioxane 7.5; tetrahydrofuran 12.6.[353] Alkylation of indolylmagnesium with allyl bromide gave almost exclusive reaction at $C_{(3)}$ in tetrahydrofuran and acetonitrile, but in HMPT allylation occurred almost completely at $N_{(1)}$.[354] The coordinating ability of the cation strongly influenced the $N_{(1)}/C_{(3)}$ ratio for the reaction of allyl bromide with indolyl anion in tetrahydrofuran, with the following values reported: Li^+ 0.27; Na^+ 1.52; K^+ 12.6; $(CH_3)_4N^+$ gave 100% $N_{(1)}$ allylation. In comparison, indolylmagnesium bromide in ether afforded an $N_{(1)}/C_{(3)}$ ratio of 0.009 for allylation.[353]

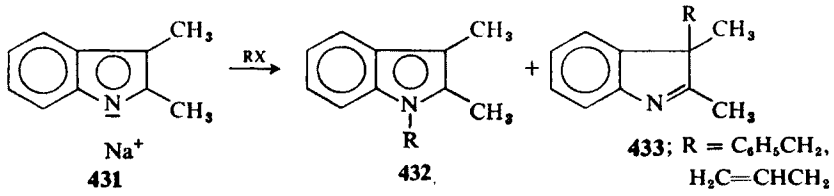
The S_N1 character of the alkyl halide also influences the ratio of substitution at $N_{(1)}$ to $C_{(3)}$. Table XVII shows the results for a series of primary halides with indolyl sodium in tetrahydrofuran. It is evident from this table that as the S_N1 character of the alkyl halide becomes stronger the proportion of $C_{(3)}$ alkylation increases. The total amount of $C_{(3)}$ alkylation may be

TABLE XVII. Products from the Alkylation of Indolyl Sodium in THF[354]

	Weight % composition of product indoles[a]			
Alkyl halide	1-Alkyl	3-Alkyl	1,3-Dialkyl	3,3-Dialkyl
Methyl bromide	96		4	(Indolenine)
Methyl iodide	85		15	
Ethyl bromide	76.5	2.3	2.6	
Ethyl iodide	63.6	12.8	10.5	
Benzyl bromide	37.5	17.5	24.5	5.5
Allyl bromide	38.3	26.1	17.7	2.7

[a] The difference between the total and 100% represents recovered indole.

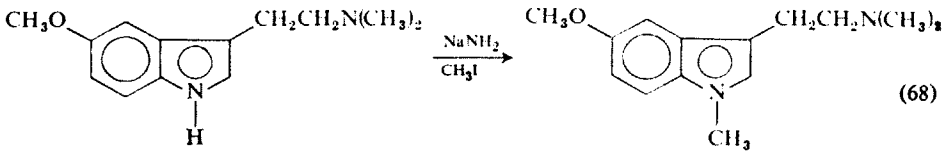
taken as the sum of 3-alkyl, 1,3-dialkyl, and 3,3-dialkylindolenine products. Similar findings were obtained in the alkylation of 2,3-dimethylindolyl sodium (**431**) in liquid ammonia.[355] Methyl iodide gave mainly 1-alkylation with **431**, whereas benzyl chloride and allyl bromide gave approximately equal amounts of 1-alkyl derivative **432** and 3-alkylated indolenine **433** (Eq. 67). In toluene **431** gave mostly 1-alkylation with methyl iodide; however, with benzyl chloride and allyl bromide mainly the indolenine **433** was obtained.[356]



431 **432** **433**; R = $C_6H_5CH_2$, $H_2C{=}CHCH_2$ (67)

During the preparation of 3,3-dialkylindolenines from 3-alkylindolylmagnesium iodides and alkyl iodides it was found that when excess methylmagnesium iodide (used to form the indolyl Grignard reagent) was present these dialkylindolenines underwent nucleophilic addition to the 1,2-double bond, affording 2,3,3-trialkylindolines.[357]

Preferential alkylation of the indole nitrogen of tryptamines may be carried out on the indolyl salt. Thus treatment of *N,N*-dimethyl-5-methoxytryptamine (**434**) with sodium amide in liquid ammonia, followed by methyl iodide, afforded its 1-methyl derivative **435** in good yield[358] (Eq. 68). Alkylation of



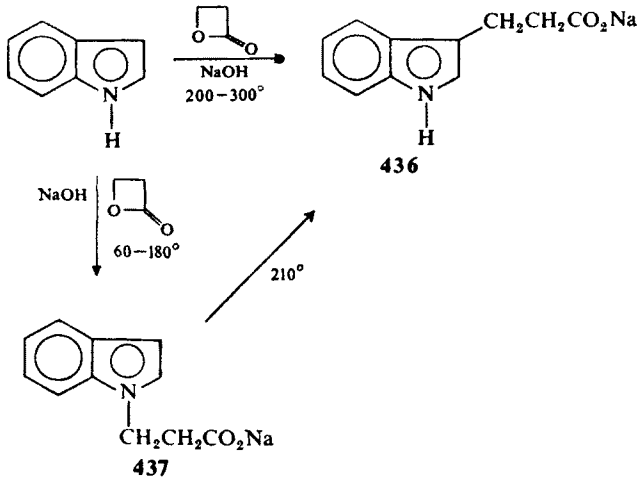
434 **435** (68)

tryptophan under similar conditions with methyl, ethyl, allyl, and benzyl halides gave the corresponding 1-alkyl tryptophans without racemization.[359] In the case of 5-benzyloxytryptamine, extensive alkylation of the side-chain nitrogen occurred with sodium amide and methyl iodide. However, exclusive 1-methylation was obtained with potassium carbonate and methyl toluenesulfonate.[360]

Alkylation of $N_{(1)}$ of indole-3-carboxaldehyde was effected with methyl iodide in the presence of such a weak base as sodium carbonate in acetone.[170]

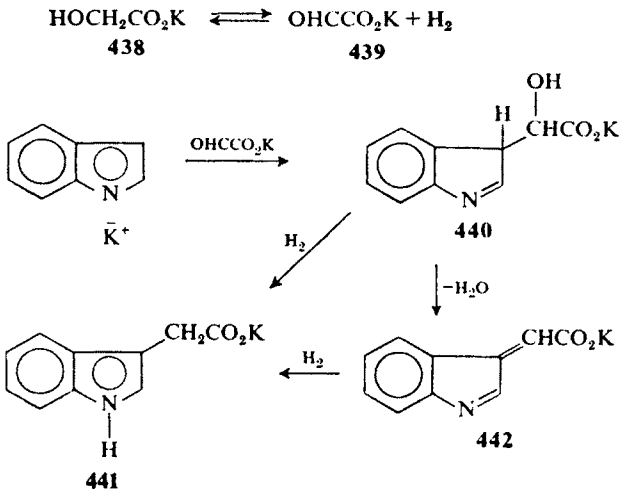
Treatment of indolyl salts with certain alcohols and related compounds has provided useful syntheses for important 3-substituted indoles. Thus a mixture of indole, sodium hydroxide, and propiolactone gave 69% of sodium

indole-3-propionate (**436**) when heated at 200–300°. The same mixture at 60–180° gave the corresponding 1-propionate **437**, which could be rearranged to **436** by heating at 210° [361] (Scheme 51). Indoles substituted at $C_{(3)}$ with



Scheme 51

homologous acids were obtained from alkylation with 5-, 6-, and 7-membered ring lactones at the higher temperatures. Indole, potassium hydroxide, and potassium glycolate furnished potassium indole-3-acetate (**441**) in 90% yield.[362] This reaction (Scheme 52) is considered to involve an equilibrium



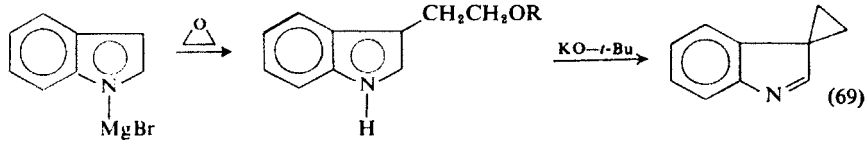
Scheme 52

between potassium glycolate (**438**) and potassium glyoxalate (**439**) plus hydrogen. Indolyl potassium adds to the potassium glyoxalate and the resulting hydroxyacetate derivative **440** loses water to give 3-methyleneindoline **442**. The hydrogen present then reduces **442** to product **441**. If the hydrogen pressure which develops in the reaction vessel is released, the yield of **441** falls. Since 1-alkylindoles do not react with potassium glycolate under identical conditions, the need for the potassium salt of indole is apparent.[362]

The 3-alkylated indoles obtained under these conditions apparently represent equilibrium control of the products, since the kinetic control products from alkylation of indolyl potassium are expected to be 1-alkyl derivatives.

Other primary and secondary alcohols, including benzyl alcohol and 2-octanol, also alkylate the 3-position of indolyl anions. In one study the neutral indoles were heated in *p*-cymene with potassium salts of these alcohols.[363] 2-Methylindole and 2-phenylindole were rapidly alkylated at $C_{(3)}$, whereas 3-methylindole was unreactive under these conditions. Potassium *t*-butoxide failed to alkylate indole, presumably because of steric hindrance in the transition state.

Hydroxyalkyl and aminoalkyl substituents have also been introduced into $C_{(3)}$ of indolyl anions. One synthesis of gramine consisted of treating indolylmagnesium bromide with dimethylaminoacetonitrile.[364] Tryptophol (**443a**) was prepared from ethylene oxide and indolylmagnesium bromide.[365, 366] Treatment of tryptophol tosylate (**443b**) with potassium *t*-butoxide afforded an interesting 3,3-dimethyleneindoline[253] (Eq. 69).

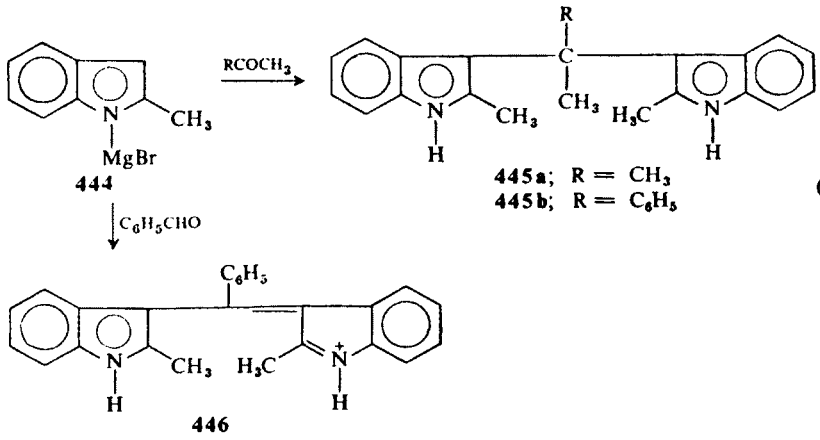


(69)

443a; R = H
443b; R = $SO_2C_7H_7$

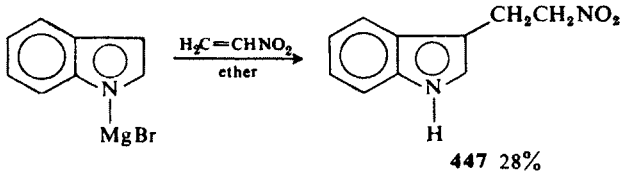
Addition of formaldehyde to indolylmagnesium bromide furnished 3-hydroxymethylindole.[367] In contrast, dimeric products (**445a** and **445b**) were obtained by reaction of 2-methylindolylmagnesium bromide (**444**) with acetone or acetophenone.[368] Treatment of **444** with benzaldehyde gave rosindole **446** after air oxidation during workup[369] (Eq. 70).

Indolyl anions readily undergo Michael-type addition to acrylic compounds. The conditions required for these reactions are milder than those of the corresponding additions with neutral indoles (Section III.C.9). For example, indole in the presence of benzyltrimethyl ammonium hydroxide added to acrylonitrile at 80°, affording 1-cyanoethylindole.[370] Indole, potassium acrylate, and a catalytic amount of potassium hydroxide at 250° gave



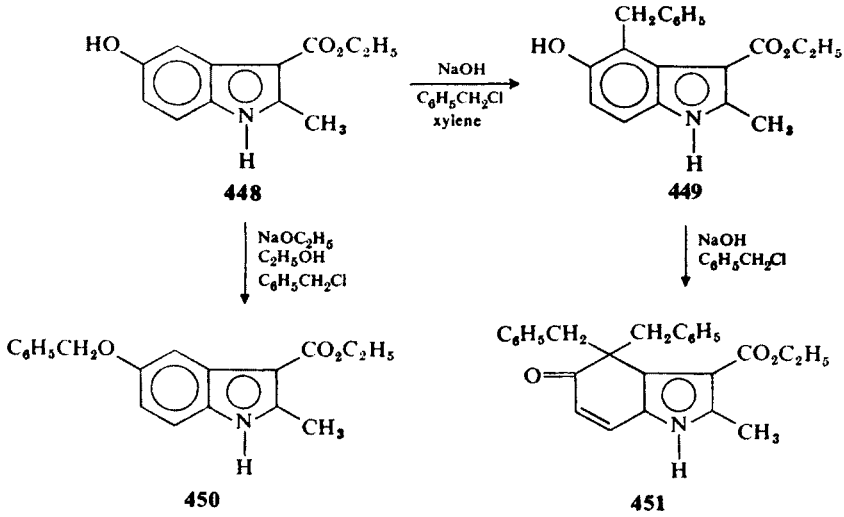
(70)

potassium indole-3-propionate; however, at 225° a 1:1 mixture of the 1- and 3-propionates was obtained.[371] A variety of indole and alkylindole magnesium iodides in ether combined with nitroethylene to give 3-(2-nitroethyl)indoles (**447**)[372, 373] (Eq. 71). The yield obtained with indolemagnesium iodide,



(71)

although low (28%), was superior to that furnished by neutral indole and nitroethylene (20%).



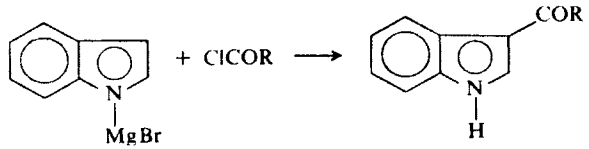
Scheme 53

Indoles substituted with hydroxyl groups in their benzene rings are converted into phenolate-type anions in the presence of base. The NH proton is not removed to a significant degree unless the base is very strong, even when it is activated by an electron-withdrawing group at $C_{(3)}$. Since the phenolate anion is more nucleophilic than the neutral indole nitrogen, the alkylation of the benzene ring of such an indole can be effected under suitable conditions. Thus treatment of ethyl 5-hydroxy-2-methylindole-3-carboxylate (**448**) with sodium hydroxide and benzyl chloride in xylene afforded 4-benzyl derivative **449**. Further alkylation to the corresponding 4,4-dibenzyl compound **451** was also possible. Other alkyl halides gave similar results. When the benzylation was carried out in the presence of sodium ethoxide in ethanol or xylene, the product was *O*-benzyl derivative **450**[374–376] (Scheme 53).

4. *Acylation and Carboxylation*

Most of the acylation and carboxylation reactions of indolyl anions have utilized magnesium halide salts in ether. Under these conditions a relatively covalent N—Mg bond is present, which should lead to a high proportion of substitution at $C_{(3)}$. This is usually true for acylation, but carboxylation appears to favor $N_{(1)}$ at lower temperatures. Higher temperatures sometimes cause the relatively unstable 1-carboxylates to rearrange to $C_{(3)}$.

Indolylmagnesium bromide and 2-methylindolylmagnesium bromide in ether afforded 3-alkanoyl derivatives (**452a**) when treated with acyl halides[377, 378] (Eq. 72). These conditions were also satisfactory for acylation with ethyl oxalyl chloride[379] or chloroacetyl chloride,[380, 381] and the acyl derivatives (**452b** and **452c**) thus obtained were important intermediates in

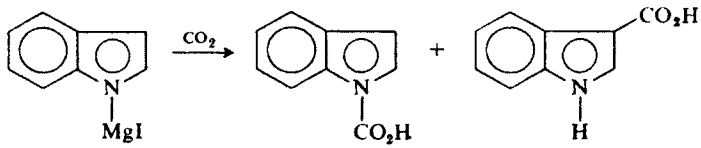


(72)

452a; R = alkyl
452b; R = $CO_2C_2H_5$
452c; R = CH_2Cl

tryptamine synthesis. 3-Methylindolylmagnesium bromide in ether gave a mixture of 1- and 2-acyl derivatives with acyl halides at low temperatures, whereas at reflux temperature only the 2-acyl derivatives were obtained.[378]

Treatment of indolylmagnesium iodide in ether with carbon dioxide afforded approximately equal amounts of the 1- and 3-carboxylic acids (**453** and **454**)[382] (Eq. 73). Ethyl chloroformate at −5° gave a mixture of the corresponding ethyl esters, somewhat richer in the 1-derivative, plus a trace of the 1,3-diester. At 35° a higher proportion of the diester was obtained.[383]

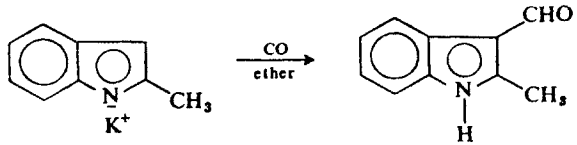


(73)

453 454

In contrast, 2-methylindolyl magnesium bromide gave only 3-carboxylic ester with ethyl chloroformate. It reacted with carbon dioxide to yield the 1-carboxylic acid at low temperatures, but at reflux temperature the 3-carboxylic acid was obtained.[384] 3-Methylindolylmagnesium bromide afforded carboxylation at $N_{(1)}$ with both carbon dioxide and ethyl chloroformate.[384] In this case rearrangement to $C_{(2)}$ or $C_{(3)}$ did not occur. However, 3-methylindolyl sodium and carbon dioxide gave the 2-carboxylic acid derivative.[385]

The potassium salts of certain 2-substituted indoles, including 2-methylindole and 2-phenylindole, reacted with carbon monoxide in ether to give the corresponding 3-carboxaldehydes (e.g., **455**) in moderate yields (56% for 2-methylindole) (Eq. 74). These formylations are thought to proceed by way



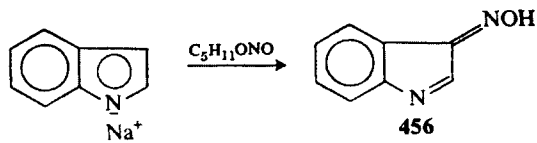
(74)

455; 56%

of unstable 1-carboxaldehydes.[386] Potassium indoline gave a stable 1-formyl derivative when treated with carbon monoxide in dimethylformamide.[386] Treatment of indolylmagnesium iodide with ethyl formate afforded a mixture of indole-3-carboxaldehyde (41% yield) and indole-1-carboxaldehyde (40% yield).[387]

5. *Nitrogen, Phosphorus, and Sulfur Derivatives*

Treatment of indolylmagnesium bromide with ethyl nitrate is the preferred method for the preparation of 3-nitroindole.[388] 3-Nitrosoindole (**456**) has been formed from indolyl sodium and amyl nitrite[389] (Eq. 75).

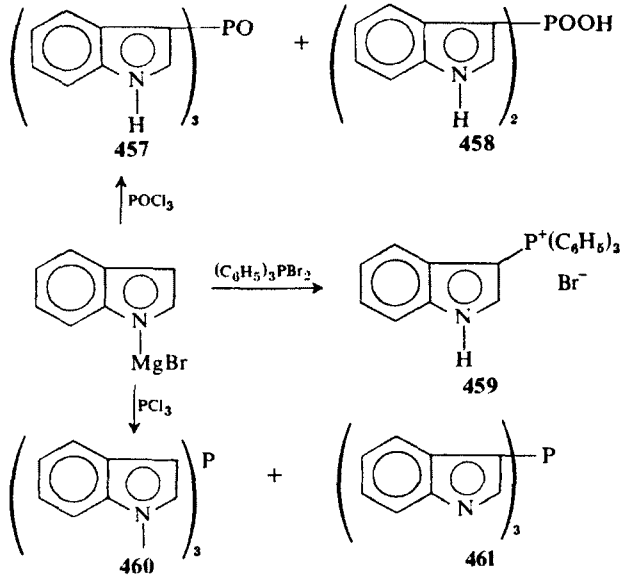


(75)

456

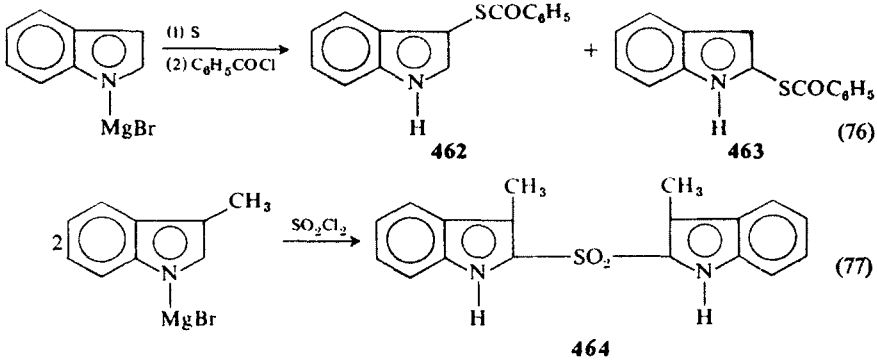
Indolylmagnesium bromide gave a mixture of 1- and 3-triindolylphosphines (**460** and **461**) with phosphorus trichloride, and a mixture of 3-triindolylphosphone **457** and 3-diindolylphosphinic acid **458** with phosphorus

oxychloride.[390] It reacted with triphenylphosphonium dibromide to yield triphenyl-3-(indolyl)phosphonium bromide (**459**)[391] (Scheme 54).



Scheme 54

When indolylmagnesium bromide in ether was treated with sulfur followed by benzoyl chloride, a mixture of benzoylthioindoxyl (**462**) and 2-benzoylthioindole (**463**) was obtained[392] (Eq. 76). 3-Methylindolylmagnesium bromide gave diindolylsulfone **464** with sulfuryl chloride[393] (Eq. 77).



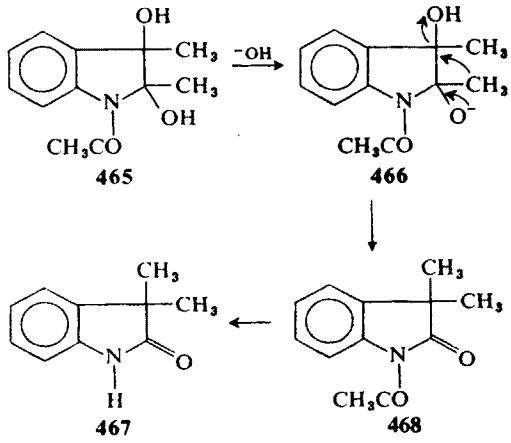
E. Rearrangements

Rearrangements of substituents between the 2- and 3-positions of indoles are common. They occur with a variety of indoles, including indoxyls,

oxindoles, indolines, and indolenines. The driving force is usually formation of a more stable indole system from a less stable one; for example, an indole from a hydroxyindoline or an oxindole from an indoxyl.

A recent comprehensive review[394] of these transformations reduced them all formally to the mechanisms of pinacol, pinacolone, or retropinacol rearrangements, with the exception of the Plancher rearrangement. This system for categorizing indole rearrangements will be followed in the present treatment.

The pinacol-type rearrangement is observed when indoline-2,3-diols further substituted at C_2 and C_3 with alkyl or aryl groups are treated with acidic or basic catalysts. For example, 1-acetyl-2,3-dimethylindoline-2,3-diol (**465**) is converted by hydroxide ion into 2,2-dimethylindoxyl (**467**)[395] (Scheme 55). This type of rearrangement may also take place in the workup

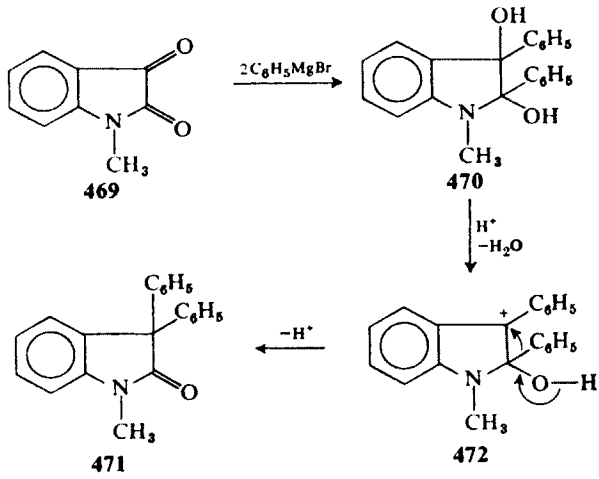


465 **466** **467** **468**

Scheme 55

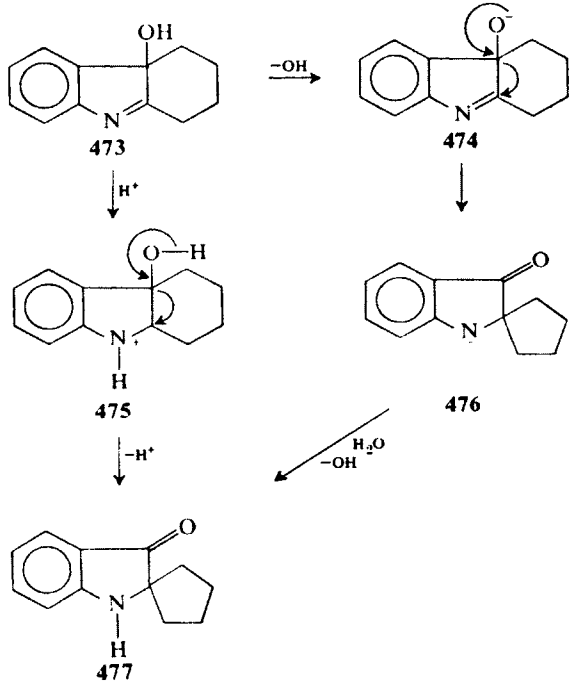
of indoline-2,3-diols derived from treatment of isatins with Grignard reagents. Thus treatment of 1-methylisatin (**469**) with two equivalents of phenylmagnesium bromide initially afforded diol **470**, but upon acidification of the reaction mixture 3,3-diphenyl-1-methyloxindole (**471**) was obtained[396, 397] (Scheme 56). Compounds such as **473** which have a 2,3-dialkyl-3-hydroxyindolenine system undergo similar rearrangement (Scheme 57), since protonation of the nitrogen affords the same type of carbonium ion intermediate (e.g., **475**). Hydroxide ion also converts **473** into **477**.[398] The rearrangement then apparently occurs by way of anions **474** and **476**, and may be considered formally analogous to a benzylic acid-type rearrangement.

The acid-catalyzed rearrangement of **473** to **477** is first order with respect to both **473** and acid, and the rate-determining step is the rearrangement of



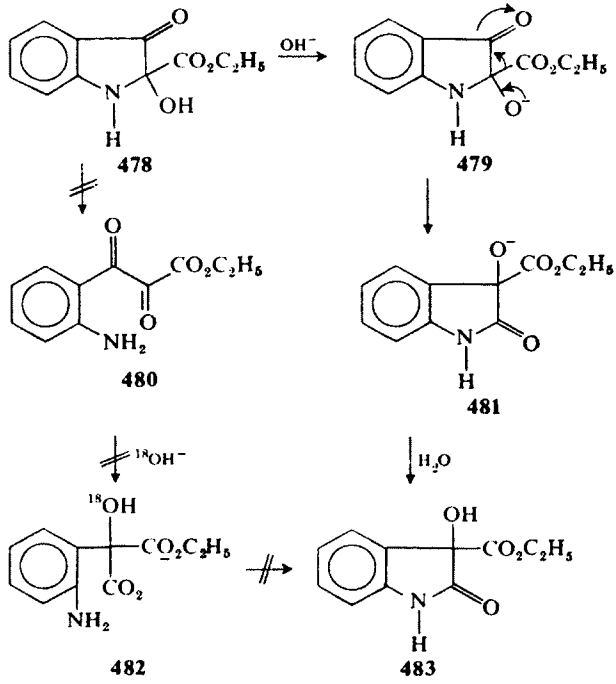
Scheme 56

the carbon skeleton by migration of carbon from $C_{(3)}$ to $C_{(2)}$. Base-catalyzed rearrangement of **473** is also first order with respect to **473** and catalyst, and the skeletal rearrangement (**474** → **476**) is the rate-determining step.[397]



Scheme 57

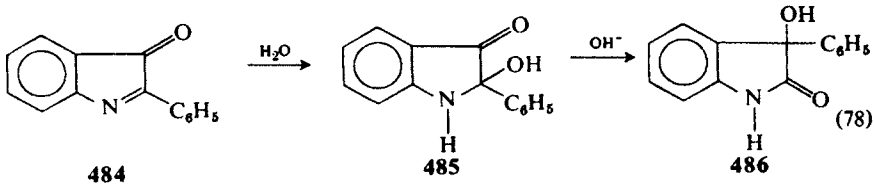
A carefully studied example of the pinacolone-type rearrangement is the base-catalyzed isomerization of ethyl 2-hydroxyindoxyl-2-carboxylate (**478**) to ethyl 3-hydroxyoxindole-3-carboxylate (**483**)[399] (Scheme 58). This



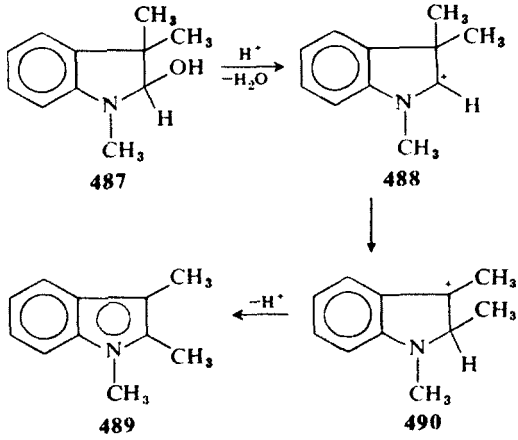
Scheme 58

isomerization appears to involve migration of the carbethoxy group in anion **479**, rather than ring opening followed by rearrangement of the resulting diketone (**480**), since only a small fraction of the ^{18}O theoretically required by the latter process was incorporated from the solvent. The driving force for this rearrangement is evidently formation of the more stable oxindole system from the indoxyl system.

Pinacolone-type rearrangement is also observed when 2-phenyl-3-oxindolenine (**484**) is treated with aqueous alkali.[394] Addition of water across its 1,2-double bond forms 2-hydroxyindoxyl **485**, the anion of which isomerizes to 3-hydroxyoxindole **486** with phenyl migration (Eq. 78).

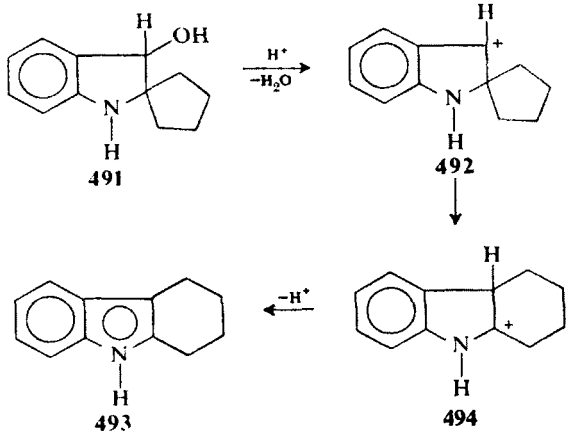


The retropinacol-type rearrangement occurs with indolines disubstituted with alkyl and/or aryl groups on either $C_{(2)}$ or $C_{(3)}$ and hydrogen and hydroxyl groups on the other of these two atoms. It involves aromatization with elimination of water. Thus 2-hydroxy-1,3,3-trimethylindoline (**487**) upon treatment with acid is converted into 1,2,3-trimethylindole (**489**)[400] (Scheme 59).

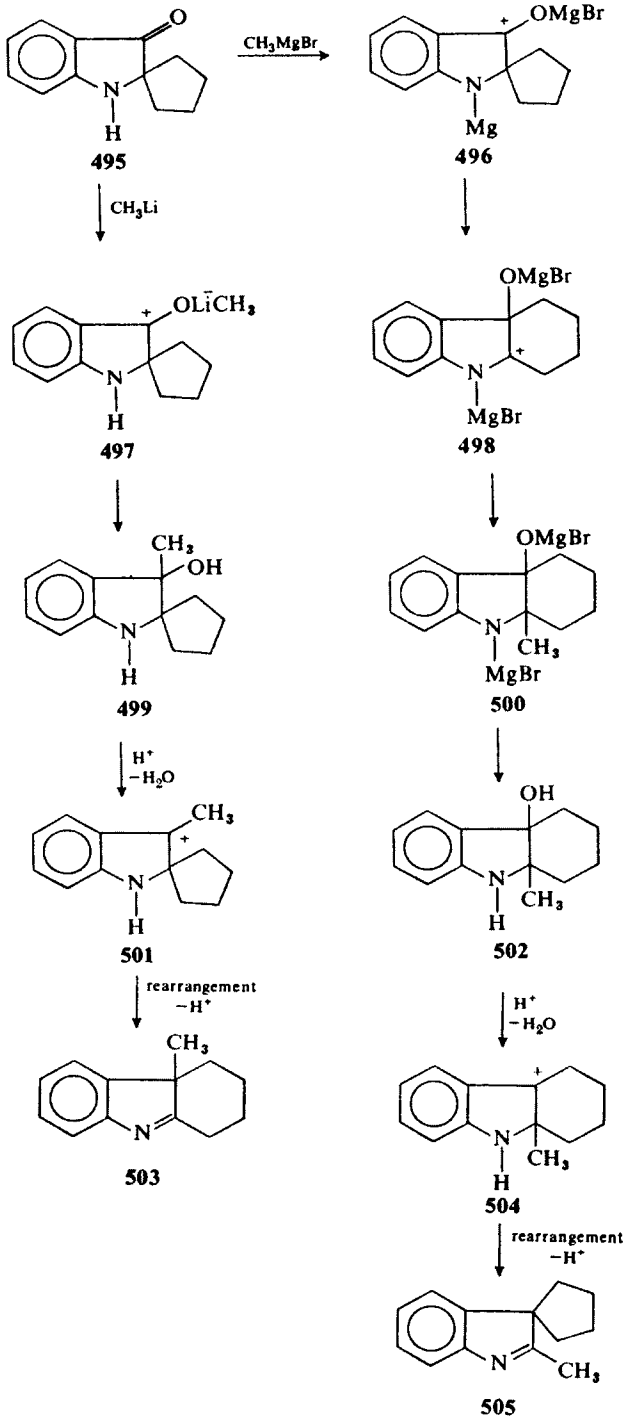


Scheme 59

Apparently a Wagner-Meerwein rearrangement from carbonium ion **488** to carbonium ion **490** is an important step in this transformation.[401] Both of these carbonium ions are stable, hence the conversion is facile. A similar type of mechanism may be written for the transformation of spiroindoline **491** into tetrahydrocarbazole **493**[402] (Scheme 60). Reduction of spiroindoxyl **495**



Scheme 60

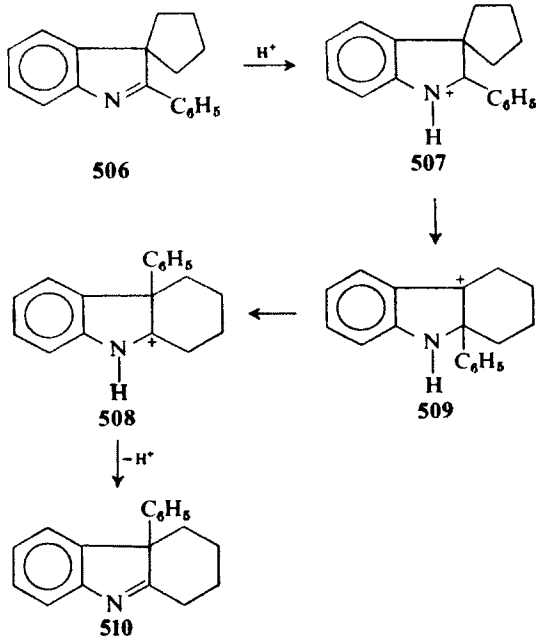

CH3MgBr
CH3Li
rearrangement
−H+
H+
−H2O
495
496
497
498
499
500
501
502
503
504
505

Scheme 61

with lithium aluminum hydride also affords **493**, presumably by way of **491** and the same carbonium ion intermediates.[403]

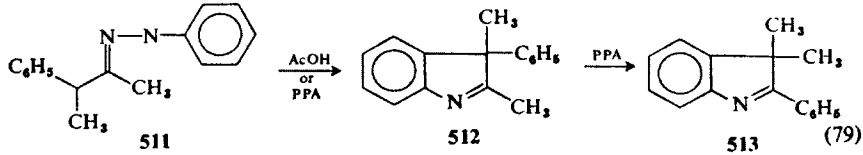
When **495** was treated with methyl lithium, carbazole derivative **503** was obtained. However, methyl magnesium iodide converted **495** into spiroindolenine **505** (Scheme 61). This rather surprising difference in alkylation products has been explained on the basis of the relative rates of alkylation and rearrangement in the magnesium and lithium coordination complexes (**496** and **497**, respectively) initially formed.[403] Thus rearrangement is faster in **496**, leading to intermolecular alkylation of cation **498**, followed by elimination of the elements of water and rearrangement to spiroindolenine **505**. In contrast, intramolecular alkylation of **497** is faster than rearrangement. The hydroxyspiroindoline (**499**) thus formed undergoes dehydrative rearrangement to **503**.[403]

The same type of indoleninium ions formed by acid-catalyzed dehydration of the hydroxyindolines described above may also be obtained by protonation of suitable 3,3-dialkylindolenines, consequently rearrangement to the same kind of products is observed in both cases. For example, spiroindolenine **506** is converted by polyphosphoric acid into carbazole derivative **510** by a twofold Wagner-Meerwein rearrangement through intermediates **507–509**[404] (Scheme 62).



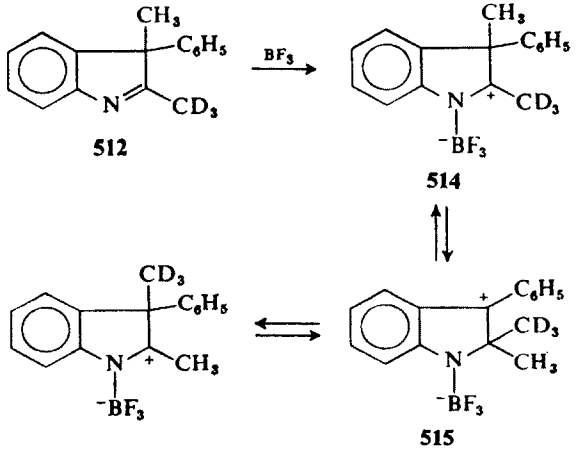
Scheme 62

Fischer indole synthesis with hydrazones derived from ketones bearing two substituents on the same α-carbon (e.g., **511**) also affords this type of indolenine, which may undergo rearrangement under suitable conditions. Thus warming hydrazone **511** in acetic acid gave only indolenine **512**; however, when polyphosphoric acid was the catalyst a mixture of **512** and the product of phenyl migration (**513**) was obtained[405] (Eq. 79).



511 **512** **513** (79)

The status of 2,3-dimethyl-3-phenylindolenine (**512**) in acid is actually more complex than it might seem at first (Scheme 63). An experiment wherein this



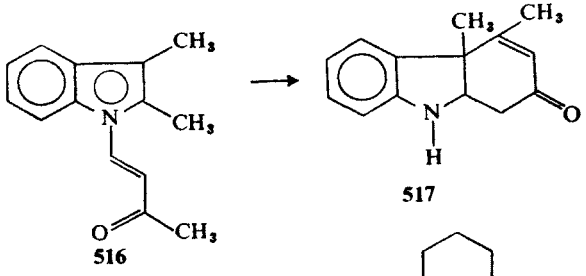
512 **514** **515**

Scheme 63

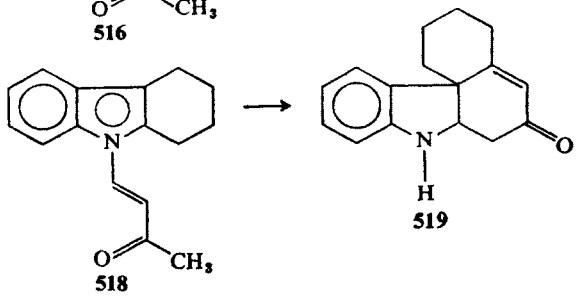
compound was completely deuterated in the methyl group on $C_{(2)}$, then treated with boron trifluoride and heated in xylene, afforded the same type of 2,3-dimethyl-3-phenylindolenine, but the CD_3 group was equally distributed between $C_{(2)}$ and $C_{(3)}$.[406] This result shows that the two methyl groups interchange in an equilibrium process (**514** ⇄ **515**). When the experiment was repeated with ^{14}C at the 2-position there was no rearrangement of this label, indicating that the methyl groups probably migrate by twofold Wagner-Meerwein rearrangement rather than by a ring-opening process.[406]

Rearrangement to 2,3-disubstituted indoles also occurs with 3,3-dialkylindoleninium ions formed by alkylation of 3-alkylindoles. Such rearrangements are entirely intramolecular and the relative migratory aptitude of each alkyl group determines which one rearranges.[190] These processes are described in more detail in Section IV.C.7.

The rearrangements observed[407] upon treatment of 2,3-dimethyl-1-(3-oxobut-1-enyl)indole (**516**) and 9-(3-oxobut-1-enyl)-1,2,3,4-tetrahydrocarbazole (**518**) with aqueous acid or alkali (Eqs. 80 and 81) are complex and the products (**517** and **519**, respectively) rather remarkable, particularly



516 **517** (80)



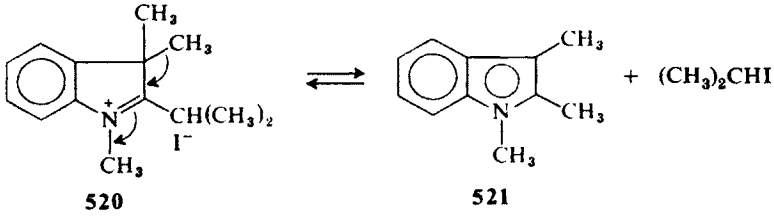
518 **519** (81)

since the indole aromaticity is destroyed without the creation of an apparently more stable system.

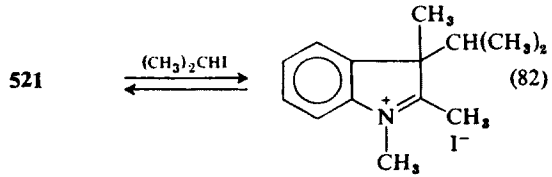
The Plancher rearrangement is characteristic of 1,2,3,3-tetraalkylindoleninium iodides and the related alkyl-aryl quaternary salts. It occurs when these salts are heated above their decomposition temperatures, giving rise initially to a 1,2,3-trisubstituted indole and an alkyl iodide. This alkyl iodide always contains the alkyl group from $C_{(2)}$, which is replaced at $C_{(2)}$ by the smallest group from $C_{(3)}$. These products then combine at some other temperature to give a new indoleninium iodide, providing that this salt is more stable than the starting material[408–410] under the experimental conditions.

For example, when 2-isopropyl-1,3,3-trimethylindoleninium iodide (**520**) was heated above its melting point, rearrangement to the corresponding 3-isopropyl-1,2,3-trimethyl compound (**522**) occurred. Isopropyl iodide and 1,2,3-trimethylindole (**521**) were the presumed intermediates in this transformation (Eq. 82).

In general, of two isomeric indoleninium iodides containing the same groups in a different arrangement at $C_{(2)}$ and $C_{(3)}$, the one with the largest group at $C_{(2)}$ melts with decomposition at a lower temperature. Therefore the other isomeride can be formed and exist at temperatures equal to or higher than this decomposition point.[410] Application of this principle to the alkylation of



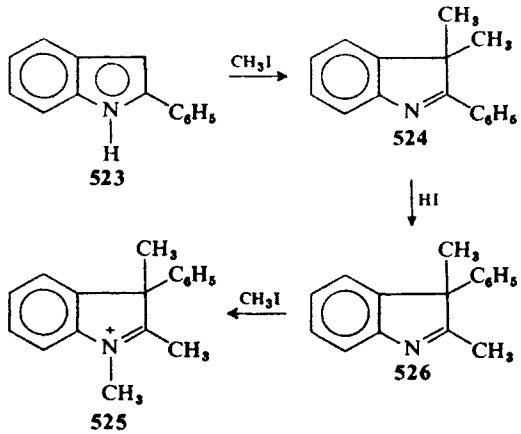
520 521



522

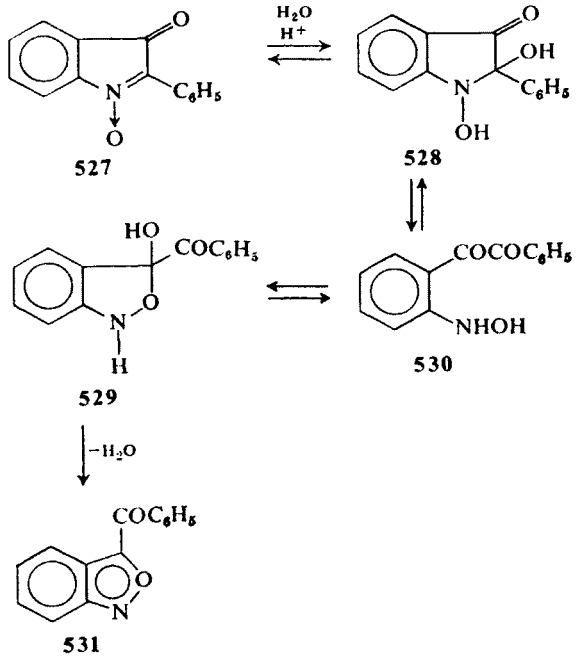
1,2,3-trialkylindoles leads to the conclusion that if the alkylation is carried out below the decomposition point of the initial product, no rearrangement takes place. However, above its decomposition temperature rearrangement would be possible.

Since complete methylation of 2-phenylindole (Section IV.C.7) gave the 3-phenyl-1,2,3-trimethyl salt (**525**) rather than the corresponding 2-phenyl derivative, it must be supposed that rearrangement of the phenyl group took place before salt formation, since the latter compound is stable under the experimental conditions. The likely stage of phenyl group migration was with indolenine **524** in the presence of liberated HI[411] (Scheme 64).



Scheme 64

2-Phenylisatogen (**527**) rearranges in sulfuric acid solution to 3-benzoylanthranil (**531**). A possible course for this transformation involves reversible hydration, ring opening, and reclosure to **529**, which then forms **531** by irreversible dehydration[412] (Scheme 65).



Scheme 65

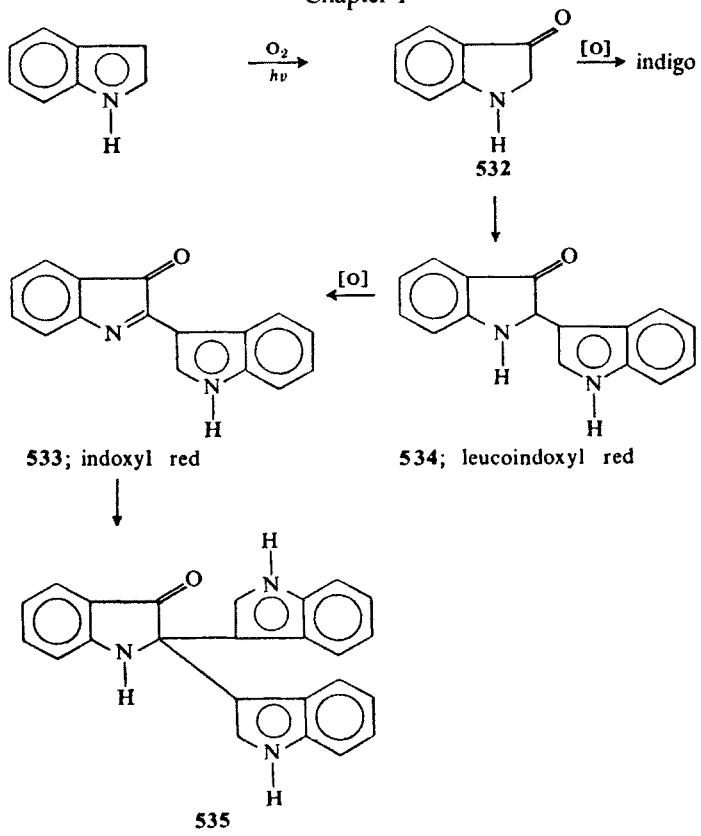
Addition of halocarbenes to indoles affords intermediates which contain cyclopropane rings. The rearrangement of these intermediates to quinolines is discussed in section IV.C.12.

Rearrangements of the indole alkaloids will not be treated here. However, this topic has been thoroughly covered in a recent review.[413]

F. Oxidation

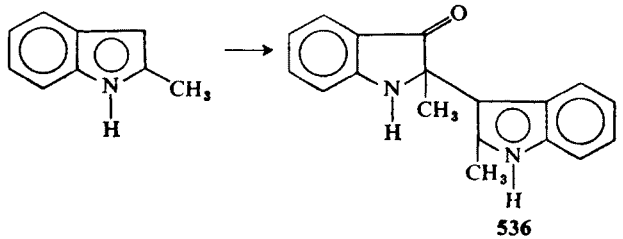
1. *Autoxidation and Catalytic Oxidation*

Autoxidation of indole by air and light affords indoxyl (**532**), which can react further to give either indigo or trimer **535**.[414] This trimer is probably formed by way of leucoindoxyl red (**534**) and indoxyl red (**533**). The latter of



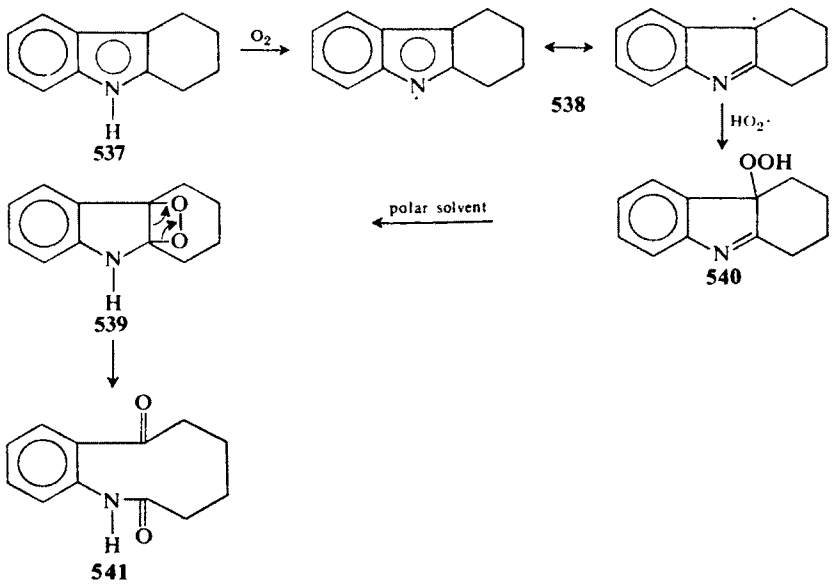
Scheme 66

these dimers is known to give **535** by combination with indole[415] (Scheme 66). 2-Methylindole is converted under similar conditions into the dimethyl derivative (**536**) of leucoindoxyl red[416] (Eq. 83).



(83)

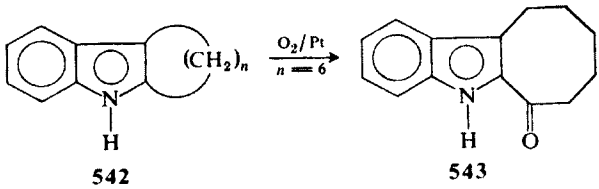
The autoxidation of tetrahydrocarbazole (**537**) has been carefully studied[417] (Scheme 67). It is thought to be a free-radical process, initiated by abstraction



Scheme 67

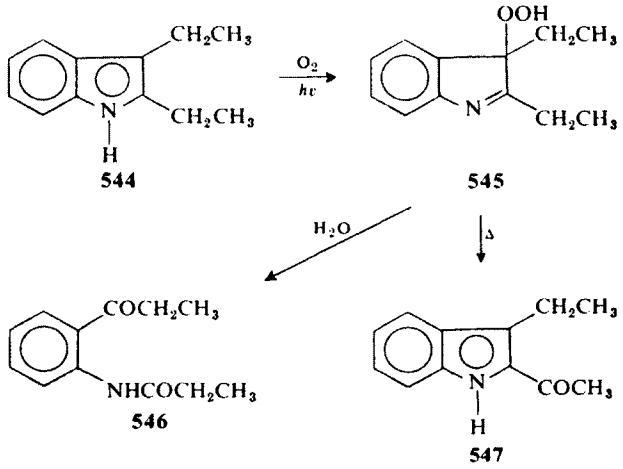
of hydrogen from the nitrogen by molecular oxygen. The resulting mesomeric carbazole radical (**538**) then combines with the hydroperoxy radical to give hydroperoxide **540** (isolated in 75% yield). This hydroperoxide is stable when dry, but it is very unstable in polar solvents. Presumably polar solvents induce further polarization of the N=C bond, promoting internal addition of oxygen to the carbon end of this bond. The quasi-four-membered cyclic intermediate (**539**) thus formed can readily open to give the isolated keto amide (**541**). This process has been suggested as the fundamental model reaction underlying most oxidations of indoles wherein the 2,3-double bond is cleaved.[417]

Related keto amides were also obtained by catalytic oxidation of indoles (**542**) having polymethylene bridges between $C_{(2)}$ and $C_{(3)}$ of three and five units; however, when the bridge contained six methylene groups the 2,3-double bond was not cleaved. Instead, a product (**543**) that had a single carbonyl group was obtained[418] (Eq. 84).



(84)

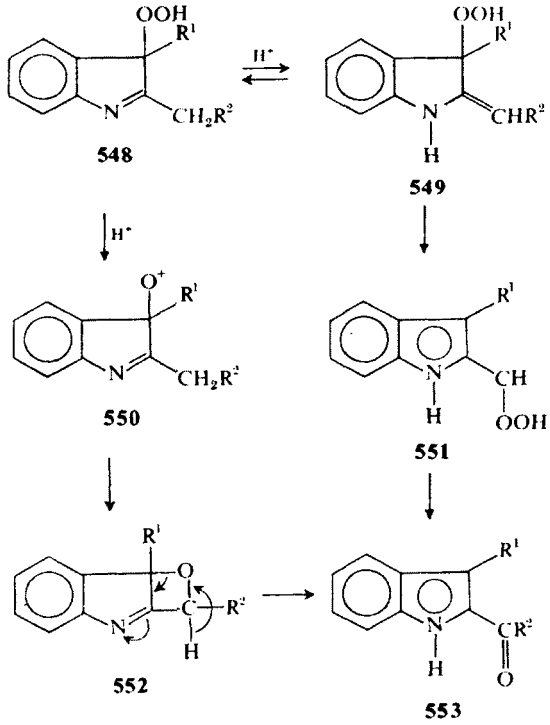
Autoxidation of 2,3-diethylindole (**544**) afforded 2-acetyl-3-ethylindole (**547**), which also had a carbonyl group adjoining $C_{(2)}$. The 3-hydroperoxyindolenine (**545**) is evidently an intermediate in this reaction, since it can be obtained in nearly quantitative yield by exposing a solution of **544** in petroleum ether to air, and it is converted into **547** in 52% yield when heated on a steam bath.[419] Treatment of **545** with boiling water gave keto amide **546**, rather than **547**, which again suggests an important role for polar solvent in promoting cleavage of the 2,3-double bond (Scheme 68).



Scheme 68

Several mechanisms have been proposed for the formation of 2-acylindoles from 3-hydroperoxyindolenines. One proposal features tautomerization of the indolenine **548** to the corresponding methyleneindoline, followed by allylic rearrangement of the hydroperoxy group (**548** → **549** → **551**),[420] whereas another suggested mechanism was based upon acid-catalyzed decomposition of the hydroperoxy group to give an intermediate (**550**) with positively charged oxygen, which is capable of insertion into a C—H bond of the methylene group attached to $C_{(2)}$.[418] The resulting intermediate **552** then could readily open to product **553**. Promotion of the reaction by acid catalysts is consistent with both of these routes (Scheme 69).

When a hexane solution of 2-isopropyl-3-methylindole was treated with oxygen, methyleneindoline hydroperoxide **554** was initially formed. Longer exposure to oxygen afforded oxindole **556** and hydroxyacylaminoacetophenone **558** (Scheme 70). These products were accounted for by a third mechanism, in which the methyleneindoline hydroperoxide **554** rearranged to dihydroxyindolenine **555**. This indolenine then added a molecule of hydrogen peroxide



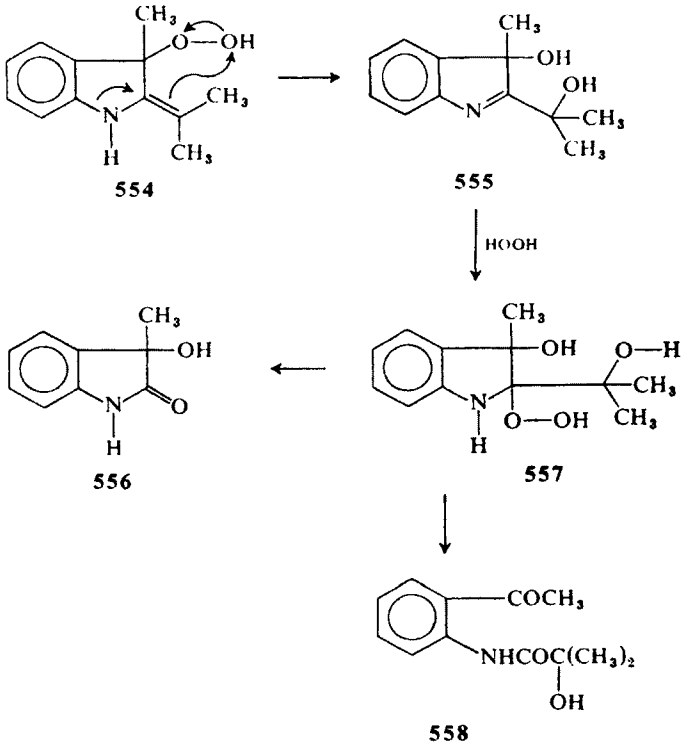
Scheme 69

to the N=C bond and the resulting 2-hydroperoxyindoline **557** decomposed in two different ways to give **556** and **558**.[421]

A 3-hydroxyoxindole (**560**) was also given by 2-benzyl-3-phenylindole (**559**) upon autoxidation. However, catalytic oxidation of **559** afforded the 2-benzoyl derivative **561** (Eq. 85). Two distinct routes appear to be operating here, since there is no conversion of **561** into **560** by air.[422] The formation of these products may be rationalized by the types of mechanism outlined above, but it is not obvious which route is preferable for **560**, or why the products are different for autoxidation and catalytic oxidation.

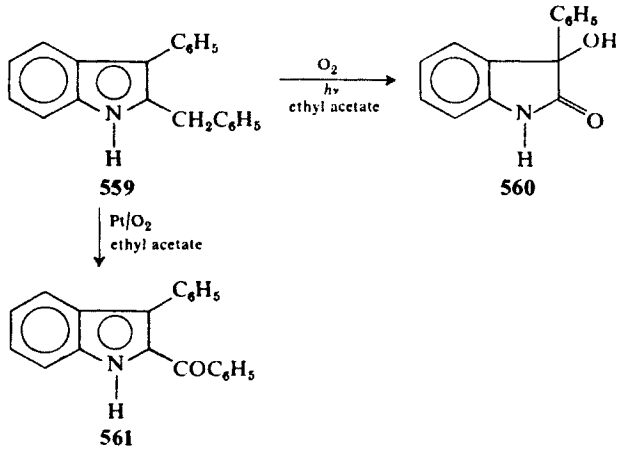
3-Methylindolenines substituted at $C_{(2)}$ with electron-releasing groups such as ethoxy, ethylthio, and piperidino (**562**) afford the corresponding 3-hydroxyindolenines (**564**) upon autoxidation[423] (Eq. 86). These transformations differ from those of other 2,3-disubstituted indoles which give the previously described 2-acylindoles or ketoamides.

The autoxidation of *N*-butylisoindoline (**567**) is a free radical chain process in which *N*-butylisoindole (**568**) is formed by oxidative dehydrogenation[424] (Scheme 71). This process proceeds readily in solvents such as

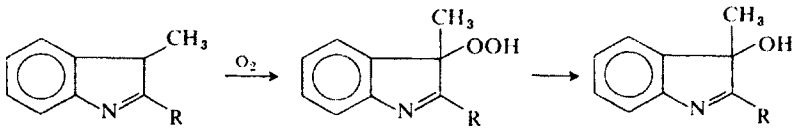


Scheme 70

methyl isopropyl ketone which can serve as hydrogen donors, but is very slow in solvents such as benzene. The intermediate *N*-butylisoindole is rapidly

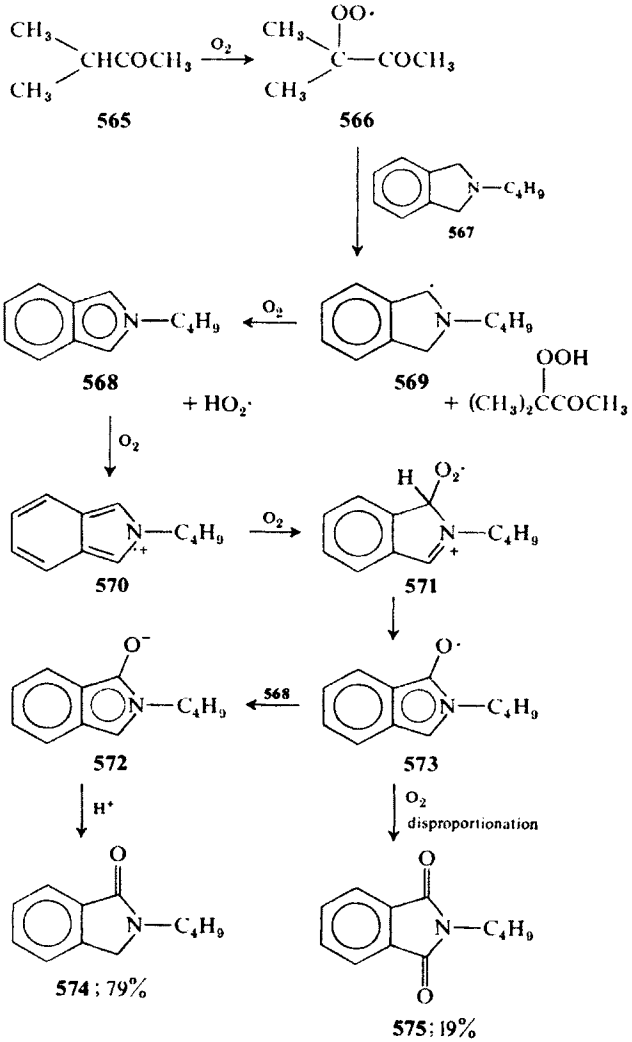


(85)



562 563 564;
R = C_2H_5O, C_2H_5S, $C_5H_{10}N$ (86)

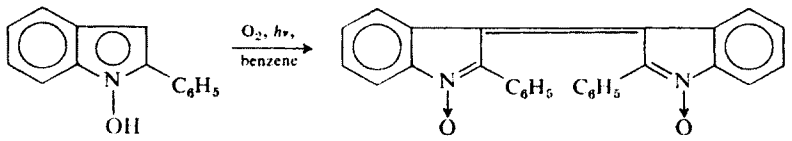
oxidized to a mixture of *N*-butylphthalimidine (**574**) and *N*-butylphthalimide (**575**) in either benzene or methyl isopropyl ketone. Attack of oxygen upon



Scheme 71

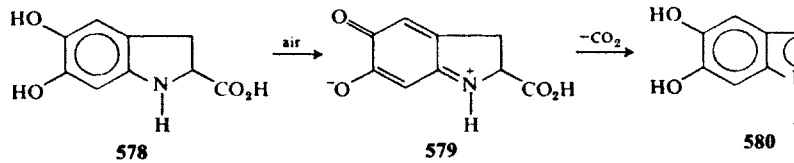
methyl isopropyl ketone (**565**) evidently initiates the chain reaction, affording a peroxyketone radical **566** which is capable of removing a hydrogen radical from the isoindoline. Interaction of the resulting isoindolinyl radical **569** with oxygen could then afford isoindole **568**. Oxidation of **568** might be at least partially initiated by electron transfer to oxygen from the isoindole π-electron system. The resulting radical cation could then combine with oxygen to give **571**. Loss of a proton from **571**, followed by loss of oxygen (disproportionation), would give **573**, which might go directly to phthalimidine anion **572** by removing an electron from **568** in a chain-continuing process. Conversion of **573** into phthalimide **575** can be considered to take place by combination of **573** with oxygen, followed by disproportion.[424]

Autoxidation of 1-hydroxy-2-phenylindole (**576**) afforded dimer **577**[425] (Eq. 87).



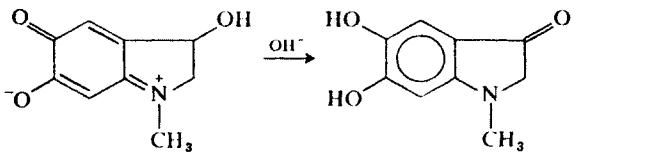
576 **577** (87)

Air oxidation affects the conversion of unstable 5,6-dihydroxyindolines such as leuco dopachrome (**578**) into the corresponding aminochromes (e.g., dopachrome **579**). These aminochromes are subject to partial rearrangement to 5,6-dihydroxyindoles (**579** → **580**), particularly if they do not have a 3-hydroxyl group (Eq. 88). When a 3-hydroxyl group is present, for example



578 **579** **580** (88)

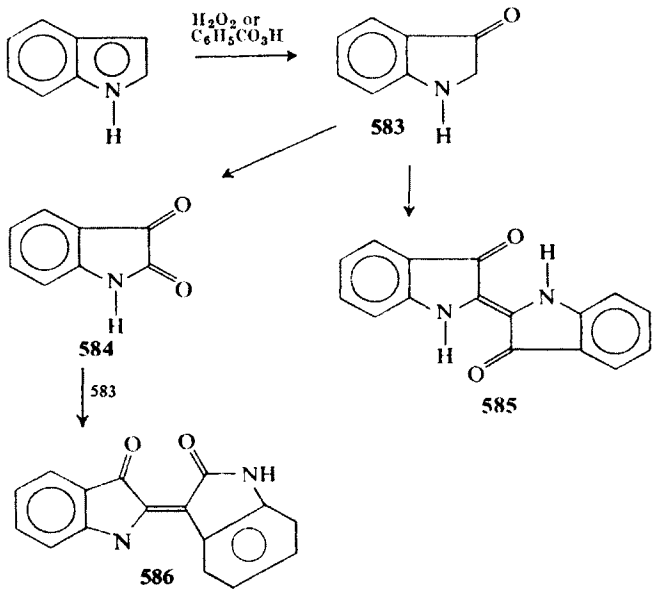
in adrenochrome **581**, base-catalyzed rearrangement to the corresponding dihydroxyindoxyl (**582**) occurs (Eq. 89). Both types of rearrangement involve the equivalent of internal redox reactions.[426]



581 **582** (89)

2. *Chemical Oxidation*

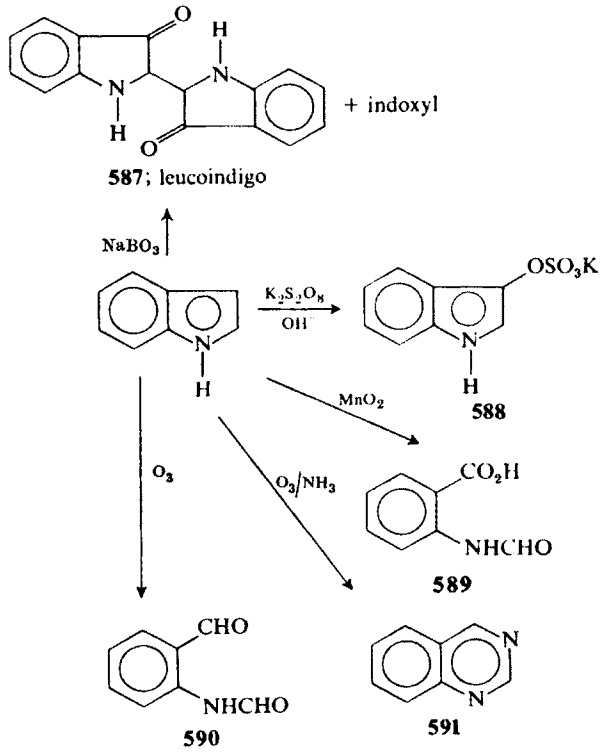
Indole is readily oxidized by a variety of reagents. The extent of oxidation depends upon the particular reagent and experimental conditions, but indoxyl is frequently observed as an intermediate in the processes. Thus hydrogen peroxide or perbenzoic acid converts indole to indoxyl (**583**) and thence to indigo (**585**) plus a small amount of indirubin (**586**) (Scheme 72). The last



Scheme 72

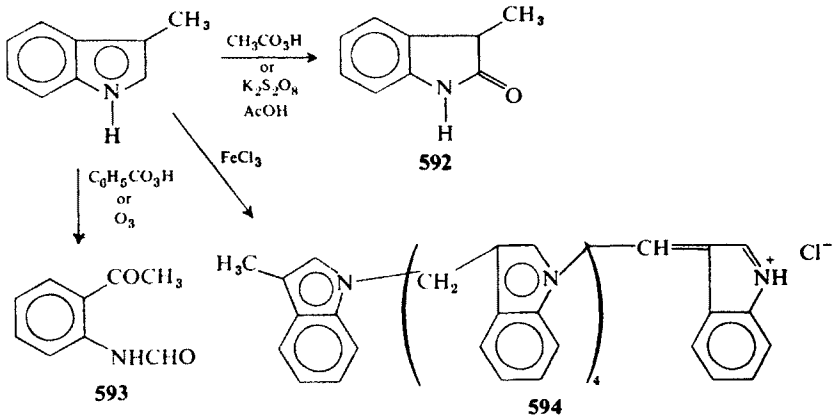
compound is presumably formed by condensation of indoxyl with the by-product isatin (**584**).[427] Sodium perborate in acetone oxidizes indole to a mixture of indoxyl and leucoindigo (**587**),[428] whereas alkaline persulfate affords indoxyl *O*-sulfate (indican, **588**).[429] Oxidative cleavage of indole is obtained by manganese dioxide[430] or ozone,[431] which furnish 2-formamidobenzoic acid (**589**) and 2-formamidobenzaldehyde (**590**), respectively. Amozonolysis (ozone in aqueous ammonia) of indole gave a 9% yield of quinazoline (**591**)[432] (Scheme 73).

In the oxidation of 3-methylindole the product afforded by peracetic acid, 3-methyloxindole (**592**), was different from that given by perbenzoic acid, 2-formamidoacetophenone (**593**).[433] Potassium persulfate and sodium acetate also furnished the former product (38%),[429] whereas ozone yielded



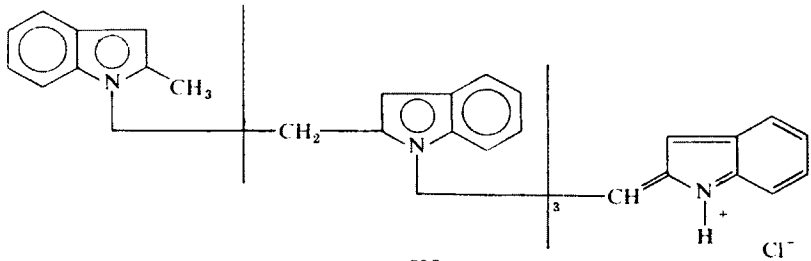
Scheme 73

the latter.[434] With ferric chloride, 3-methylindole gave a red crystalline dye **594** consisting of six monomeric units, thought to be linked through $N_{(1)}$ and the substituent on $C_{(3)}$ as depicted in Scheme 74.[428]



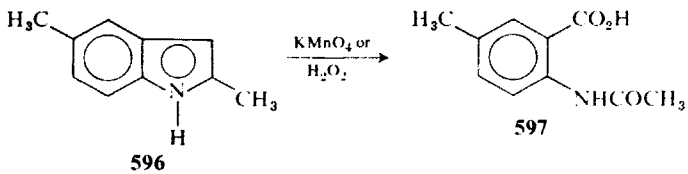
Scheme 74

Oxidation of 2-methylindole with hydrogen peroxide or peracetic acid gives the same dimeric product **536** that was obtained by autoxidation.[433] Ferric chloride converts 2-methylindole into a copper-colored crystalline dye **595**,



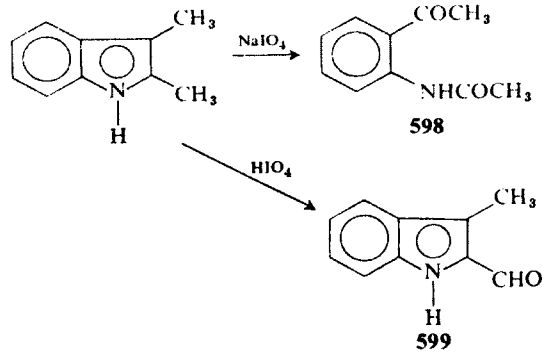
595

containing five units linked through $N_{(1)}$ and the substituent on $C_{(2)}$.[435] Techniques for the determination of structures of 2-methylindoles substituted with additional methyl groups in the benzene ring have been based on oxidation to the corresponding *N*-acetylanthranilic acids by alkaline permanganate or hydrogen peroxide. For example, 2,5-dimethylindole (**596**) afforded *N*-acetyl-4-methylanthranilic acid (**597**)[436] (Eq. 90).



596 **597** (90)

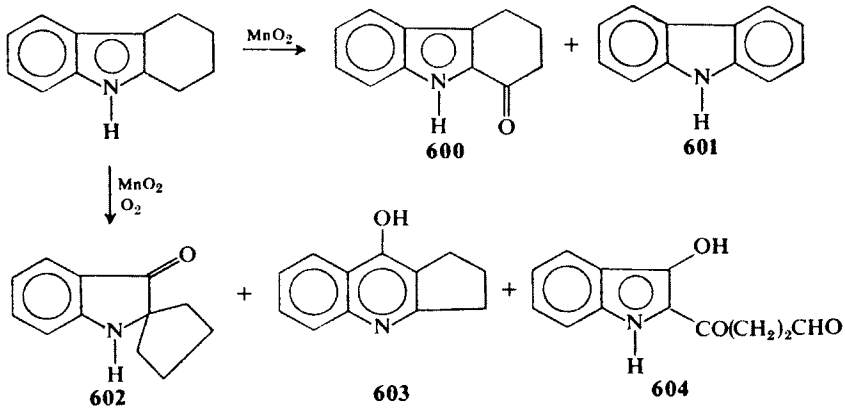
2,3-Dimethylindole undergoes oxidative cleavage to the ketoamide **598** when treated with sodium metaperiodate; however, periodic acid converts it into 3-methylindole-2-carboxaldehyde (**599**) (Eq. 91). Analogous results were



598 **599** (91)

obtained with tetrahydrocarbazole.[437] Manganese dioxide in benzene under nitrogen oxidizes tetrahydrocarbazole to a mixture of carbazole (**601**) and

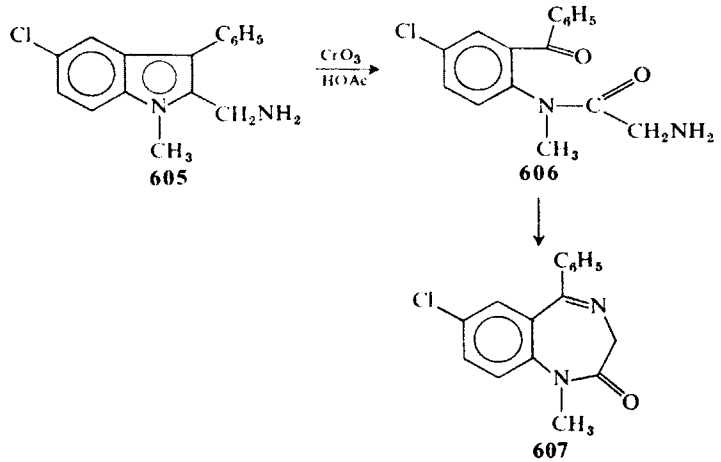
1-oxotetrahydrocarbazole (**600**). If air is admitted to the reaction mixture the products are spiroindoxyl **602**, quinoline **603**, and indole **604**[430] (Scheme 75).



Scheme 75

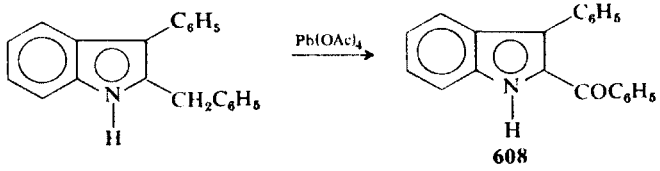
These products presumably derive from hydroperoxyindolenine intermediates.

An important commercial application of oxidative cleavage of the indole 2,3-double bond is the preparation of benzodiazepinone **607** by treatment of indole derivative **605** with chromium trioxide in acetic acid. This process occurs by way of ketoamide **606**[418] (Eq. 92).

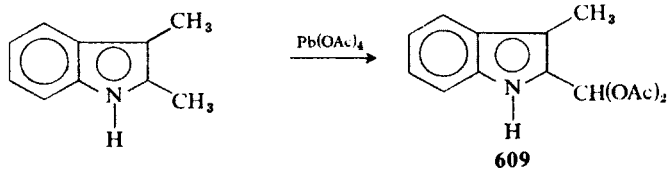


(92)

Lead tetraacetate oxidized 2-benzyl-3-phenylindole to 1-acetyl-2-benzoyl-3-phenylindole (**608**) (Eq. 93), and it converted 2,3-dimethylindole into diacetate **609**[419] (Eq. 94).

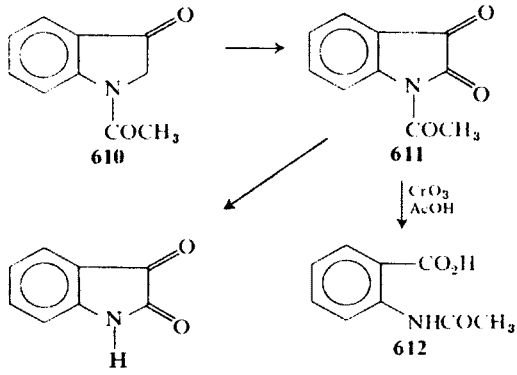


608 (93)



609 (94)

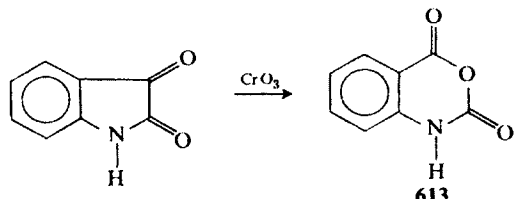
N-Acetylindoxyl (**610**) was converted to isatin by acidic ferric chloride, whereas potassium permanganate oxidized it to *N*-acetylanthranilic acid (**612**).[438] *N*-Acetyl isatin (**611**) is probably an intermediate in both transformations. In support of this postulate the conversion of **611** to **612** by chromic acid has been observed[439] (Scheme 76). Isatin itself was oxidized to



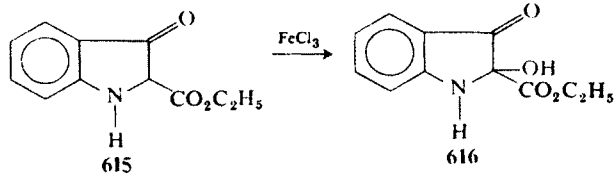
Scheme 76

isatoic anhydride (**613**) by chromic acid,[439] and it afforded anthranilic acid (**614**) when treated with alkaline peroxide[440] (Eq. 95). Oxidation of nitroindoles to isatin and anthranilic acid derivatives during the nitration of indoles was noted in Section IV.C.3. Ferric chloride introduced a 2-hydroxyl group into ethyl indoxyl-2-carboxylate (**615** → **616**)[441] (Eq. 96).

Fremy's salt (potassium nitrosodisulfonate) is a stable free radical which oxidizes phenol and aniline-type compounds to quinones and quinoneimines. With indolines **617** the reaction is initiated by abstraction of the acidic

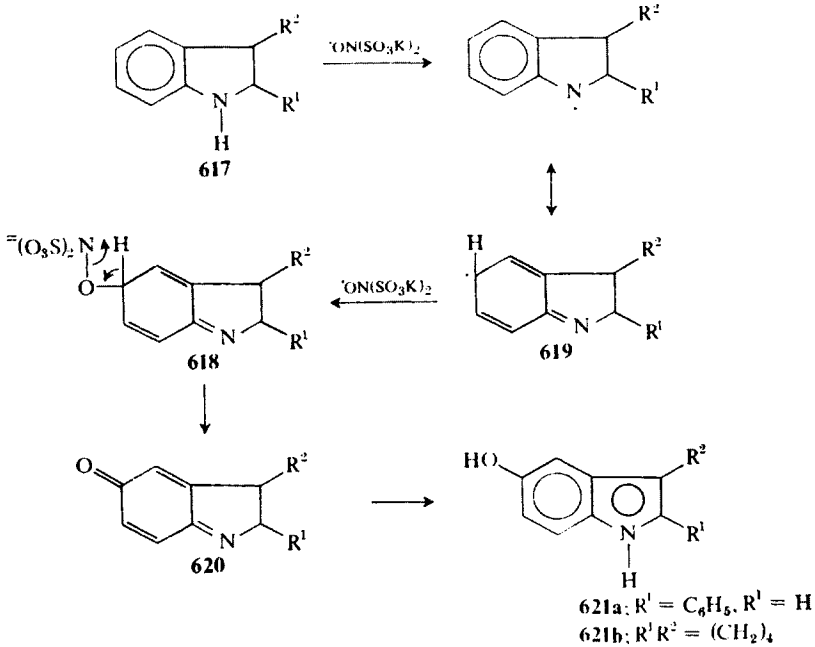


(95)



(96)

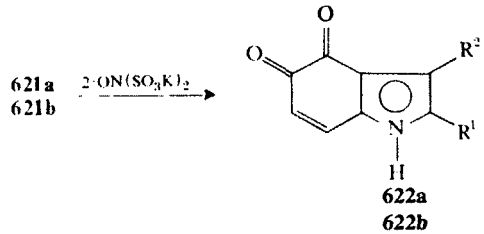
hydrogen on nitrogen. The resulting radical **619** combines with another nitrosodisulfonate radical to afford intermediates of type **618**, which decompose to quinoneimines **620**. These quinoneimines can rearrange to the



Scheme 77

corresponding 5-hydroxyindoles **621** by the equivalent of intramolecular redox reactions[442] (Scheme 77). This process is quite reasonable since, as discussed below, quinones are one of the most important types of reagents for the oxidation of indolines to indoles. Examples of indolines converted to the corresponding 5-hydroxyindoles by Fremy's salt include 3-methylindole, 2-phenylindole, 2,3-dimethylindole, and tetrahydrocarbazole.[442]

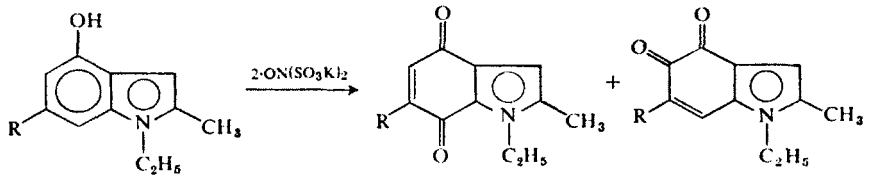
Indoles with hydroxyl groups in the benzene ring, including those formed from indolines, are oxidized by Fremy's salt to indoloquinones.[442, 443] 5-Hydroxyindoles give 4,5-quinones, whereas 4-hydroxyindoles afford mixtures of 4,7-quinones and 4,5-quinones. With hydroxyindoles the oxidation starts with abstraction of the acidic proton on oxygen, then proceeds to the quinone by the same type of mechanism as described above. Thus 5-hydroxy-2-phenylindole (**621a**) and 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**621b**)[443] afforded quinones **622a** and **622b**, respectively (Eq. 97).



622a
622b

(97)

1-Ethyl-4-hydroxy-2-methylindole (**623a**) yielded 68% of *p*-quinone **624a** and 12% of *o*-quinone **625a**[444]; however, its 6-methyl homolog **623b** gave only 5% yields of each type of quinone[445] (Eq. 98). 4-Aminoindoles also give



623a; R = H
623b; R = CH_3

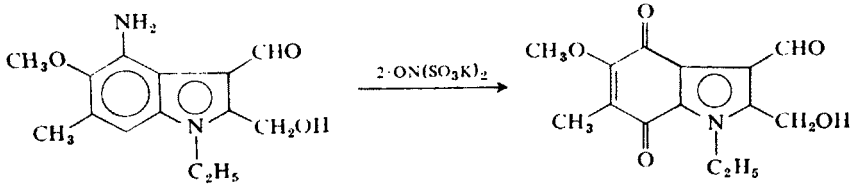
624a; R = H
624b; R = CH_3

625a; R = H
625b; R = CH_3

(98)

quinones upon treatment with Fremy's salt. For example, **626** was converted into quinone **627** by this method[446] (Eq. 99). Noteworthy in this transformation is the fact that the carboxaldehyde and hydroxymethyl groups of **627** were not oxidized by the mild conditions of Fremy's salt reactions.

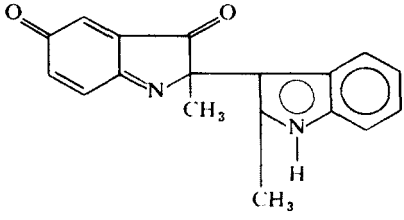
Several examples of the oxidation of indoles without hydroxyl groups by Fremy's salt have been reported. Thus 2-methylindole afforded in acid



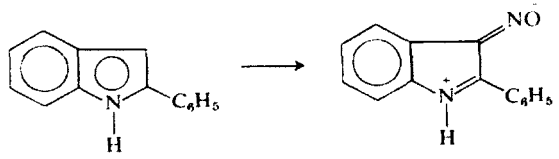
626 627 41%

(99)

solution **587**, the product of its oxidation by several other agents. In neutral solution **587** was further oxidized to blue quinoneimine **628**. 2-Phenylindole gave 3-nitrosoderivative **629** when treated with Fermy's salt[447] (Eq. 100).



628



629

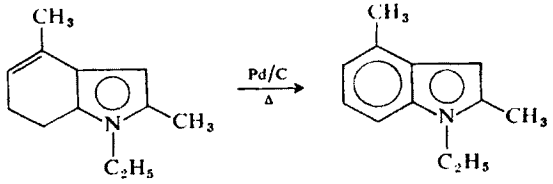
(100)

3. *Dehydrogenation of Indolines and Other Reduced Indoles*

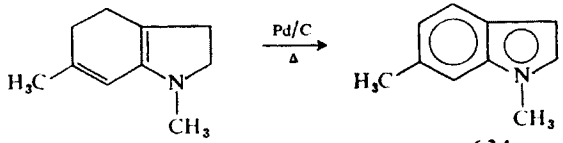
The dehydrogenation of indolines and other hydrogenated indole derivatives to fully aromatic systems has been important in indole chemistry, particularly since certain transformations that fail with the indoles may be carried out on their reduced analogs. Both catalytic and chemical methods are effective for these dehydrogenations; however, it is necessary to select a method suitable to the particular indole.

Catalytic dehydrogenation is usually effected by palladium on charcoal in an aromatic solvent such as cumene or mesitylene, with a hydrogen acceptor such as cinnamic acid sometimes added.[448] Raney nickel has also been used successfully, especially in the conversion of indoline to indole (82%).[419] Indoles partially reduced in the benzene ring, such as 6,7-dihydroindole **630**[330] and 2,3,4,5-tetrahydroindole **632**,[452] have been dehydrogenated to the

indoles **631** and **634** by palladium on charcoal (Eqs. 101 and 102). This method has also been useful for the conversion of 4-oxo-4,5,6,7-tetrahydroindoles **635** (R groups are hydrogen or alkyl) into the corresponding

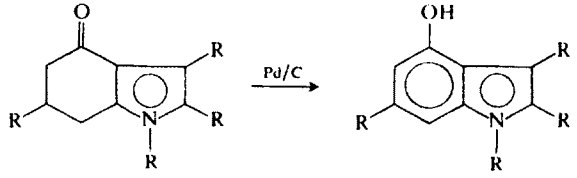


630 631 (101)



632 634 (102)

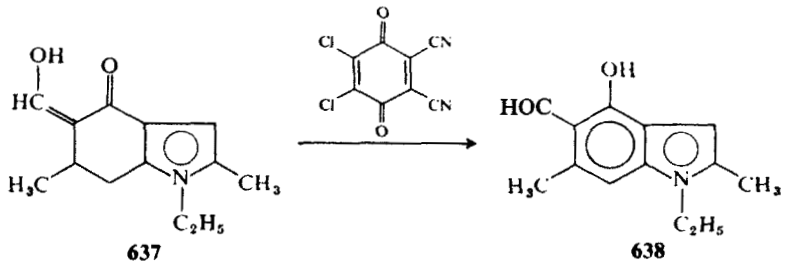
4-hydroxyindoles **636**[330, 450, 451] (Eq. 103). The presence of a 5-methyl substituent appears to strongly inhibit the dehydrogenation of 4-oxotetrahydroindoles.[330]



635 636 (103)

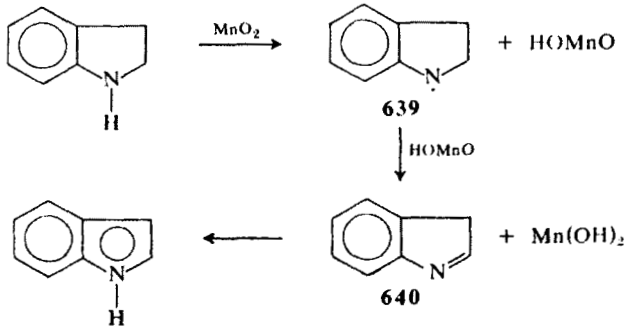
The most important chemical reagents for the formation of indoles from their reduced derivatives appear to be quinones, particularly those of high oxidation potential such as chloranil and dichlorodicyanobenzoquinone (DDQ). Chloranil was used to dehydrogenate indoline, 2-methylindoline, and a variety of 5-acylindolines to the corresponding indoles in generally good yields (95% for indole).[314] Although 4-oxotetrahydroindoles of type **635** gave polymeric products upon treatment with DDQ, when a carboxaldehyde group was present the product hydroxyindole could be isolated. For example, **637** afforded **638** in 65% yield (Eq. 104). Certain 6,7-dihydroindoles with carboxaldehyde substituents also gave the corresponding indoles with DDQ.[330]

Manganese dioxide readily converted indoline into indole.[453] This reaction was described as a free radical process wherein MnO_2 removes a hydrogen



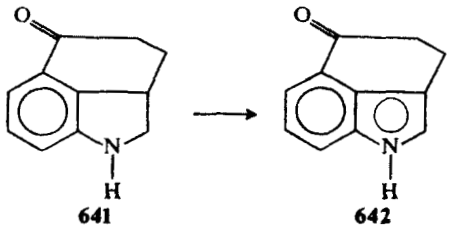
637 638 (104)

radical from indoline. The resulting indolinyl radical **639** apparently then gives up a second hydrogen radical in going to indolenine **640**, which is tautomeric with indole (Scheme 78). Manganese dioxide was the most



Scheme 78

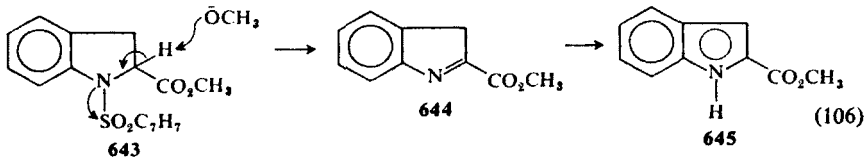
effective reagent for the dehydrogenation of tricyclic indolenine **641** to the corresponding indole **642** (Eq. 105). It gave a 64% yield of **642**, whereas nickel peroxide gave 30% and palladium on charcoal afforded only 5% of **642**.[454]



641 642 (105)

Other chemical reagents that have been used for the dehydrogenation of indolines to indoles include selenium,[455] silver sulfate,[456] cuprous oxide in warm air,[457] and sodium amide in liquid ammonia.[458]

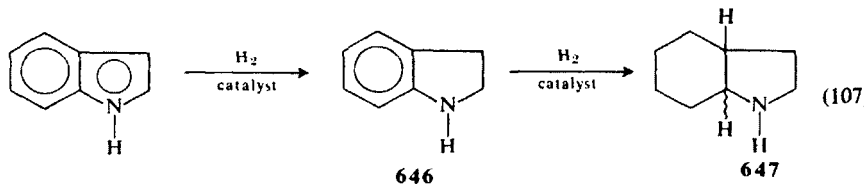
Methylindoline-2-carboxylate was converted into the corresponding indole-2-carboxylate **645** by treatment of its *N*-tosylate **643** with sodium methoxide[459] (Eq. 106).



G. Reduction

1. *Catalytic*

The appreciable resonance energy of the indole nucleus is evident in its resistance to catalytic reduction under neutral conditions. High temperatures and pressures, combined with catalysts such as Raney nickel or copper chromite, are required for hydrogenation, and under these conditions the reduction often proceeds beyond the indoline stage to the octahydroindole stage. For example, indole furnished high yields of octahydroindole (**647**) when treated with hydrogen at 250 atm and 250° in the presence of nickel[460] or at 80 atm and 150° in the presence of ruthenium.[461] Under somewhat milder conditions, Raney nickel in ethanol with hydrogen at 85 atm and 90–100°, indole afforded 82% of indoline (**646**) and only 5% of actahydroindole (**647**)[462] (Eq. 107). For 2,3-disubstituted indoles the equilibrium between

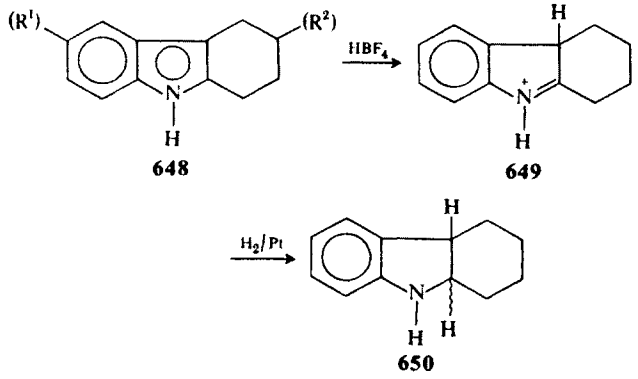


the indoles and hydrogen and the corresponding indolines is not favorable for high yields of the indolines, particularly in the presence of copper chromite.[463] Even Raney nickel does not give efficient reductions of tetrahydrocarbazoles.[464]

In one case the hydrogenation of indole in the presence of nickel at high temperature and pressure was reported to proceed beyond octahydroindole to 2-ethylaniline.[465] It was also claimed that hydrogenation of melted indole at 200° with nickel catalyst afforded *o*-toluidine.[466]

Hydrogenation of indoles in the presence of acids occurs at much lower temperatures (20–60°) and pressures (1–6 atm) than under neutral conditions. Apparently the acid protonates the indole, at least to some extent in equilibrium, and the resulting indolinium cation (for example, **649**) is highly susceptible to hydrogenation. In order for this method to succeed the

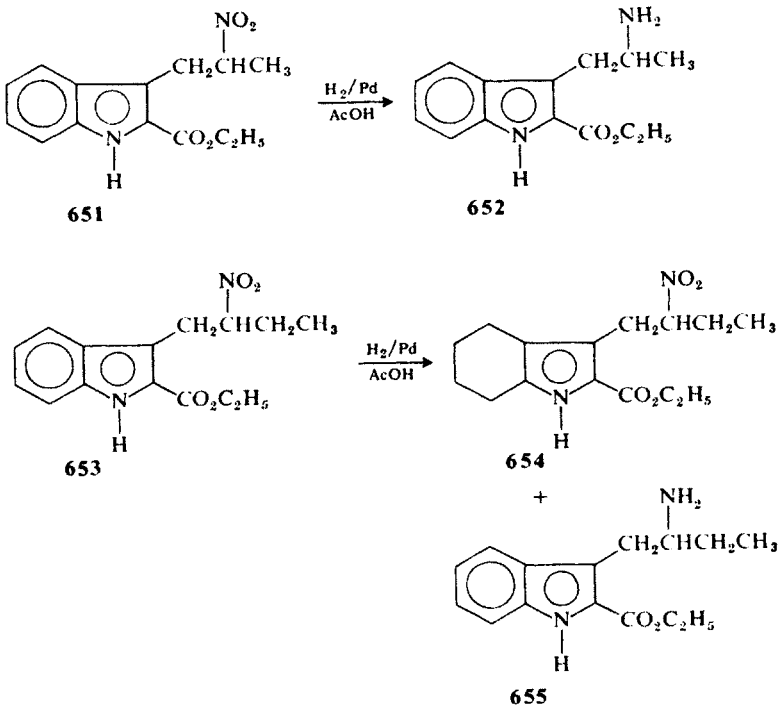
indole must be stable in acidic solution or at least hydrogenate faster than it polymerizes. Thus indole and 3-methylindole were reduced in excellent yields to indoline and 3-methylindoline with platinum in 1:1 ethanol–aqueous fluoboric acid at room temperature and atmospheric pressure.[467] This method also afforded hydrogenation of 1,2,3,4-tetrahydrocarbazoles **648** to the corresponding hexahydrocarbazoles **650** (Eq. 108). In these reductions the yields were quantitative and only one isomer (*cis*?) was obtained.[467]



648 **649** **650** (108)

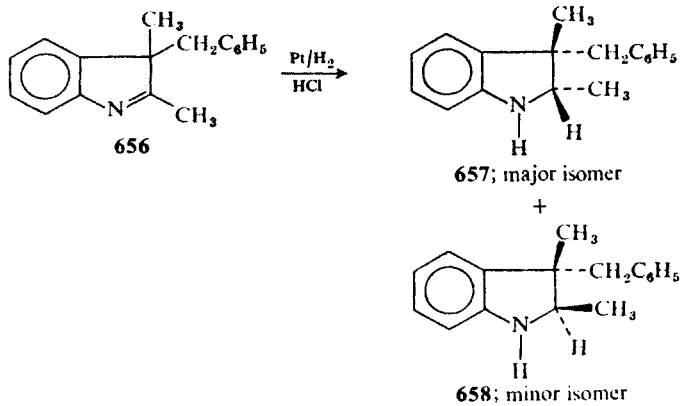
Indole and its 1-methyl, 2-methyl, and 1,2-dimethyl homologs were readily reduced to the corresponding octahydroindoles in acetic acid solution with hydrogen at room temperature and 3 atm in the presence of 30% palladium on charcoal.[468] Under the same conditions ethylindole-2-carboxylate gave its 4,5,6,7-tetrahydro derivative. The pyrrole ring is apparently deactivated toward hydrogenation by conjugation with the carbethoxy group, which reduces the double bond character of the 2,3-bond.[468] An interesting observation was made in the relative rates of hydrogenation for the nitro group and the nucleus of ethyl 3-(2-nitropropyl)indole-2-carboxylate (**651**) and ethyl 3-(2-nitrobutyl)indole-2-carboxylate (**653**). The former compound was readily reduced to the corresponding 2-aminopropyl derivative (**652**), whereas in the latter compound the additional methyl group in the side chain so depressed the rate of reduction of the nitro group that reduction of the benzene ring was competitive[469] to give a mixture of **654** and **655** (Scheme 79).

Indolenines have been hydrogenated with platinum catalyst in methanol containing hydrochloric acid. When the substituents at $C_{(3)}$ differed in size, the predominant indoline diasteriomer resulted from addition of hydrogen to the indolenine face opposite to the larger group. Thus 3-benzyl-2,3-dimethylindolenine (**656**) afforded diasteriomers **657** and **658** in a ratio of approximately 9:1 (Eq. 109). The ratio of corresponding diasteriomeric



Scheme 79

indolines from hydrogenation of 2,3-diethyl-3-methylindolenine was about 4:1. These hydrogenations took place at room temperature and atmospheric pressure.[470]



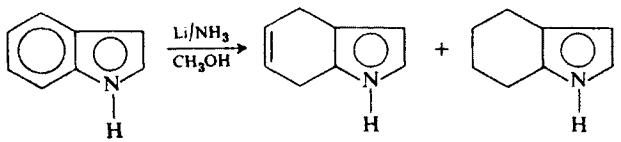
(109)

2. *Chemical*

The same factors which influence the catalytic reduction of indoles are also important in their chemical reduction. Under neutral conditions their appreciable resonance energy and relative richness in electrons makes them resistant to most of the common reducing agents. However, in acid solution both of these factors are diminished and conversion to the corresponding indolines is possible, providing that polymerization is not too rapid. A variety of procedures, including zinc dust in 85% phosphoric acid,[471] tin in hydrochloric acid, and electrolysis in acid solution,[472] have been used for the preparation of indolines. The zinc in polyphosphoric acid method was particularly effective for the reduction of 2,3-dimethylindole and 1,2,3,4-tetrahydrocarbazole.[471]

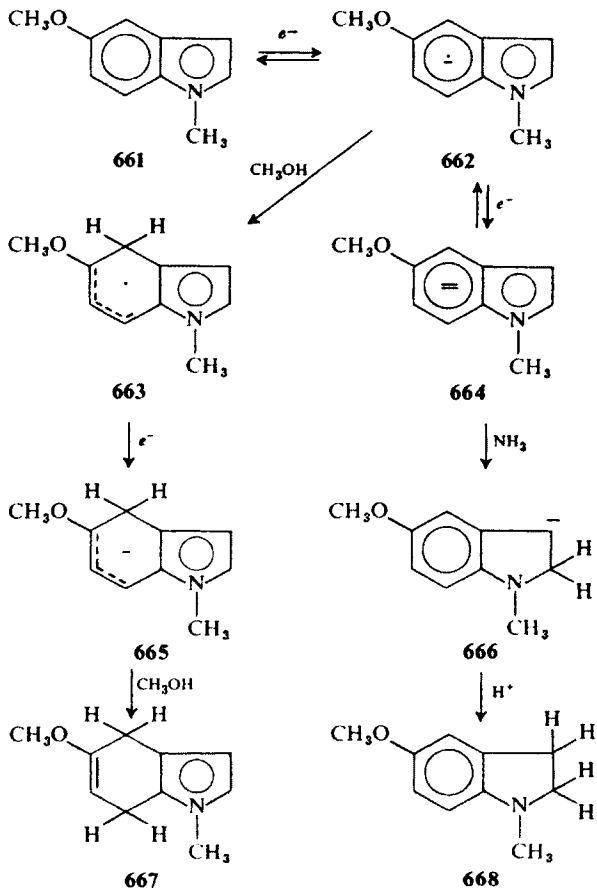
An electrophilic reagent such as diborane would seem well suited to the reduction of indoles; however, in the experiments reported thus far the yields of indoline obtained from indole have not been above 48%.[473] Indole-2-carboxamide was conveniently reduced to indoline-2-carboxamide by phosphonium iodide and hydriodic acid.[474]

Powerful reducing systems such as alkali metals in liquid ammonia are capable of reducing indoles. The products obtained from these reductions depend upon the presence of a proton source and whether or not the indole nitrogen is substituted. Indole and derivatives unsubstituted on nitrogen are reduced to only a small extent (in the benzene ring) when lithium is added to their solutions in liquid ammonia. Most of the indole is converted to the lithium salt, which is not reduced. However, addition of a proton source to the mixture releases the indole from its salt and reduction occurs rapidly if excess lithium is present.[475] Methanol was the most active among a series of alcohols in promoting indole reduction, possibly because it is acidic enough to free most of the indole from its salt, but not so acidic as to compete for the lithium in a hydrogen-forming reaction (as water does). Under these conditions indole was reduced to a mixture of 4,7-dihydroindole (**659**) and 4,5,6,7-tetrahydroindole (**660**); no reduction occurred in the pyrrole ring[475] (Eq. 110).



659 **660** (110)

A study on the reduction of 5-methoxy-1-methylindole[476] (Scheme 80) showed that when lithium was added to a mixture of it and excess methanol



Scheme 80

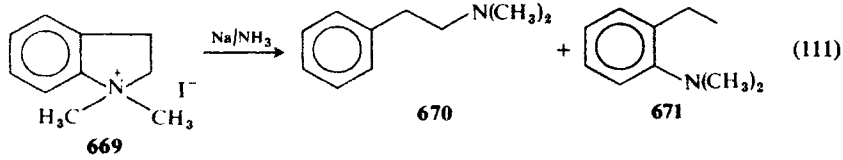
in liquid ammonia, reduction occurred rapidly and almost exclusively in the benzene ring, affording 4,7-dihydro-5-methoxy-1-methylindole (**667**). In the absence of methanol the corresponding indoline **668** was formed in a relatively slow reaction.[476] An explanation of these observations was based upon the ease of addition of electrons to the π-system of the indole. Since the lowest unoccupied molecular orbital of indoles lies at an energy below that of the corresponding orbital for benzene (Section III.B.3), it is expected that one electron would add to give the corresponding radical anion **662** in a very rapid equilibrium. Addition of methanol would cause protonation of this radical anion, presumably at $C_{(4)}$, in an exothermic and rapid reaction. The resulting radical **663** would then go on to product **667** by addition of another electron and protonation at $C_{(7)}$. When methanol is omitted the radical anion cannot be protonated by ammonia (pK 34); instead, it adds a second electron

in what is probably an unfavorable equilibrium. The resulting dianion **664** is more basic than ammonia and it accepts a proton at $C_{(2)}$ in going to benzyl carbanion **666**, which gives indoline **668** upon workup. To explain the different sites of initial protonation in the dianion and radical anion, it was noted that they have different patterns of π-electron density.[476]

5-Methoxyindole also formed the lithium salt when treated with excess lithium in ammonia. It gave the same reduction product, 4.7-dihydro-5-methoxyindole in yields of 80–82%, whether methanol was added to this mixture or the lithium was added to a mixture of the indole and methanol in ammonia. Apparently the radical anion of 5-methoxyindole is discharged by methanol before it can go on to dianion in either case, hence only benzene ring reduction is observed.[476]

The reduction of 1-methylindole by addition of sodium to its solution in ammonia containing methanol was less specific than those noted in the previous examples. It gave both 1-methylindoline and 4,7-dihydro-1-methylindole.[475]

Reductive cleavage of quaternary indolinium salts such as **669** by sodium in ammonia occurred readily. Under anhydrous conditions, products (**670** and **671**) derived from cleavage of both *N*-alkyl and *N*-aryl linkages were

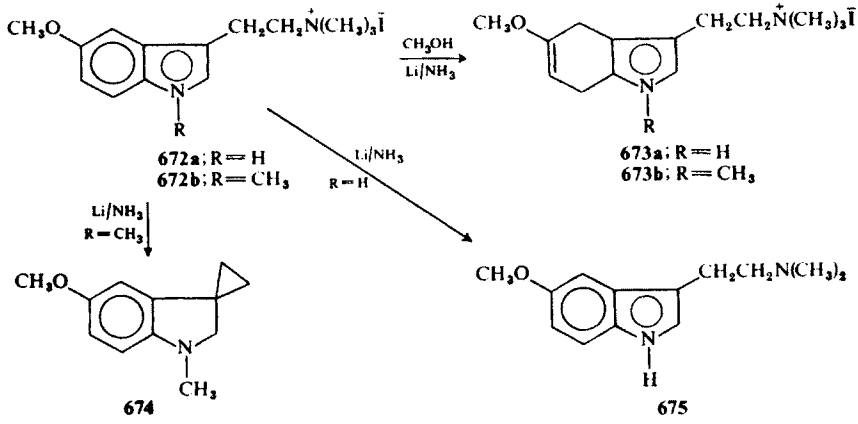


669 **670** **671** (111)

obtained; however, in the presence of 0.5% water only the *N*-aryl linkage was cleaved (Eq. 111). Similar results were obtained with the methiodide of *N*-methyl-1,2,3,4,10,11-hexahydrocarbazole.[477]

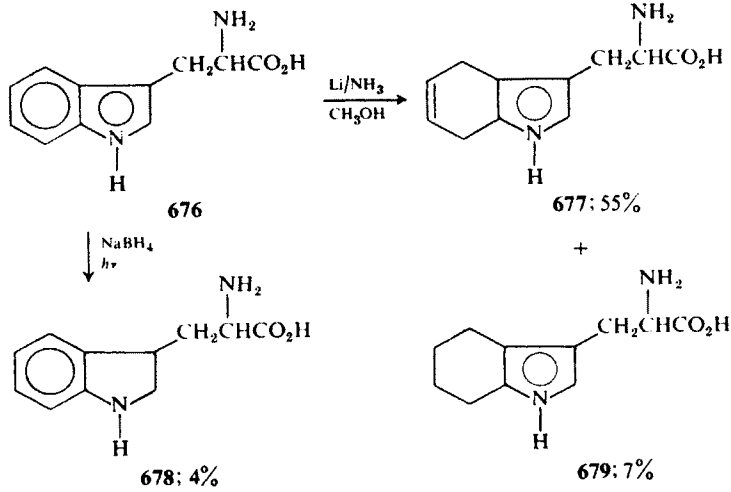
The presence of excess methanol inhibited cleavage of quaternary tryptamine salts **672a** and **672b**, permitting selective reduction of the benzene ring to afford 4,7-dihydrotryptamine quaternary salts **673a** and **673b**.[478] In the absence of methanol the quaternary centers of **672a** and **672b** were cleaved, but the mode of cleavage depended upon the presence or absence of a substituent on the indole nitrogen. Thus the compound with unsubstituted nitrogen, **672a**, afforded the corresponding dimethyltryptamine **675** by loss of a methyl group from the quaternary center, whereas the ind-*N*-methyl compound (**672b**) gave spiroindoline **674** by cleavage of trimethylamine (Scheme 81). The latter example presumably involves addition of an electron to the indole π-electron system prior to cleavage.[478]

Tryptophan (**676**) was reduced by lithium and methanol in ammonia to a mixture of 4,7-dihydrotryptophan (**677**) and a little 4,5,6,7-tetrahydrotryptophan (**679**).[479] Photochemical reduction of tryptophan in the presence of



Scheme 81

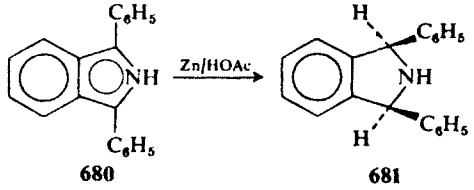
aqueous sodium borohydride afforded low yields of **677** and 2,3-dihydrotryptophan (**678**), plus traces of tryptamine and indolepropionic acid (Scheme 82). The mechanism of this photochemical reaction is not known, but the involvement of hydrogen atoms was suggested.[479]



Scheme 82

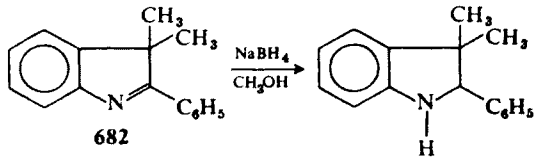
1,3-Diphenylisoindole **680** was readily reduced by zinc and acetic acid to *cis*-1,3-diphenylisoindoline **681**[480] (Eq. 112).

Indolenines have been converted to indolines by a variety of reducing agents including sodium in alcohol,[481] zinc in acetic acid,[482] zinc amalgam and hydrochloric acid,[483] sodium borohydride,[484] and lithium aluminum



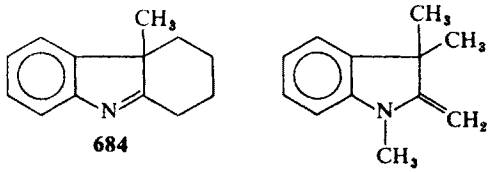
680 681 (112)

hydride.[484] For example, 3,3-dimethyl-2-phenylindolenine (**682**) gave indoline **683** when treated with sodium borohydride in methanol[484] (Eq. 113).



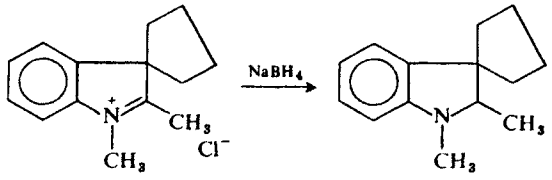
682 683 (113)

Polarographic half-wave potentials for the reduction of indolenine **684** and 2-methyleneindoline **685** in alkaline borate buffer were −1.58 and −1.16 V,



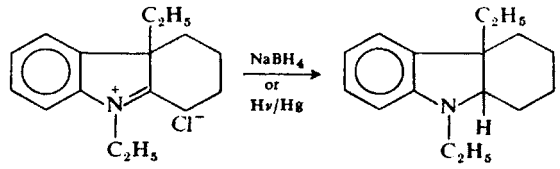
684 685

respectively, versus the normal calomel electrode.[485] Indole was not reduced in this system. Indoleninium salts such as **686** and **688** are readily converted into indolines (e.g., **687** and **689**) by sodium borohydride[486, 487] (Eqs. 114, 115). Mercury sensitized photoreduction of **688** also gave **689**, among other products.[487]



686 687 (114)

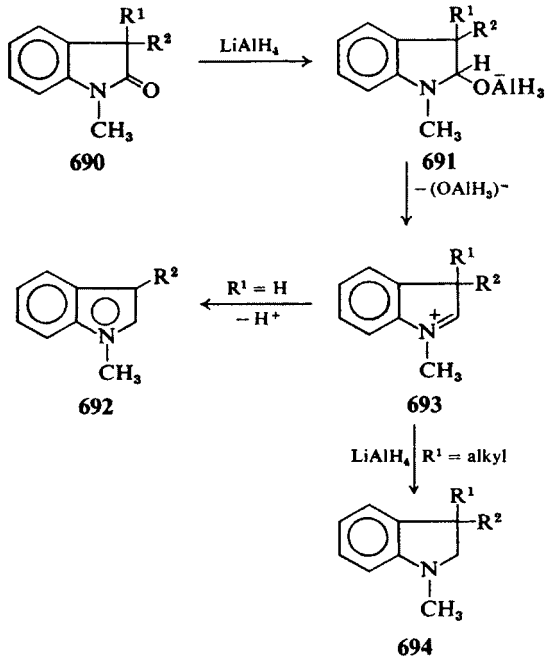
Oxindoles unsubstituted on nitrogen form salts when treated with lithium aluminum hydride or sodium borohydride, and these salts are resistant to reduction.[488] Externally generated diborane is also a poor reagent for the reduction of oxindole. It gives much hydrogen evolution and the yield of indoline is only 15–25%.[473, 489] In contrast, when the diborane is generated



(115)

from BF_3·etherate and sodium borohydride in the presence of oxindole, an 85% yield of indoline is obtained.[473] 2-Ethoxyindole, which has been prepared by treatment of oxindole with the Meerwein reagent, was reduced to 66% indole and 10% indoline with a limited amount of diborane.[489]

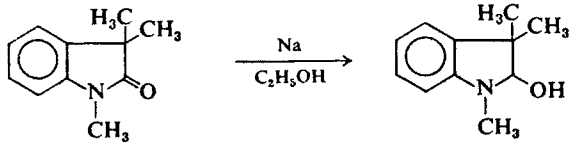
1-Methyloxindole is reduced by diborane to a mixture of 41% 1-methylindole and 27% 1-methylindoline.[489] Lithium aluminum hydride converts *N*-substituted oxindoles **690** into the corresponding indoles **692** if they have no more than one substituent at $C_{(3)}$[490, 491] (Scheme 83). Presumably aluminate



Scheme 83

ion is eliminated from intermediate **691** in going to indoleninium ion **693**, then loss of a proton from **693** gives the indole **692**. If two substituents are present at $C_{(3)}$ the indoleninium ion **693** is reduced to indoline **694** by additional lithium aluminum hydride. 1,3,3-Trimethyloxindole (**695**) was reduced to

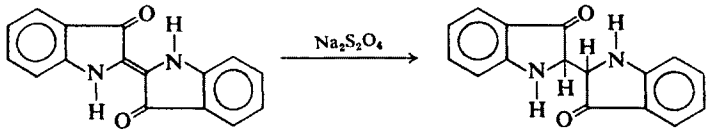
2-hydroxyindoline **696** by sodium in ethanol (Eq. 116). Apparently **696** did not lose hydroxide ion to form an indoleninium ion under these conditions.



(116)

695 **696**

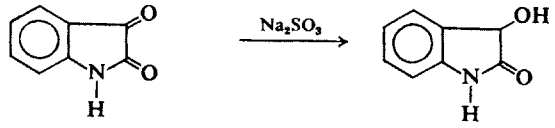
Lithium aluminum hydride in ether reduced indoxyl to a mixture which contained indole (25%), 3-hydroxyindoline (5%), and indigo (10%). 2,2-Dimethylindoxyl was reduced cleanly to 2,2-dimethylindoline (38%) under these conditions, whereas dioxindole (**700**) gave 15% of 3-hydroxyindoline, plus some indigo and indirubin.[492] The reduction of indigo to leucoindigo (**697** → **698**) (Eq. 117) was effected by a variety of reagents including sodium



(117)

697 **698**

hydrosulfite, which was particularly important in vat dyeing with indigo.[493] Dioxindole (**700**) has been obtained from isatin (**699**) by reduction with such



(118)

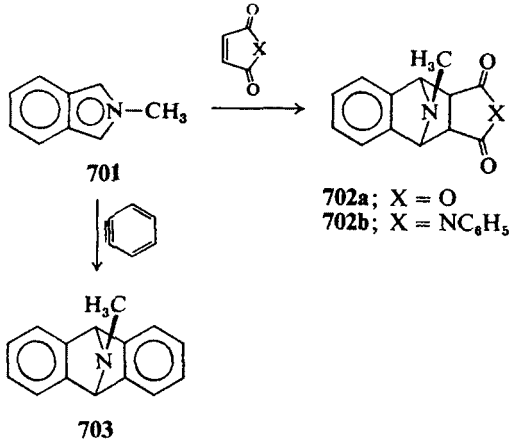
699 **700**

agents as sodium sulfite, sodium hydrosulfite, and zinc in acetic acid[494] (Eq. 118). Preferential reduction of the 3-carbonyl group of isatin is expected, since the 2-carbonyl group has considerable amide character.

H. Cycloadditions

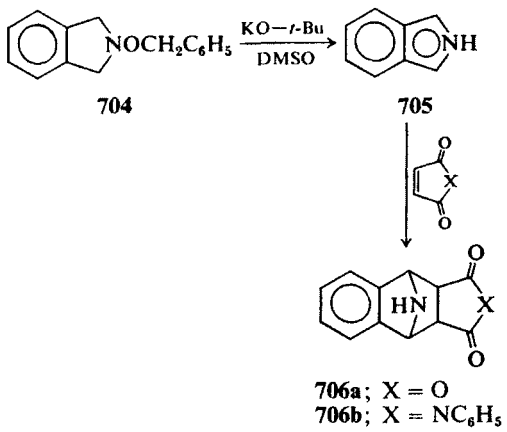
Although indoles generally react with dienophiles to afford the type of product associated with electrophilic substitution, symmetrical isoindoles give a Diels-Alder-type adduct with a bridge across the heterocyclic ring of the isoindole. In a formal sense this reaction can be depicted as a cyclo-addition between the dienophile and the isoindole, although the actual mechanism has not been established.

The formation of adducts with dienophiles has been important in elucidation of isoindole structures. Thus the first isoindole prepared, 1-methylisoindole (**701**), was converted into maleic anhydride adduct **702a**.[495, 496] It has also been possible to form an adduct (**703**) between **701** and benzyne[497]



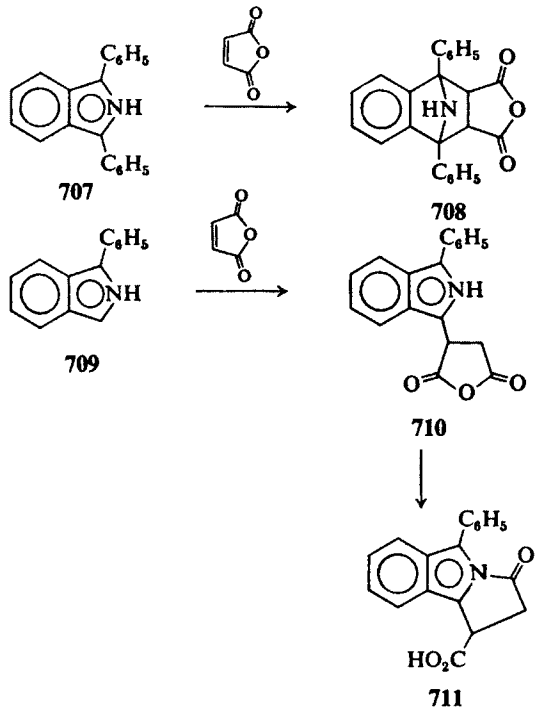
(119)

(Eq. 119). Other *N*-alkylisoindoles have given adducts with maleic anhydride and *N*-phenylmaleimide.[498] Isoindole itself has never been isolated, but its formation from *N*-benzyloxyisoindoline (**704**) and base was demonstrated by trapping with maleic anhydride and with *N*-phenylmaleimide (**705** → **706**)[2] (Eq. 120).



(120)

1,3-Diphenylisoindole (**707**) afforded cycloadduct **708** when treated with maleic anhydride[62] (Eq. 121). In contrast, a product (**710**) typical of electrophilic substitution was obtained from 1-phenylisoindole (**709**) and maleic anhydride. Compound **710** was unstable with respect to isomer **711**[115] (Eq.

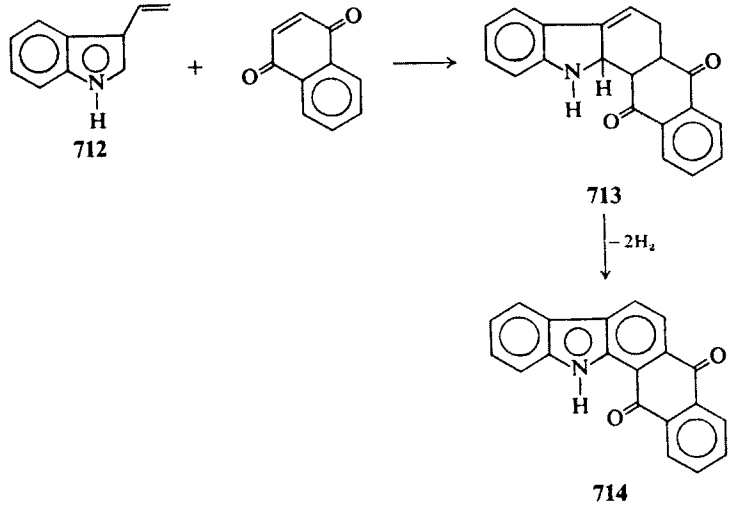


(121)

(122)

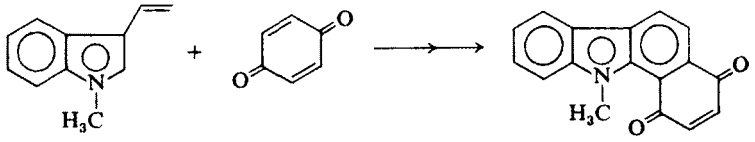
122). Cycloadducts were also obtained from **707** and benzyne or diethyl acetylenedicarboxylate.[62, 499]

3-Vinylindole (**712**) gave naphthocarbazole **714** when treated with 1,4-naphthoquinone in dimethylsulfoxide[73] (Eq. 123). In an analogous reaction



(123)

1-methyl-3-vinylindole (**715**) and 1,4-benzoquinone afforded benzocarbazole **716**[334] (Eq. 124). These products can be considered in a formal sense to derive

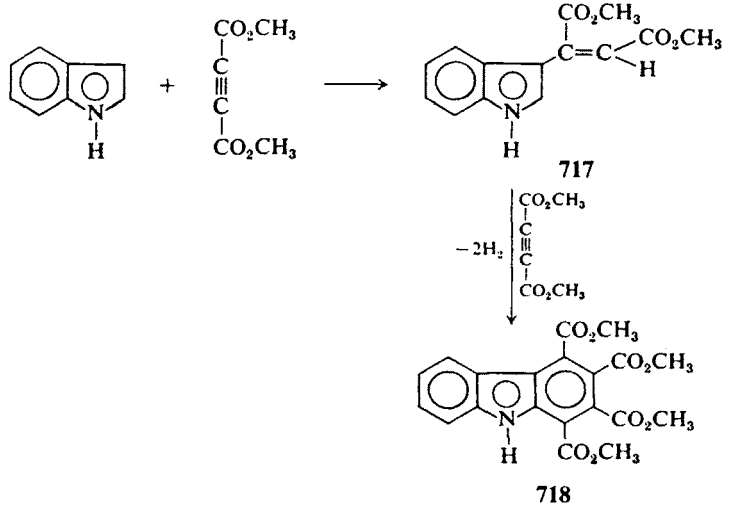


(124)

715 **716**

from cycloadditions involving the quinone, the vinyl group, and the indole 2,3-bond, followed by loss of 2 moles of hydrogen.

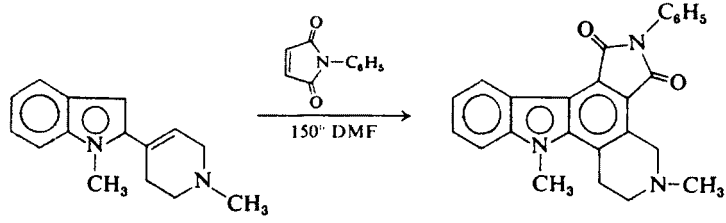
A related process was obtained upon treatment of indole with dimethyl acetylenedicarboxylate, wherein the initially formed 3-vinyl derivative **717** added another mole of the acetylene to give carbazole derivative **718**[400] (Eq. 125).



(125)

717 **718**

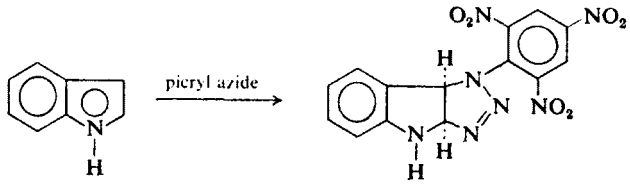
2-Vinylindoles can also be supposed to undergo cycloaddition, as in the formation of **720** from **719** and *N*-phenylmaleimide[501] (Eq. 126).



(126)

719 **720**

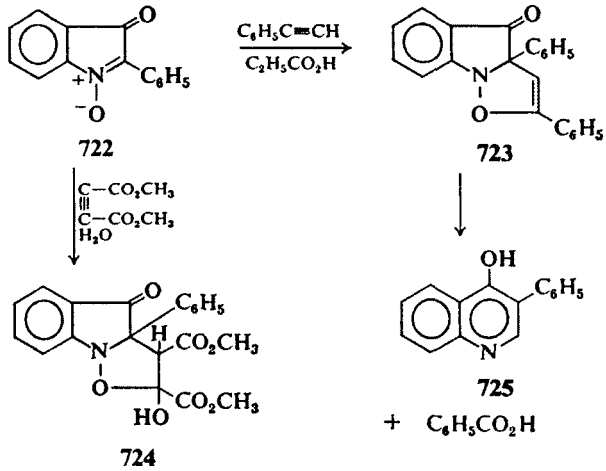
Treatment of indole with picryl azide afforded a 1,3-dipolar cycloaddition reaction in which the 2,3-double bond of indole acted as the dipolarophile. Formation of the product **721** occurs at a rate three times that of the corresponding cycloaddition with styrene[502] (Eq. 127).



(127)

721

2-Phenylisatogen (**722**) can act as a 1,3-dipolar reagent in the presence of dipolarophiles such as phenylacetylene and dimethyl acetylenedicarboxylate.[503] In the case of phenylacetylene (with propionic acid) the cycloadduct was unstable with respect to a ring expansion which furnished 4-hydroxy-3-phenylquinoline (**725**). A hydrated adduct (**724**) was isolated from reaction of **722** and dimethyl acetylenedicarboxylate (Scheme 84).



Scheme 84

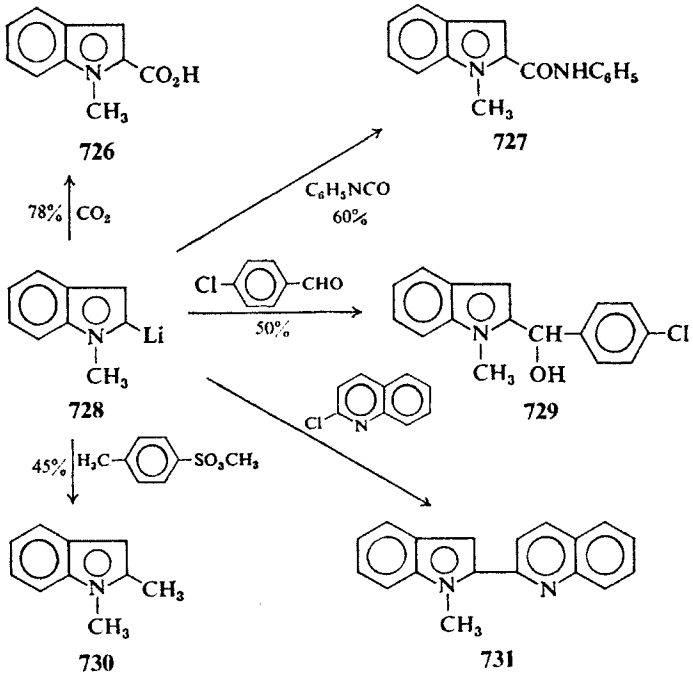
The additions of carbenes to the 2,3-double bond of indoles (Section IV.C.12) also can be considered examples of cycloadditions.

I. Metalation

Treatment of indole with *n*-butyllithium in ether afforded only the *N*-lithio derivative. It was not possible to effect a second metalation on carbon, even when excess *n*-butyllithium and higher-boiling ethers were utilized.[504]

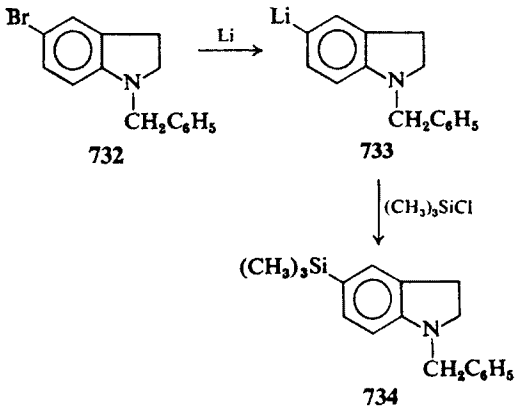
Dimetalation of carbazole is possible, presumably because charge delocalization is facilitated by its more extensive π-electron system.[504]

1-Methylindole is metalated smoothly by *n*-butyllithium.[504, 505] In the resulting lithio derivative **728** the lithium has evidently replaced the hydrogen on $C_{(2)}$, as indicated by formation of 1-methylindole-2-carboxylic acid **726** upon carbonation.[504] Such metalation of 1-alkylindoles offers the possibility for convenient preparations of certain 2-substituted indoles. Since indoles normally alkylate and acylate at $C_{(3)}$, it is difficult to obtain indoles with substituents at $C_{(2)}$ and not at $C_{(3)}$, unless these substituents can be established prior to formation of the indole nucleus. However, substituents such as carboxamido, methyl, (*p*-chlorophenyl)carbinol,[504] and 2-quinolyl[506] were readily introduced at $C_{(2)}$ upon treatment of **728** with appropriate reagents (Scheme 85).



Scheme 85 2-Substituted indoles derived from *N*-methyl-2-lithioindole.

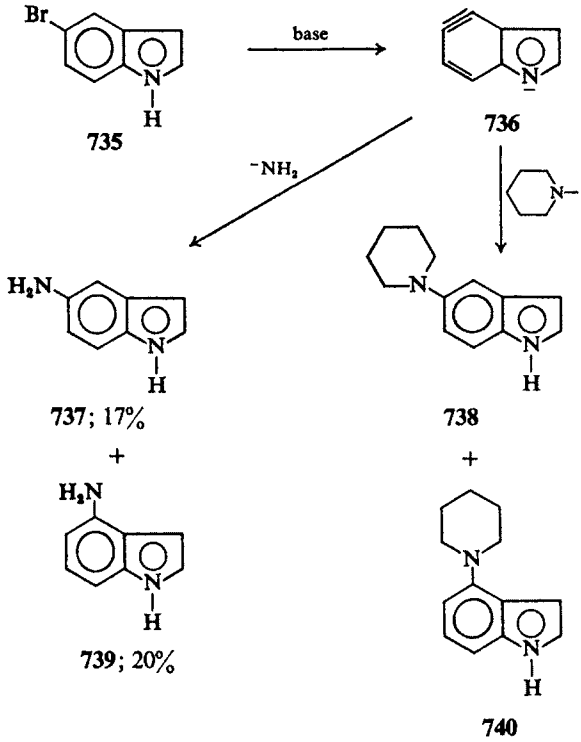
1-Benzyl-5-lithioindoline (**733**), which was prepared by treatment of the corresponding 5-bromo compound **732** with lithium in ether, afforded 5-trimethylsilyl derivative **734** when treated with trimethylsilyl chloride[507] (Eq. 128).



(128)

J. Aryne Formation

5-Bromoindole (**735**) was converted by sodium amide in liquid ammonia to a mixture of 4-aminoindole (**739**) and 5-aminoindole (**737**). The corresponding 4- and 5-piperindinoindoles (**738** and **740**) were obtained when **735**

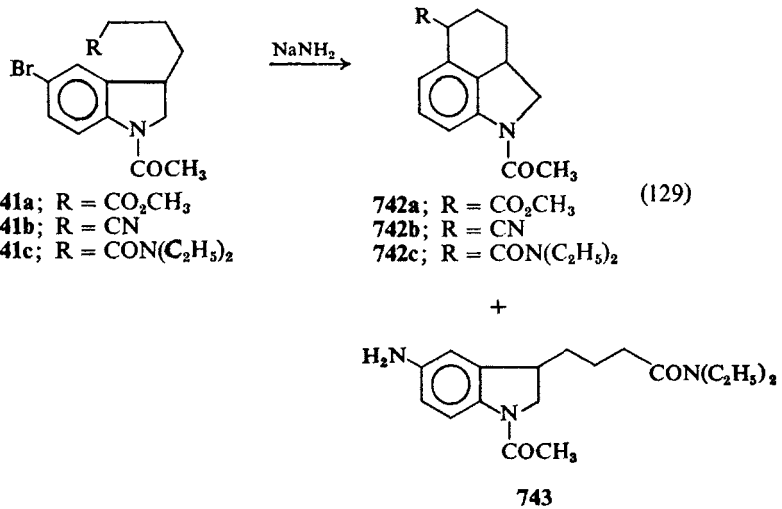


Scheme 86

was treated with the lithium salt of piperidine[508] (Scheme 86). In neither case was any substitution at $C_{(6)}$ observed. These results have been explained by the formation of aryne intermediate **736**, which adds amide ion or piperidide ion at both $C_{(4)}$ and $C_{(5)}$.[508] Aryne **736** is apparently formed by removal of the hydrogen from $C_{(4)}$ followed by loss of bromide ion. Since no substitution occurred at $C_{(6)}$, it is likely that none of the isomeric aryne with a 5,6-triple bond was formed.

Indolines also have been converted into products derived from aryne intermediates. Thus 1-acetyl-5-bromoindoline gave a mixture of 4- and 5-amino derivatives upon treatment with potassium amide in ammonia.[508]

Conversion of methyl 4-(*N*-acetyl-5-bromo-3-indolinyl)butyrate (**741a**) into tricyclic product **742a** was effected by treatment with sodium or potassium amide in liquid ammonia[509] (Eq. 129). Cyclization was also obtained with the corresponding nitrile **741b** and diethylamide **741c**. In the case of the amide some uncyclized 5-amino derivative **743** was also obtained. Higher yields of



cyclized products were obtained with sodium amide than with potassium amide. This superiority of sodium amide was thought to be due to a lower concentration of amide ion in its suspensions in liquid ammonia.[510]

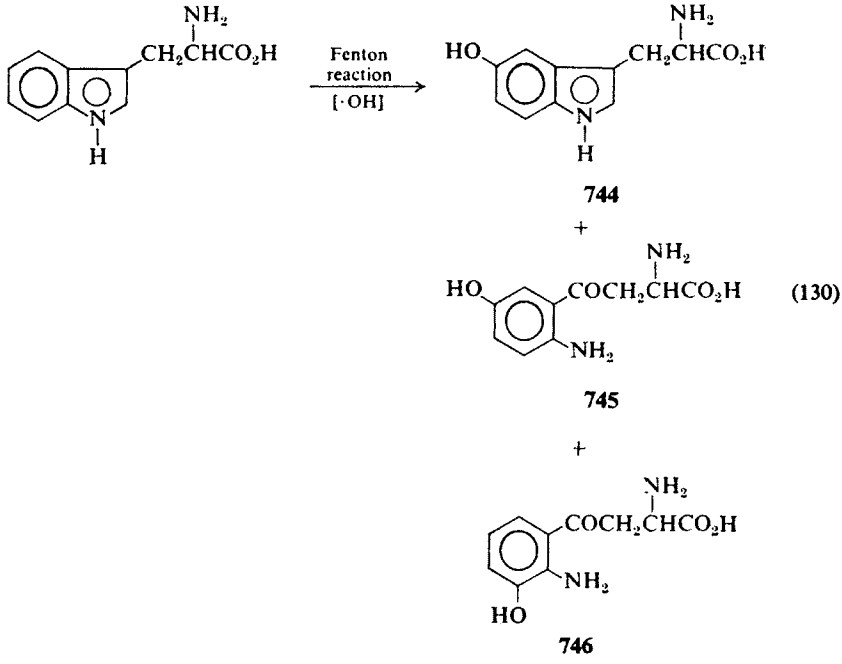
K. Free Radical Reactions

Indoles are not especially reactive to homolytic substitution. In those examples where substitution occurs, the yields are generally low and mixtures of isomeric products are formed. Homolytic benzylation of indole gave a complex mixture of 1-benzylindole, 3-benzylindole, 1,3-dibenzylindole,

2,3-dibenzylindole, α-(1-indolyl)dibenzyl, and trace amounts of products benzylated in the benzene ring of the indole. The yields were very low for each product.[511]

Preparative hydroxylation of indole with 3% hydrogen peroxide and ferrous sulfate in phosphate buffer containing disodium ethylenediaminetetraacetic acid afforded a mixture of 4-, 5-, 6-, and 7-hydroxyindoles which was separable on thin-layer chromatography.[512] Oxidation of 3-methylindole with potassium persulfate also furnished the corresponding 4-, 5-, 6-, and 7-hydroxy derivatives, along with products of oxidation and cleavage of the 2,3-bond, such as 3-methyloxindole, 2-aminoacetophenone, and 2-formamidoacetophenone.[513]

The free hydroxyl radicals generated by the Fenton reaction converted tryptophan into a mixture of 5-hydroxytryptophan (**744**), 3-hydroxykynurenine (**745**), and 5-hydroxykynurenine (**746**) (Eq. 130). Indole-3-acetic acid gave 5-hydroxyindole-3-acetic acid under the same conditions.[514]

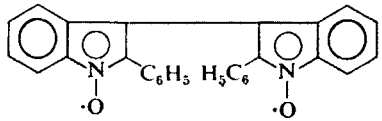


(130)

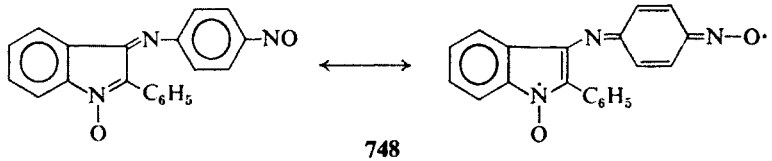
Several important oxidation reactions which proceed by free radical pathways are discussed in Section IV.F. These reactions include autoxidation of indoles, manganese dioxide oxidation of indolines, and Fremy's salt oxidation of indolines and hydroxyindoles.

Indole nitroxide diradicals such as **747** and **748** are moderately active

oxidizing agents. For example, **747** converted toluene to benzyl alcohol[515] and **748** liberated iodine from potassium iodide solutions.[516]



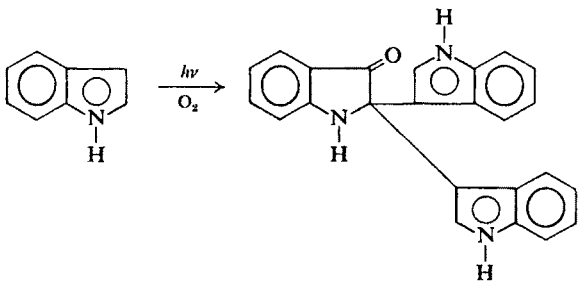
747



748

L. Photochemical Reactions

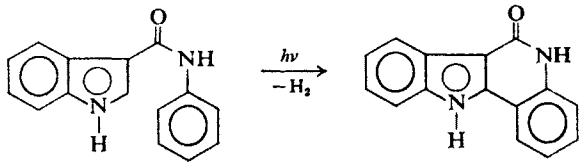
The photochemical reactions of indoles reported thus far constitute a small and highly diverse group including oxidation, reduction, and cyclization processes. When a solution of indole in aqueous alcohol was exposed to air and sunlight, photochemical oxidation to 2,2-bis(3-indolyl)indoxyl (**749**) and some anthranilic acid occurred[517] (Eq. 131). Indoxyl was suggested as



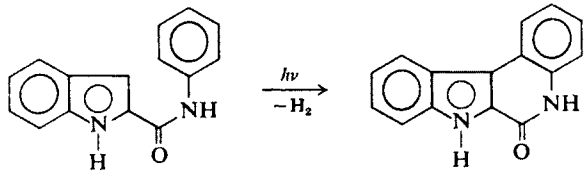
(131)

749

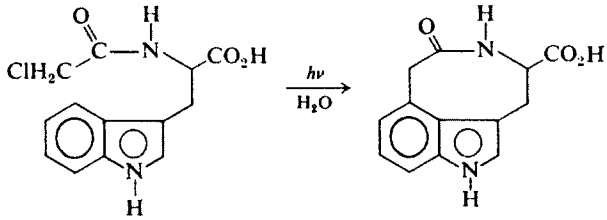
an intermediate in these transformations. Photochemical cyclodehydrogenations were obtained with the anilides (**750** and **752**) of indole 2- and 3-carboxylic acids when their solutions in dioxane were irradiated with a medium pressure mercury lamp[518] (Eqs. 132 and 133). A novel photocyclization of *N*-chloroacetyltryptophan (**754**) to **755** was effected by irradiation in neutral aqueous solution (Eq. 134). Homolysis of the C—Cl bond was considered to be the initial reaction in this cyclization sequence, although displacement of chloride by $C_{(4)}$ of the indole in an excited state was not ruled out.[479]



750 751 (132)

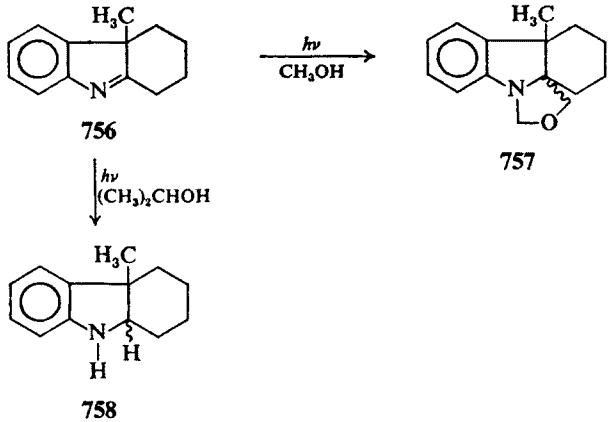


752 753 (133)



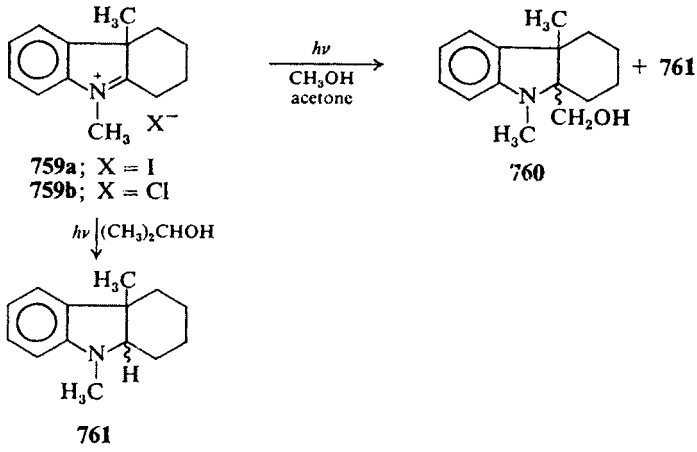
754 755 (134)

Irradiation of indolenines in alcohol solutions afforded either reduction or addition reactions, depending on the particular alcohol and the wavelength of light.[487] Thus a solution of indolenine **756** in methanol afforded oxazolocarbazole **757** when irradiated by a low-pressure mercury lamp. In contrast, irradiation of **756** in pure isopropanol with light from a high-pressure lamp gave hexahydrocarbazole **758** (Scheme 87). Similar results were obtained with



756 **757** **758**

Scheme 87

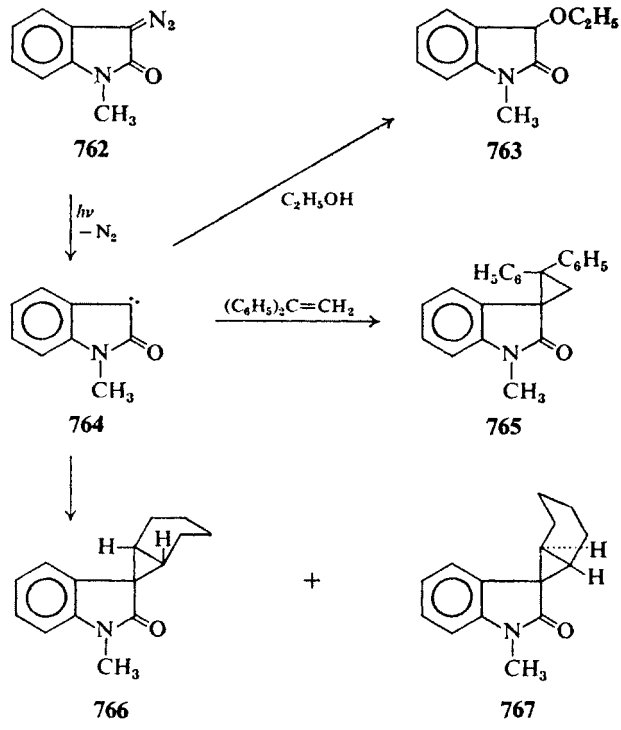


759a; X = I
759b; X = Cl

760

761

Scheme 88



762

763

764

765

766

767

Scheme 89

the corresponding indoleninium salts **759** (Scheme 88). Irradiation of a solution of **759a** in 1:1 methanol–acetone with light from the low-pressure lamp gave mainly hydroxymethyl derivative **760**, apparently by addition of a hydroxymethylene radical. A small amount of reduction to **761** also occurred. However, when isopropanol was the solvent and the high-pressure lamp was used, chloride salt **759b** was converted exclusively to **761**.[487] The reduction of tryptophan to its 2,3- and 4,7-dihydro derivatives by photolysis in the presence of aqueous sodium borohydride was described in Section IV.G.2.

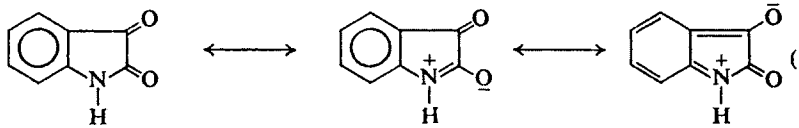
Photolysis of 1-methyl-3-diazooxindole (**762**) (Scheme 89) generated resonance-stabilized carbene **764**, which added to cyclohexene in a *cis* manner, affording spirooxindoles **766** and **767**. The stereospecificity of this addition was considered to indicate a singlet state for this carbene. A cyclopropyl derivative (**765**) was also obtained by addition of **764** to 1,1-diphenylethylene. In the presence of ethanol, photolysis of **762** afforded 3-ethoxyoxindole **763**, whereas photolysis in a hexane solution open to the air gave 1-methylisatin.[519]

M. Reactions Involving the Carbonyl Systems of Indoles with Oxygen at $C_{(2)}$ and $C_{(3)}$

An extensive treatment of the reactions of the carbonyl groups of isatin or the active methylene groups of oxindole and indoxyl will not be undertaken in this chapter, since these topics are primary concerns of later chapters. However, a brief summary of this important chemistry will be given in order to place it properly within the context of indole reactions.

1. *Carbonyl Reactivity of Isatin*

The two carbonyl groups of isatin differ considerably from each other in their reactivity toward nucleophilic reagents. The most important single factor in creating this difference is that the 2-carbonyl group has considerable amide character due to its position adjacent to the nitrogen atom. This nitrogen atom has an electron pair that can be readily delocalized onto the 2-carbonyl group (**768** ↔ **769**), thus reducing its electrophilic properties (Eq. 135). Conjugation of the nitrogen with the $C_{(3)}$ carbonyl group is also possible (**768** ↔ **770**), but this process destroys the aromaticity of the

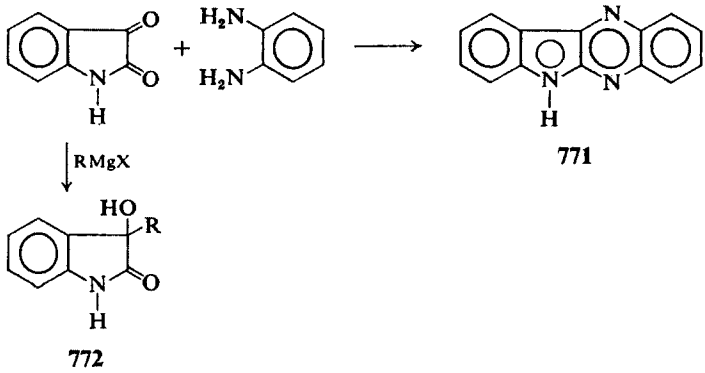


(135)

768 **769** **770**

benzene ring and is thus not favored. The mutually activating interaction between the two carbonyl groups is superimposed upon the foregoing effects.

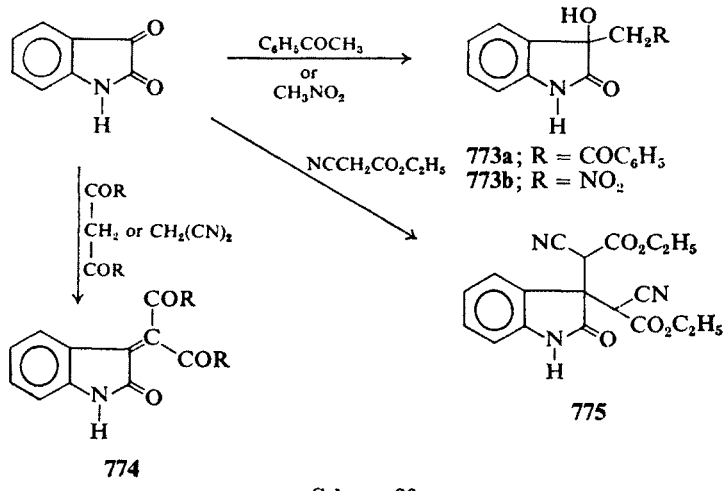
It is therefore anticipated that the 3-carbonyl group will be relatively reactive toward nucleophiles, but the 2-carbonyl group will be less reactive, and on this basis selective substitution at $C_{(3)}$ should be possible. In agreement with this suggestion the 3-carbonyl group forms monoderivatives with typical carbonyl reagents such as HCN, sodium bisulfite, hydroxylamine, and phenylhydrazine.[520–522] *o*-Phenylenediamine reacts with both carbonyls to give indoloquinoxaline (**771**)[523] (Eq. 136).



771 **772** (136)

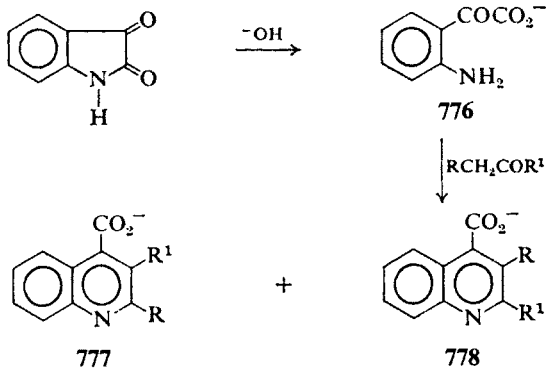
The NH group of isatin is sufficiently acidic that isatin is soluble in dilute alkali; however, the formation of isatinyl salts in the presence of bases does not preclude reaction at $C_{(3)}$ in these salts. Possibly this is because most of the negative charge is delocalized onto the 2-carbonyl group. Excess Grignard reagent adds to the 3-carbonyl group of isatin to give the corresponding dioxindole **772**, but no addition occurs at $C_{(2)}$.[524] In contrast, both carbonyl groups of 1-alkylisatins react with Grignard reagents.[525]

A number of condensations of active methylene groups with the 3-carbonyl group of isatin are known. They are generally carried out in the presence of mild bases such as diethylamine and piperidine. The products are either of the 3-substituted-dioxindole type or the 3-alkylidineoxindole type, depending upon the particular reagent and experimental conditions. In some cases these products undergo ring expansion to quinolones as the result of acid or alkaline treatment during workup (Section IV.N). Thus isatin afforded 3-substituted dioxindoles **773a** and **773b** upon treatment with acetophenone and with nitromethane in the presence of secondary amines.[526, 527] Alkylidineoxindoles (**774**) were obtained by condensation of oxindole with a variety of malonic acid derivatives, such as the esters, nitriles, and amides.[528] In the case of ethylcyanoacetate, bismalonyl derivative **775** was obtained[527] (Scheme 90). Condensation of active methylene compounds such as hydantoin and rhodanine also occurs readily at $C_{(3)}$ of isatin.[539]



Scheme 90

In the presence of strong alkali the amide group of isatin is cleaved to form a salt of isatinic acid (**776**). Condensations of ketones with isatin in the presence of alkali afforded isomeric quinoline-4-carboxylic acids **777** and **778**, which are apparently derived from reaction of the ketones with **776** (Scheme 91). This process, known as the Pfitzinger reaction, has been



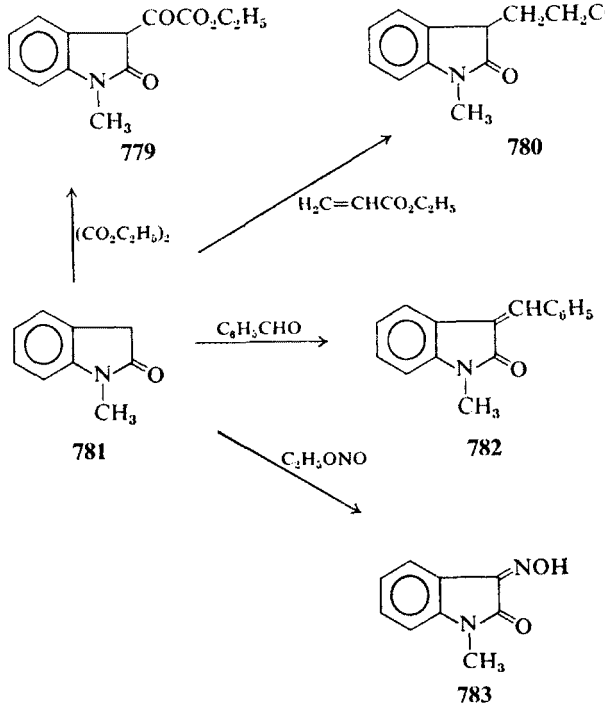
Scheme 91

carefully studied with regard to the scope and influence of steric factors on the relative amounts of isomers formed.[530, 521]

2. *Reactions of the Methylene Groups of Oxindole and Indoxyl*

Since the methylene group of oxindole is situated between a carbonyl group and a benzene ring, removal of a proton from it should give an anion

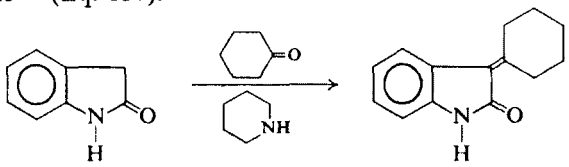
which is well stabilized by delocalization. Thus it is anticipated that this methylene group should readily undergo base-catalyzed condensation reactions, particularly when the nitrogen is substituted with an alkyl group. Examples of condensations with 1-methyloxindole (**781**) include those with ethyl oxalate, ethyl acrylate, benzaldehyde, and ethyl nitrite (Scheme 92).[532]



Scheme 92

A moderately strong base such as ethoxide ion is frequently used to catalyze these reactions. The Mannich condensation also has been carried out on **781**.[533]

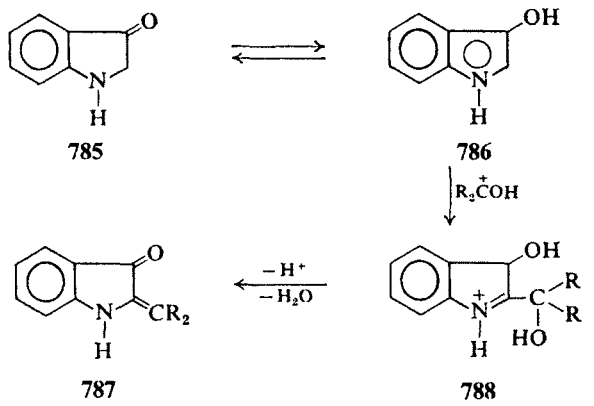
When the oxindole nitrogen is unsubstituted, the relatively acidic NH proton is removed by strong bases and condensation at the methylene group is unlikely. However, a mild base such as piperidine was effective in promoting the formation of 3-oxindolylidene derivative (**784**) from oxindole and cyclohexanone[534] (Eq. 137).



(137)

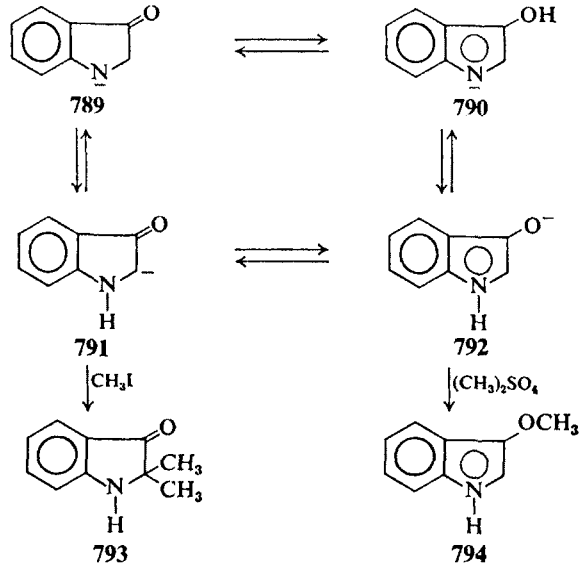
784

Base-catalyzed reactions of indoxyl present an interesting situation because of the facile tautomerism between the 3-oxoindoline (**785**) and 3-hydroxyindole (**786**) forms of this compound (Scheme 93) (Section II.H). The impor-



Scheme 93

tance of form **786** lies in its hydroxyl group, which would be more acidic than the NH group of **785**. In alkaline solution an equilibrium among anions **789**, **790**, **791**, and **792** may be assumed (Scheme 94). It is not obvious



Scheme 94

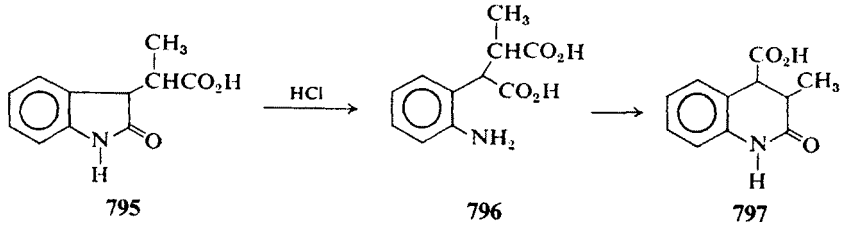
which species predominate; however, the results of alkylation studies suggest a greater importance for **791** and **792**. Thus treatment of indoxyl with potassium carbonate and methyl iodide afforded 2,2-dimethylindoxyl (**793**),[535] whereas the same base and dimethyl sulfate furnished 3-methoxyindole (**794**).[536] No *N*-alkylation was reported in either case.

A variety of acid-catalyzed substitutions at $C_{(2)}$ of indoxyl have been reported. These substitutions almost certainly involve electrophilic attack on 3-hydroxyindole tautomer **786**. The nitrosation of indoxyl was discussed in Section IV.C.4. Another important example of these electrophilic substitutions is the formation of indogenides (**787**) from indoxyl and ketones[537] (Scheme 93).

N. Ring Expansion of the Pyrrole Ring of Indoles

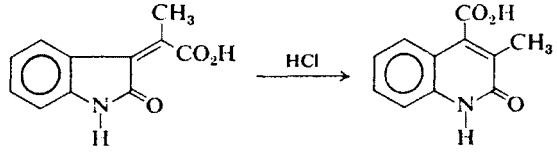
Ring expansion to 6-membered heterocyclic rings is an important process for the pyrrole rings of certain indoles. Most of these ring-expansion reactions appear to fall in three separate classes: (*1*) opening of the 1,2-bond of 2-oxoindoles followed by recyclization: (*2*) opening of the 1,2-bond of indoxyls followed by recyclization; (*3*) migration of the $C_{(3a)}$ atom onto an electron-deficient carbon atom attached to $C_{(3)}$.

The Pfitzinger reaction, described in Section IV.M is in the first category. It involves opening of isatin to isatinic acid followed by condensation with a ketone to give a quinoline-4-carboxylic acid. Another example is the acid-catalyzed rearrangement of 2-(3-oxindolyl)propionic acid (**795**) to 3,4-dihydro-2-quinolone-4-carboxylic acid (**797**)[538] (Eq. 138). *o*-Aminophenylmethylsuccinic acid (**796**) is the presumed intermediate in this reaction. A similar ring-expansion (**798** → **799**) takes place with alkylidine oxindole **798** (Eq. 139). The conversion of *N*-acetylisatin (**800**) to quinazoline **802** by



795 **796** **797**

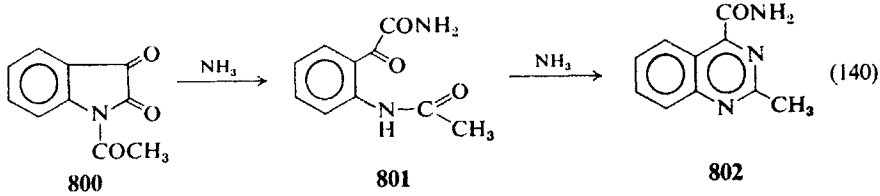
(138)



798 **799**

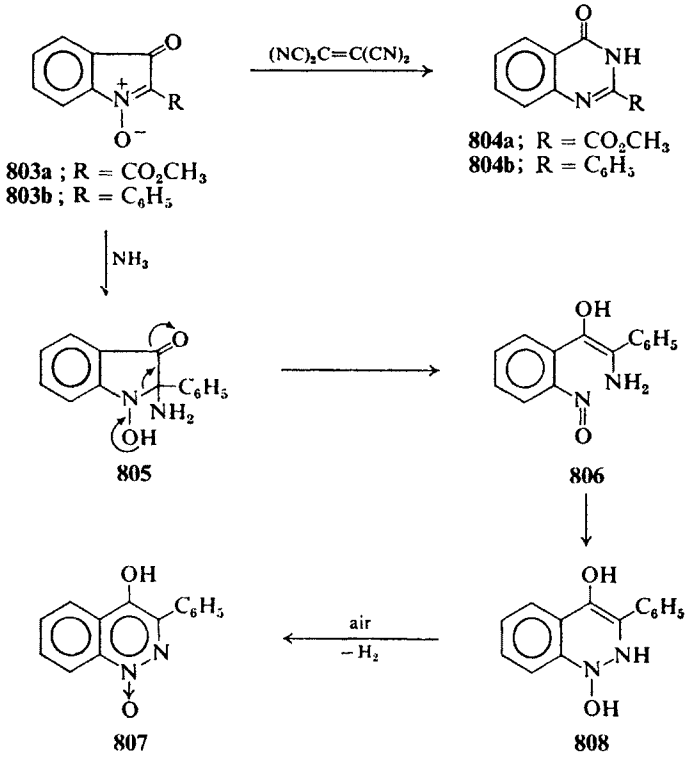
(139)

ammonia also belongs in this category of ring-expansion reactions[539] (Eq. 140).



800 801 802 (140)

Examples of the second type of ring-expansion process include the conversion of 2-phenylisatogen (**803b**) to cinnoline oxide **807** by ammonia, and the formations of quinazolones **804a** and **804b** upon treatment of methyl isatogen-2-carboxylate **803a** and **803b** with tetracyanoethylene[540] (Scheme 95). The mechanism of such quinazolone formation is not known.



803a; R = CO_2CH_3
803b; R = C_6H_5

804a; R = CO_2CH_3
804b; R = C_6H_5

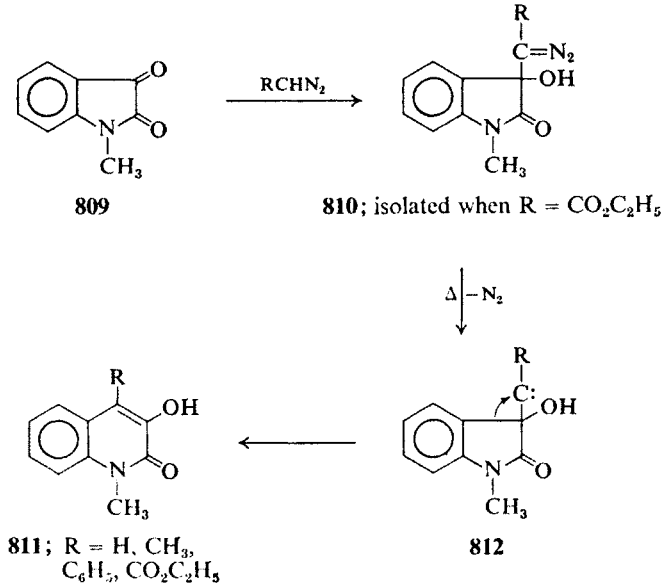
805 **806** **807** **808**

Scheme 95

In Section IV.H the formation of 4-hydroxy-3-phenylquinoline by rearrangement of the indoxyl intermediate obtained upon addition of phenylacetylene

to 2-phenylisatogen was noted. This reaction may also be considered to fall into the second category.

A number of examples in which indoles undergo ring expansion to quinolines appear to involve migration onto an electron-deficient carbon atom. Treatment of *N*-methylisatin (**809**) with diazomethane or substituted diazomethanes afforded carbostyrils **811**[541] (Scheme 96). When **809** was



809

810; isolated when R = $CO_2C_2H_5$

811; R = H, CH_3, C_6H_5, $CO_2C_2H_5$

812

Scheme 96

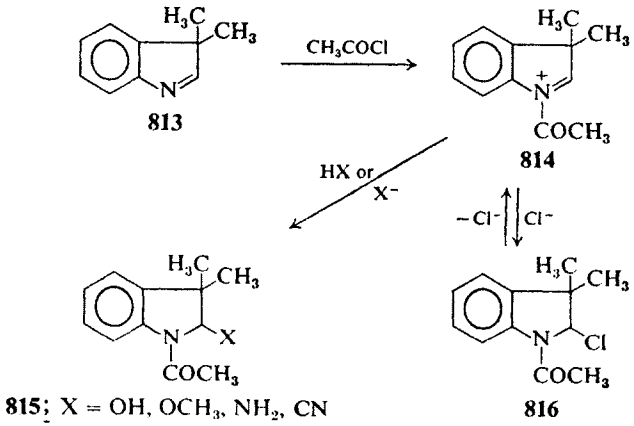
treated with ethyl diazoacetate an unstable diazo compound (**810**) was isolated. It readily gave the carbostyrils **811** when heated or dissolved in methanol. In these examples there is an apparent migration of $C_{(3a)}$ onto the electron-deficient carbon.[544] The preparation of quinolines by reaction of indoles with halocarbenes was described in Section IV.C.12. These reactions are usually viewed as ring openings of 2,3-cyclopropane derivatives, rather than as migrations onto electron-deficient carbon atoms. The proposed formation of quinolinium ions from 1- and 2-alkylindoles under electron impact (Section II.F.6) may be considered examples of migration onto an electron-deficient carbon atom.

O. Addition Reactions of the C=N Bonds of Indolenines and Isatogens

The 1,2-double bonds of indolenines undergo addition reactions with acid chlorides and acid anhydrides. Acylation of the nitrogen is probably the

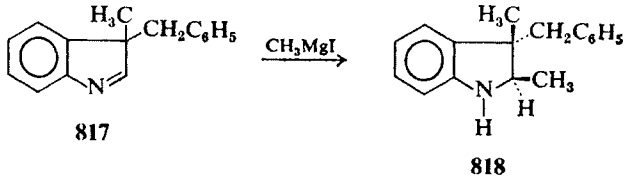
first step in these reactions. The resulting immonium ions (e.g., **814**) then add the anion at $C_{(2)}$. Such 2-substituents are very labile and have been displaced by a variety of groups, including hydroxy, amino, methoxy, and cyano. These displacements possibly occur by S_N1 type processes, in which the immonium ion is an intermediate; however, this suggestion requires confirmation by kinetic studies.

As an illustration of the above-described processes, 3,3-dimethylindolenine (**813**) was readily converted by acetyl chloride into its 1-acetyl-2-chloro derivative **816**.[542] This derivative reacted rapidly with sodium hydroxide to give 2-hydroxyindoline **815**. Treatment of **816** with methanol, ammonia, or silver cyanide gave the corresponding 2-methoxy, amino, and cyano derivatives[542] (Scheme 97).



Scheme 97

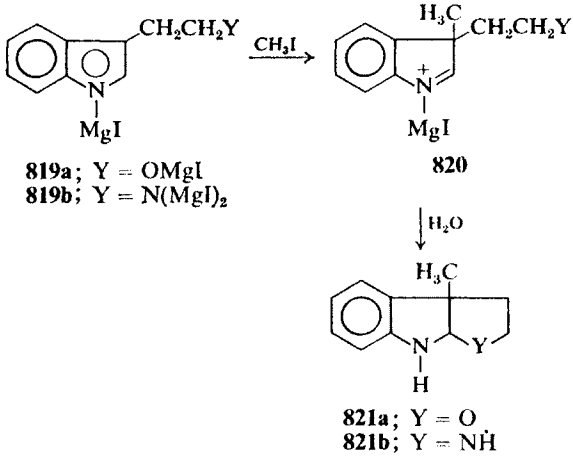
3,3-Disubstituted indolenines readily undergo addition by Grignard reagents to give 2,3,3-trisubstituted indolines. If one of the 3-substituents is considerably larger than the other, only one indoline isomer is formed. For example, addition of methylmagnesium iodide to 3-benzyl-3-methylindolenine (**817**) afforded the *cis* dimethylindoline **818** stereospecifically[470] (Eq. 141).



(141)

The magnesium derivative of malonic ester can also be added to the 1,2-double bond of indolenines.[470]

The indoleninium salts **820** formed by alkylation of tryptamine or tryptophol Grignard reagents (**819a** and **819b**) undergo intramolecular addition of oxygen or nitrogen to the immonium system, affording cycloindolines **821a** and **821b**, respectively[543, 544] (Eq. 142).



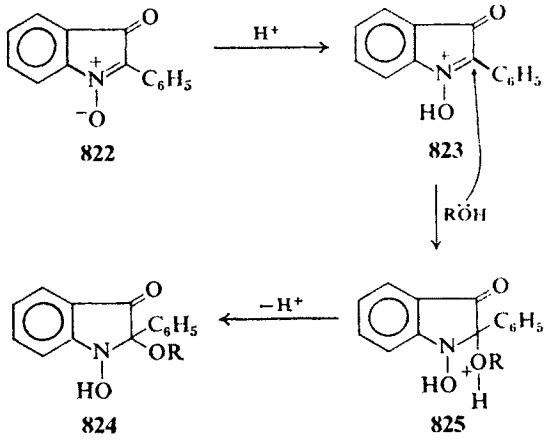
819a; Y = OMgI
819b; Y = $N(MgI)_2$

820

821a; Y = O
821b; Y = NH

(142)

Isatogens (**822**) also undergo addition to the 1,2-double bond.[545] Methanol or ethanol add in the presence of acid to give the corresponding 1-hydroxy-2-alkoxyindoxyls **824**[545] (Scheme 98). Presumably protonation of the oxygen

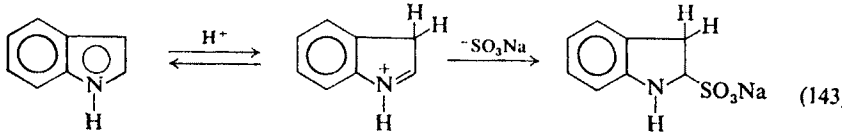


822 **823** **824** **825**

Scheme 98

atom on $N_{(1)}$ occurs first, followed by nucleophilic addition to the resulting immonium ion **823**. Acetyl chloride and acetic anhydride also add to isatogens, probably by way of initial acylation of the oxygen atom on $N_{(1)}$.[546]

The strongly nucleophilic bisulfite anion adds readily to indoleninium cation even in dilute acid, affording sodium 2-indolinesulfonate (**827**) (Eq. 143). This compound, as its *N*-acetyl derivative, can be substituted in the



826 **827** (143)

benzene ring by electrophiles. Hydrolysis of the resulting product then affords the corresponding indole with a substituent at $C_{(5)}$.[547]

V. The Effects of the Indole Nucleus upon Substituents

In the most general sense the effects of the indole nucleus upon substituents would include all of the functional group chemistry of indoles. The description of this chemistry is given in detail in a number of subsequent chapters. For the present chapter, no attempt will be made to fully survey this very large area. Instead, attention will be focused on those aspects in which the reactivity of the functional group is significantly altered as a result of its interaction with the indole nucleus.

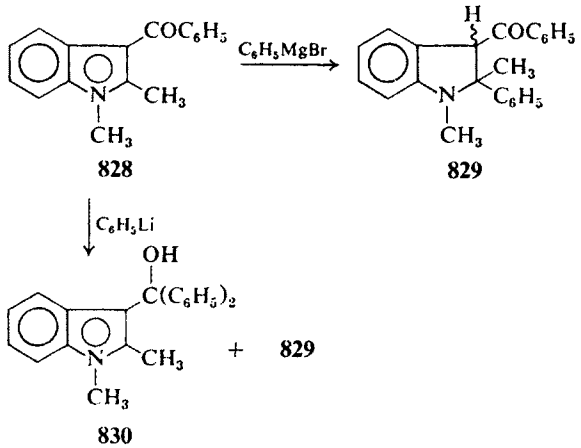
A. Substituents at $C_{(3)}$

1. *Carbonyl Groups*

The most pronounced effects of the indole nucleus upon substituents occur at $C_{(3)}$. This position is in direct conjugation with the nitrogen and receives the largest single contribution of the electrons delocalized from it. For a carbonyl group attached to $C_{(3)}$ the conjugation extends to the carbonyl oxygen, allowing polarized structures with a negative charge on oxygen and a positive charge on nitrogen to make important contributions to the resonance hybrid. The effects of these structures on the physical properties of indole-3-carbonyl compounds were discussed in Section II. The chemical reactivity of the carbonyl groups is also affected by this conjugation. They become less active than carbonyl groups on a benzene ring (e.g., benzaldehyde) toward nucleophiles. Thus indole-3-carboxaldehyde does not form a bisulfite adduct or undergo the benzoin or Perkin condensations. It also fails to give tests with the Tollens, Fehlings, or fuchsin reagents. However, it does give an oxime,

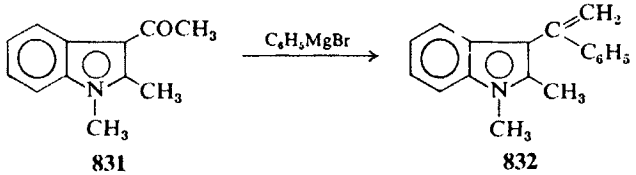
phenylhydrazone, and semicarbazone, and it condenses with active methylene compounds such as nitromethane, malonates, hydantoin, and barbituric acids.[548, 549]

The bonding in indole-3-carbonyl compounds apparently differs considerably from that in other aromatic aldehydes since certain of the former undergo 1,4-addition. For example, treatment of 1,2-dimethyl-3-benzoylindole (**828**) with phenylmagnesium bromide afforded the corresponding 2-phenylindoline.[550] Even phenyllithium, which normally adds 1,2 to carbonyl groups, gave some 2-phenyl derivative **829**, in addition to the anticipated tertiary alcohol **830**[550] (Eq. 144). That the phenyl substituent on the carbonyl group



(144)

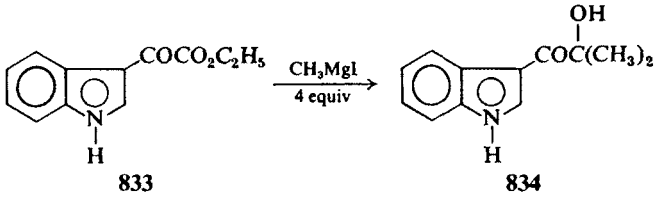
was also influencing the course of addition to **828** was demonstrated by isolation only of the product of 1,2-addition **832** when 3-acetyl-1,2-dimethylindole **831** was treated with phenylmagnesium bromide[550] (Eq. 145).



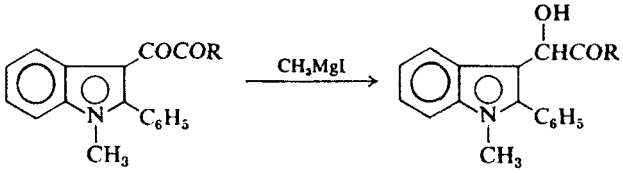
(145)

The relative reactivities of the two carbonyl groups in indole-3-glyoxalyl compounds toward Grignard reagents is highly sensitive to the possibility of forming an organomagnesium derivative on the indole nitrogen. Such derivatives would have greater ability to delocalize electrons onto the carbonyl group directly attached to $C_{(3)}$ than would the corresponding *N*-alkylindoles. In the case of indole-3-glyoxylic esters this factor leads to alkylation of either the ketonic or the ester carbonyl groups by methylmagnesium iodide. Thus ethyl indole-3-glyoxylate (**833**) gave a product **834**

derived from alkylation of the ester carbonyl[551] (Eq. 146), whereas ethyl-1-methyl-2-phenylindole-3-glyoxylate **835a** and the corresponding diethylamide **835b** afforded glycolate derivatives **836a** and **836b**, respectively[552] (Eq. 147). As anticipated, diketone **837** was selectively methylated at the carbonyl group not conjugated with the indole nucleus[551] to give **838** (Eq. 148).

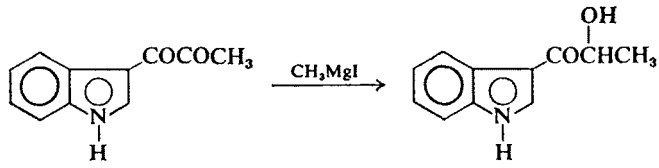


833 **834** (146)



835a; R = OC_2H_5
835b; R = $N(C_2H_5)_2$

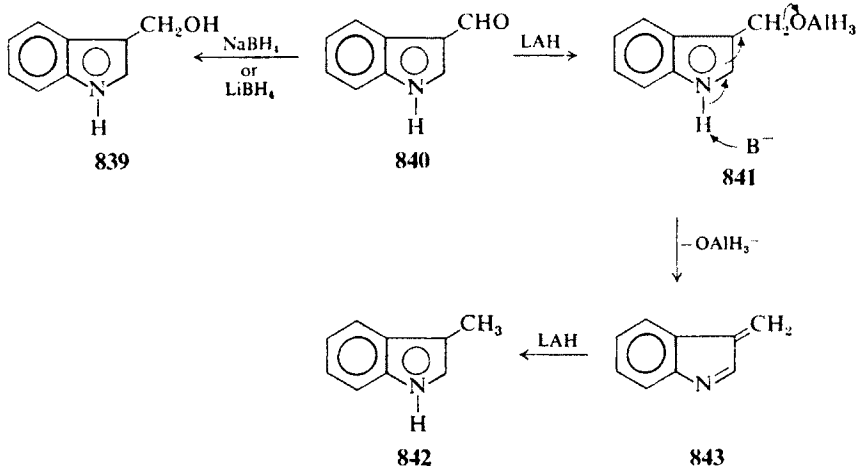
836a; R = OC_2H_5
836b; R = $N(C_2H_5)_2$ (147)



837 **838** (148)

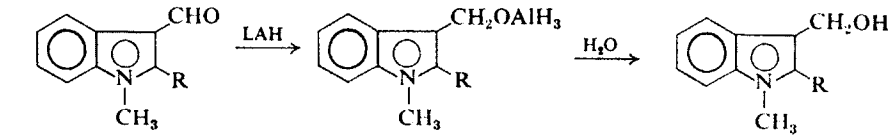
Chemical reduction of carbonyl groups attached to the $C_{(3)}$ of indoles is also strongly influenced by the conjugation of these groups with the nucleus. Indole-3-carboxaldehyde (**840**) has been reduced to 3-hydroxymethylindole (**839**) in high yields by sodium borohydride or lithium borohydride.[553–556] With stronger reducing agents such as lithium aluminum hydride (LAH)[199, 553, 554] or diborane[473] the reduction does not stop at this stage, but goes on to give 3-methylindole (**842**) (Scheme 99). The diborane reduction also gave significant amounts of dimers **851** and **853**.[473] For indole-3-carboxaldehydes with alkyl substituents on nitrogen (e.g., **844** and **847**) reduction with LAH stops at the 3-hydroxymethyl stage (**846**)[199, 554] (Eq. 149); however, the diborane reduction affords 3-methyl derivatives **852** (in certain cases the main products) plus dimers **851** and **853**[473] (Scheme 100).

The above results have been interpreted in the following manner.[473]



Scheme 99

Reduction with LAH initially forms aluminate complex **841**. When the nitrogen is unsubstituted, this intermediate loses $^{-}OAlH_3$, assisted by concerted (or prior) removal of the proton on nitrogen. The resulting 3-methyleneindolenine **843** (3*H*-pseudoindole) is subsequently reduced to 3-methylindole **842**. If the indole nitrogen is substituted, the elimination of $^{-}OAlH_3$ is not assisted by proton removal and hence does not occur. The intermediate aluminate complex then gives alcohol **846** upon workup.

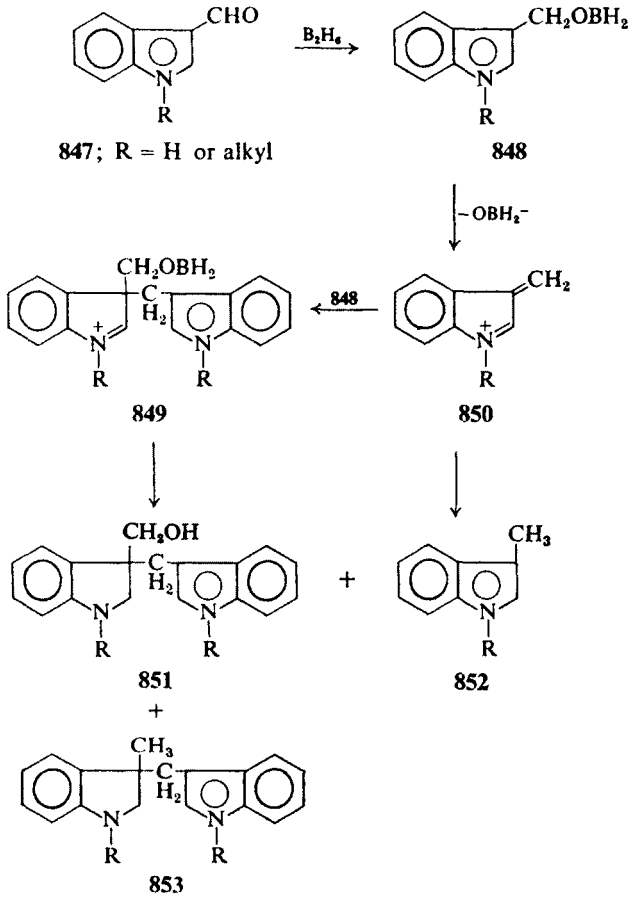


844; R = H, alkyl, aryl — **845** — **846**

(149)

In contrast, the diborane reduction affords borate intermediate **848** which is able to undergo $^{-}OBH_2$ elimination even if the indole nitrogen is alkylated. The resulting 3-methyleneindoleninium ion **850** is either reduced by diborane to **852** or adds to borate intermediate **848**, furnishing **849** which is then converted into dimers **851** and **853**[473] (Scheme 100).

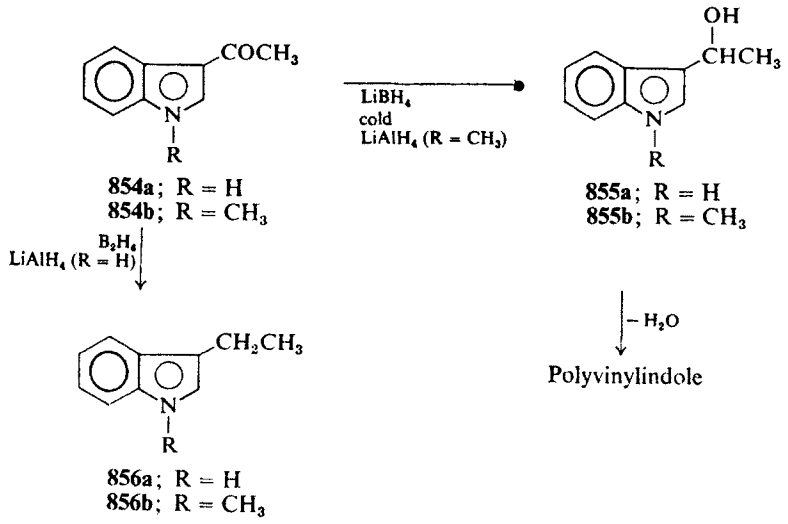
Reduction of 3-acetylindoles proceeds in a manner analogous to that of the corresponding 3-carboxaldehydes. Thus 3-acetylindole (**854a**) afforded hydroxyethyl derivative **855a** (poor conversion) when treated with lithium borohydride (LBH) in cold tetrahydrofuran, whereas LAH, diborane, and LBH in hot tetrahydrofuran reduced it to 3-ethylindole **856a**[556] (Scheme 101).



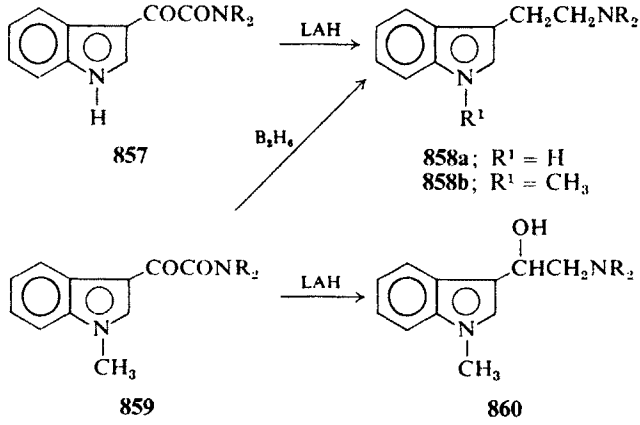
Scheme 100

3-Acetyl-1-methylindole (**854b**) was converted initially by LAH to hydroxyethyl indole **855b**, but this compound was unstable and underwent dehydration and polymerization.[557] Diborane[473] or a mixture of LAH and aluminum chloride[557] reduced **854b** to 3-ethyl-1-methylindole (**856b**). The role of the aluminum chloride was to promote decomposition of the intermediate indole–aluminate complex to a 3-ethylidineindolenium ion (related to **850**), which was then reduced to **856b**.[557]

Reduction of indole-3-glyoxalyl amides to tryptamines is a highly important process in indole chemistry. When $N_{(1)}$ is unsubstituted this transformation (**857** → **858a**) can be readily effected in one step with LAH; however, $N_{(1)}$-alkyl analogs **859** are reduced only to β-hydroxytryptamines **860** with this reagent.[199, 310, 554] It has been reported that diborane affords tryptamines **858b** directly with the $N_{(1)}$-alkyl compounds[473] (Scheme 102).

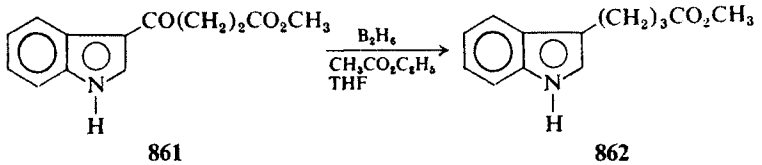


Scheme 101



Scheme 102

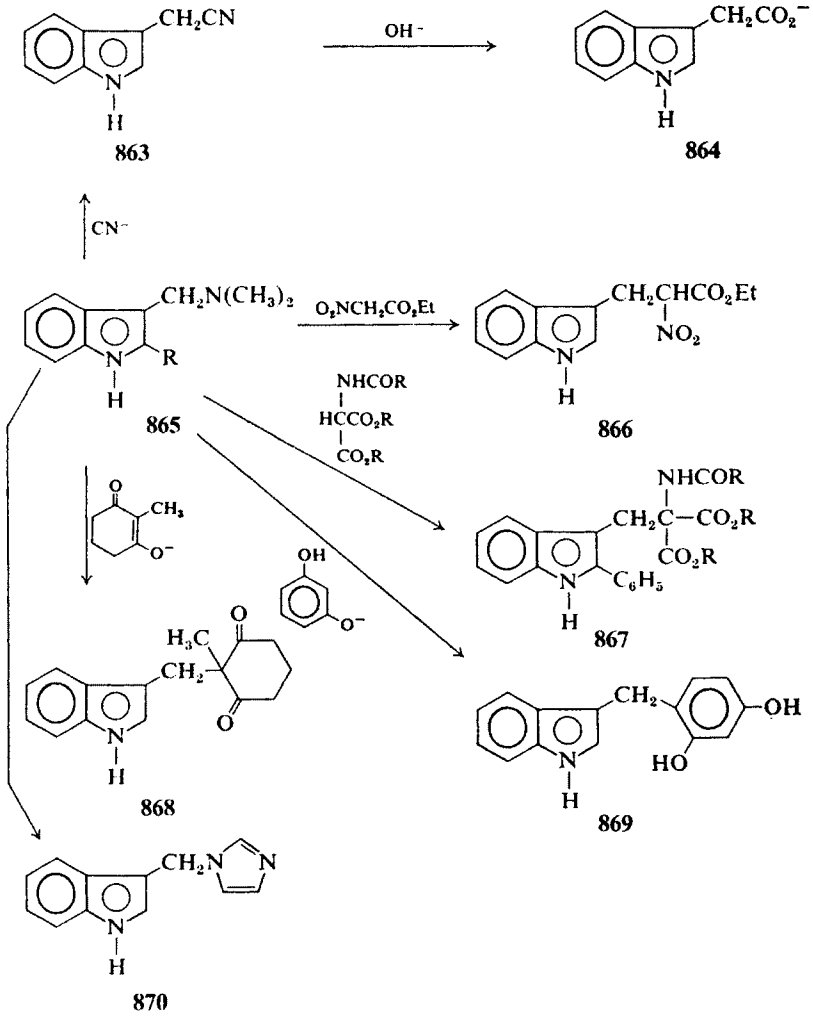
Selective reduction of the ketonic carbonyl group of methyl 4-(3-indolyl)-4-oxobutyrate (**861**) was afforded by diborane in tetrahydrofuran containing ethyl acetate[190] (Eq. 150).



(150)

2. *Alkylations with Gramine and Related Compounds*

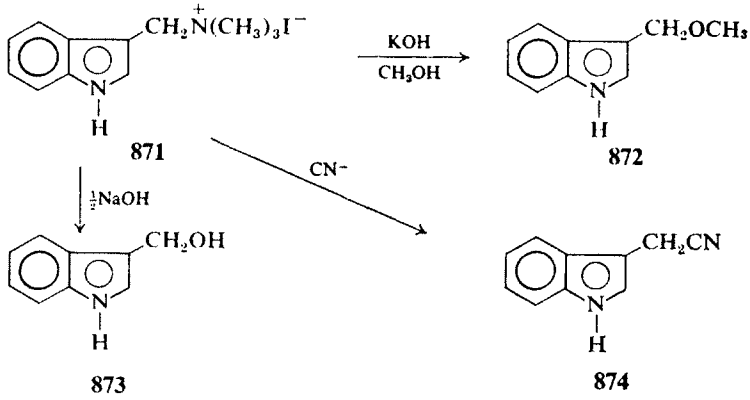
Gramine derivatives **865** have been of considerable importance in the development of various side chains at $C_{(3)}$. Their value lies in the fact that nucleophiles such as carbanions are able to displace dimethylamine from the 3-methylene group, affording intermediates in which the chain has been extended. Some typical reactions are shown in Scheme 103. Thus, displacement



Scheme 103

by cyanide ion in aqueous medium afforded a convenient indole-3-acetate synthesis (**865** → **864**).[558] Displacement by acetamidomalonic ester or by ethyl nitroacetate in the presence of base furnished intermediates **866** and **867** which were converted into tryptophan derivatives.[559, 560] Enolate and phenolate anions gave products (**868** and **869**) which were the result of carbon, rather than oxygen, displacement on the methylene group.[561, 562] However, with imidazole, bonding to the nucleophile occurred on a nitrogen atom (**865** → **870**).[562]

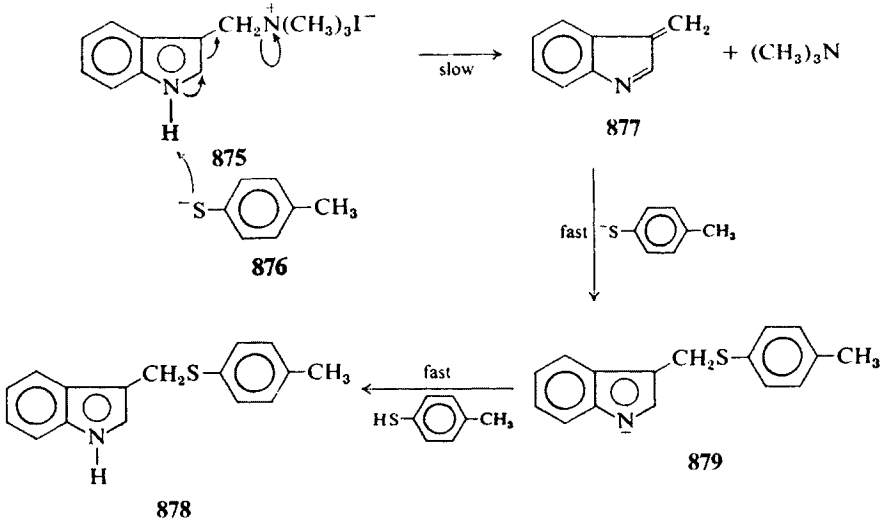
The methiodide (**871**) of gramine is even more reactive than gramine toward nucleophiles since it loses trimethylamine, a very effective leaving group. Under mild conditions **871** was converted into the corresponding hydroxy, methoxy, and cyano derivatives **873**, **872**, and **874**, respectively[563, 564, 565] (Scheme 104). The reaction of 1-methylgramine methiodide with aqueous



Scheme 104

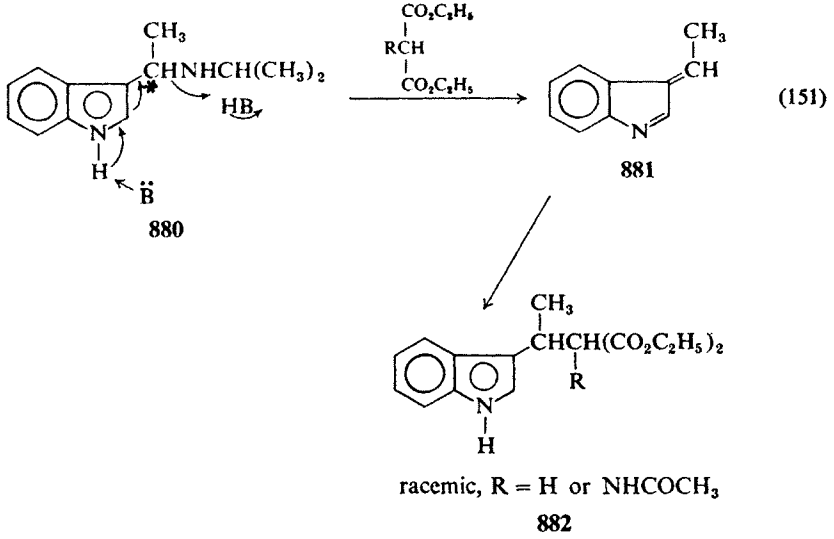
sodium cyanide was much faster than similar reactions of benzyl quaternary salts.[564]

Two different mechanisms have been proposed for the reaction of gramine and its methiodide with nucleophiles.[566, 567] They are elimination-addition and direct displacement. The elimination-addition mechanism appears to operate generally for gramine derivatives unsubstituted on $N_{(1)}$. Thus the reaction of the anion from *p*-toluenethiol (**876**) with gramine methiodide was first order in both reactants and a plot of the second-order rate constant against the reciprocal of the *p*-toluenethiol anion concentration decreased in linear fashion. These data suggested that the initial, rate-determining step was a concerted elimination which gave 3-methyleneindoline **877**. *p*-Toluenethiol then added to **877** in a faster step[567] to give **879** and **878** (Scheme 105). In support of this mechanism it was found that **877**, prepared by neutralization of its sulfuric acid salt, added sodiomalonic ester, piperidine, and ethanol in



Scheme 105

good yields at room temperature.[566] Furthermore, when optically active gramine analog **880** was treated with diethyl malonate, diethyl acetamidomalonate, or piperidine, racemic product (**882**) was obtained.[566] This loss of optical activity rules out an S_N2 displacement with inversion of configuration and supports a symmetrical intermediate such as **881** (Eq. 151).

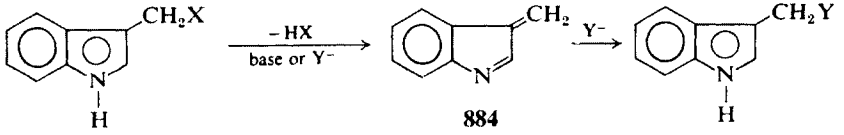


(151)

In contrast to the preceding examples, the reaction of 1-methylgramine methiodide with the anion of *p*-toluenethiol is considered to be a direct

displacement, probably S_N2 with partial S_N1 character. This reaction is first order with respect to each reactant but it is 5×10^5 times slower than the corresponding reaction of **875**, and the second-order rate constant is not influenced by the concentration of *p*-toluenethiol anion.

In addition to the gramine derivatives, certain other indoles substituted at $C_{(3)}$ with methylene groups bearing potential leaving groups undergo useful elimination-addition type reactions. For example, 3-hydroxymethylindole (**883a**) has been converted into the corresponding 3-piperidinomethyl, 3-cyanomethyl, and 3-ethoxymethyl derivatives (**885a**, **885b**, and **885c** respectively).[199,568,569] 3-Piperidinomethylindole (**885a**) was also obtained by the reaction of piperidine with 3-methoxymethylindole (**883b**) and with 3-ethylthiomethylindole (**883c**)[566] (Eq. 152).



883a; X = OH
883b; X = OCH_3
883c; X = SC_2H_5

884

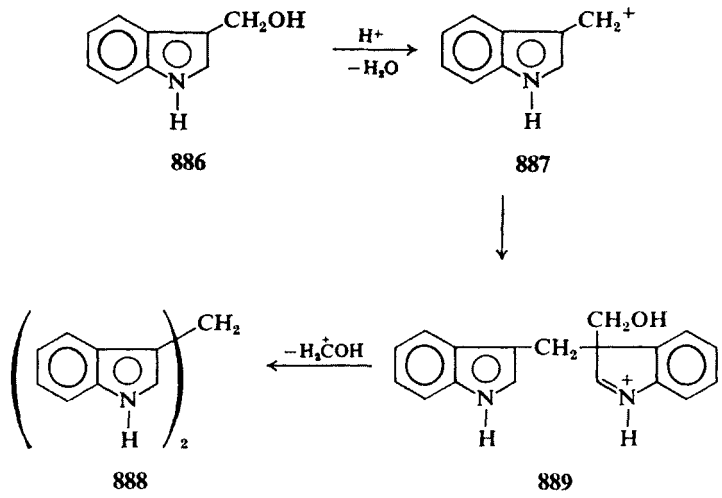
885a; Y = N

885b; Y = CN
885c; Y = OC_2H_5

(152)

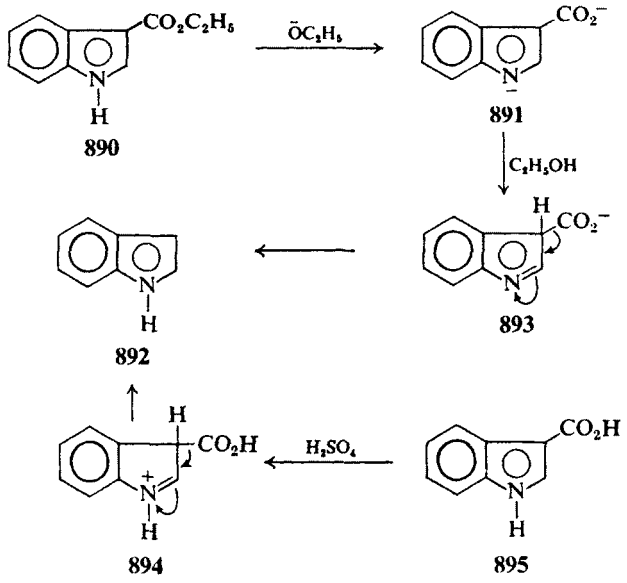
3. *Cleavage of 3-Substituents*

The cleavage of substituents from the 3-position of indoles is sometimes encountered. Depending upon the particular substituent, the cleavage may take place under acidic or basic conditions varying from extremely mild to vigorous. One of the most facile cleavage reactions occurs in the formation of diindolylmethanes from 3-hydroxymethylindoles in the presence of acid. Even water or methanol may serve as the acid when there are alkyl groups at $N_{(1)}$ and $C_{(2)}$.[199] 3-Hydroxymethylindole itself (**886**) formed diindolylmethane **888** in aqueous solution at pH 5.5 (dissolved CO_2), but was stable in the presence of a trace of alkali[553] (Scheme 106). Other 3-hydroxymethylindoles are converted by boiling water to diindolylmethanes.[199] These conversions may be interpreted as first involving an acid-catalyzed dehydration to a resonance-stabilized carbonium ion **887**, which is able to effect electrophilic substitution at $C_{(3)}$ of a molecule of starting material. The resulting intermediate **889** eliminates the conjugate acid of formaldehyde. Electron-withdrawing substituents, such as carbonyl and carboxylic ester at $C_{(2)}$,[326,570] or a quinone function in the benzenoid ring,[571] stabilize the 3-hydroxymethyl group toward diindolylmethane formation.



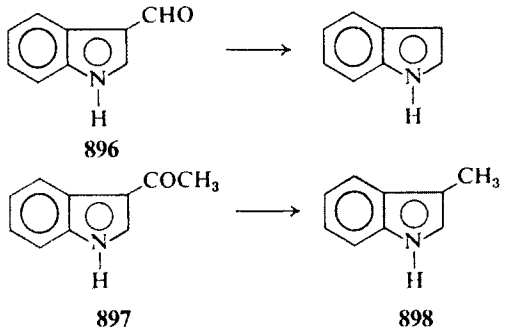
Scheme 106

Ethyl-3-indolecarboxylate (**890**) is cleaved in high yields to indole within 18 hr at 78° by either 4% sulfuric acid or 0.1 *N* sodium hydroxide in ethanol. The formation of indole from indole-3-carboxylic acid (**895**) in sulfuric acid required somewhat more vigorous conditions. These cleavages have been considered as requiring tautomerization to the corresponding indolenines (**893** and **894**) prior to cleavage[572] (Scheme 107).



Scheme 107

Indole-3-carboxaldehyde (**896**) and 3-acetylindole (**897**) were not cleaved in dilute aqueous base, but **896** gave indole when heated at 100° in 60% potassium hydroxide. Sodium methoxide in methanol converted **897** into 3-methylindole (**898**), presumably by methylation of intermediate indole



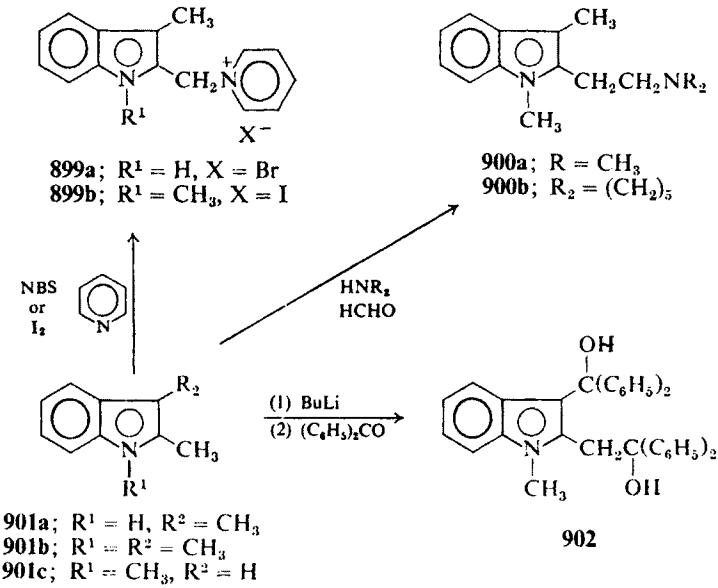
896 **897** **898** (153)

(Eq. 153). The need for forcing conditions in the cleavage of indole-3-carbonyl compounds is probably due to the stability of their anions toward tautomerism.[572]

Examples of cleavage with indole-3-carboxaldehyde under acidic conditions include the formation of urorosein in perchloric or sulfuric acids (Section IV.C.10) and the replacement of carboxaldehyde by a nitro group during nitration in acetic acid (Section IV.C.3).

B. Substituents at $C_{(2)}$

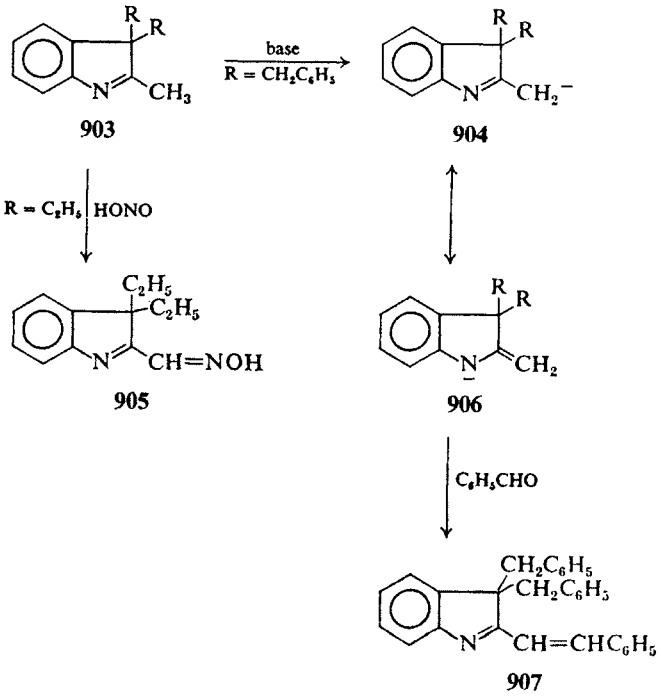
A methyl group at $C_{(2)}$ of indoles resembles methyl groups on other aromatic nuclei in its reactivity toward bases and free radicals. It is more active than a methyl group at $C_{(3)}$ under these conditions, probably because it receives only a small amount of deactivating electron donation from nitrogen, whereas $C_{(3)}$ receives a relatively large electron donation. Thus treatment of 2,3-dimethylindole (**901a**) with NBS in pyridine afforded 2-methylpyridinium derivative **899a** in good yield.[573] A related salt **899b** was obtained from 1,2,3-trimethylindole (**901b**) and iodine in pyridine.[574] No substitution on the 3-methyl group was observed under these conditions. The Mannich condensation of **901b** with formaldehyde and dimethylamine or piperidine also occurred on the 2-methyl group, forming **900a** and **900b**, respectively.[575] Treatment of 1,2-dimethylindole (**901c**) with *n*-butyllithium followed by benzophenone gave product **902** in which substitution had taken place on the 2-methyl group as well as the nucleus[550] (Scheme 108).



Scheme 108

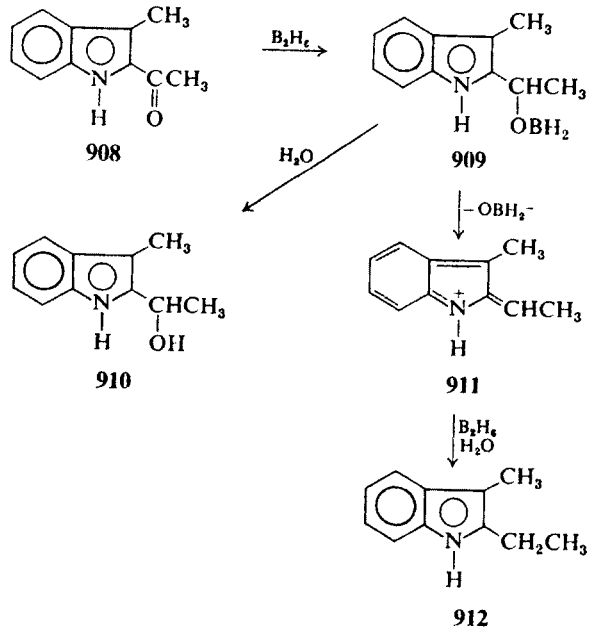
The 2-methyl groups of indolenines **903** are in direct conjugation with an imine type nitrogen, hence anions created by loss of a proton from them are stabilized by delocalization onto this nitrogen (**904**↔**906**). As a consequence, these methyl groups are comparable to those of 2-picoline in reactivity.[576] They protonate Grignard reagents, and form benzylidines (**907**) when treated with benzaldehyde. In the presence of nitrous acid they afford oximes (**905**)[576] (Scheme 109).

Carbonyl groups substituted onto $C_{(2)}$ of indoles are readily reduced by sodium borohydride to the corresponding alcohols, which unlike the isomeric 3-hydroxyalkylindoles are stable toward diindolylmethane formation.[554] Reduction of 2-acetyl-3-methylindole (**908**) with diborane (Scheme 110) gave a mixture of 2-ethyl and 2-hydroxethyl derivatives (**910** and **912**). Isolation of **910** showed that the intermediate alkoxyborane **909** has less tendency than corresponding alkoxyboranes formed from 3-acetylindoles[473] to dissociate to a methylene intermediate (**911**). Alcohols were not isolated in diborane reductions of 3-acetylindoles. The greater stability of the alkoxyborane intermediates **909** from 2-acetylindoles is probably due to the higher energy of the methylene intermediates **911** that have lost benzene-ring aromaticity.[473] An interesting comparison of the relative reactivities toward nucleophilic and electrophilic reducing agents of carbonyl groups attached to the 2- and 3-indole positions was afforded by pyrroloindole **913**. Treatment



903 904 905 906 907

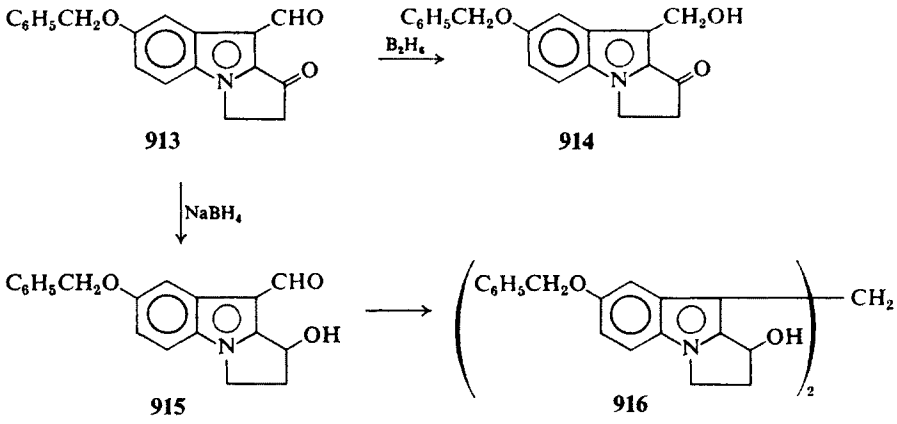
Scheme 109



908 909 910 911 912

Scheme 110

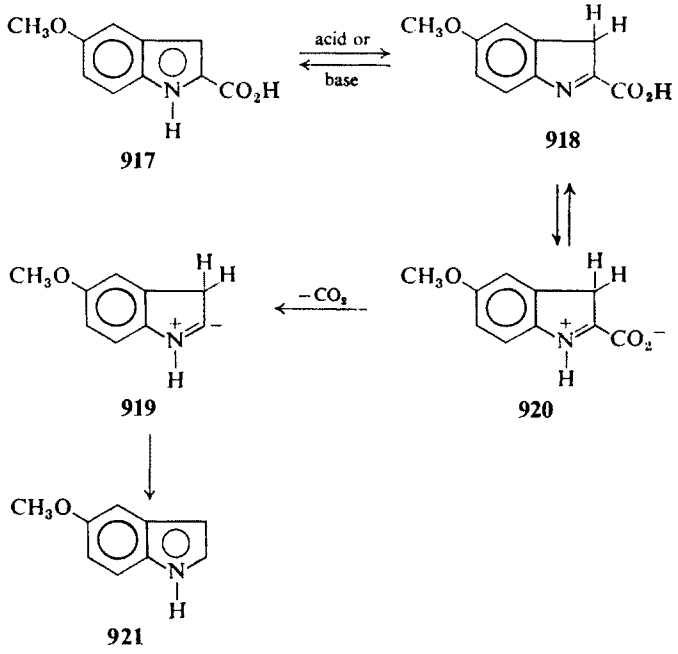
of this compound with alcoholic sodium borohydride initially gave reduction of the carbonyl group at $C_{(2)}$ (uv evidence), followed by reduction of the carbonyl group at $C_{(3)}$ and diindolylmethane formation (**913** → **915** → **916**) (Scheme 111). However, the electrophilic reagent diborane, in limited



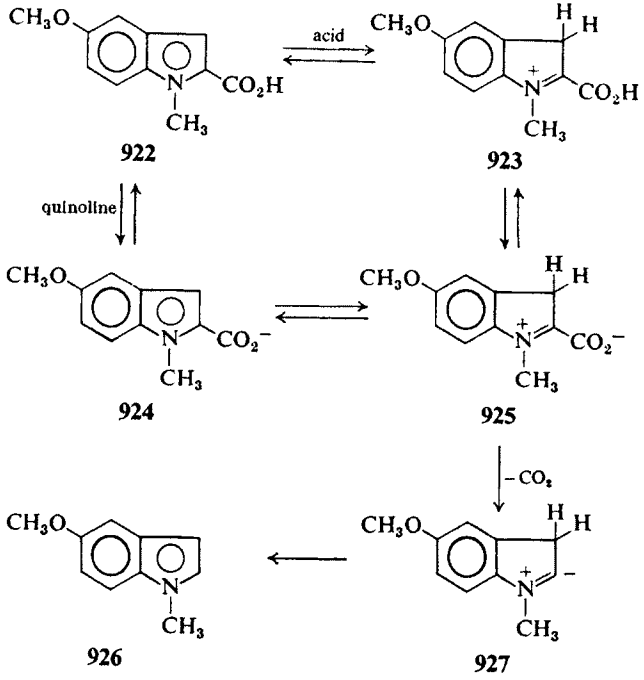
Scheme 111

amount, selectively reduced the carbonyl group at $C_{(3)}$ (**913** → **914**).[326] In **914** the carbonyl group at $C_{(2)}$ stabilized the 3-hydroxymethyl group toward diindolylmethane formation.

Indole-2-carboxylic acids are more readily decarboxylated than indole-3-carboxylic acids.[577] Acid, bases, and metal ions catalyze the decarboxylation of the 2-carboxylic acids, with bases such as quinoline being the most effective catalysts. All of these reactions are accelerated by electron-releasing substitutents at $C_{(5)}$ and retarded by electron-withdrawing substituents at this position.[578, 579] These results might be explained by a mechanism in which the indole-2-carboxylic acid (e.g., **917**) undergoes tautomerization to the corresponding indolenine **918** prior to decarboxylation.[578] The species that actually undergoes the decarboxylation is possibly a zwitterion such as **920** (Scheme 112). This step would be analogous to the decarboxylation of quinoline-2-carboxylic acids.[580] The function of the electron-releasing substituent in this process is to stabilize the indoleninium ion formed by protonation at $C_{(3)}$ and also possibly to stabilize the positive charge in the zwitterion. Quinoline would be effective in promoting tautomerization to the indolenine and in ionizing the carboxyl group. With 5-methoxy-1-methyl-indole-2-carboxylic acid **922** protonation at $C_{(3)}$, followed by loss of a proton from the carboxylic acid, would give an equivalent zwitterion (**925**). The decarboxylation of **922** is even faster than that of **917** in both acid and base[578] (Scheme 113).



Scheme 112

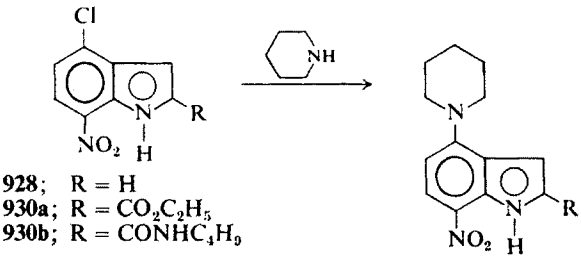


Scheme 113

C. Substituents on the Benzenoid Ring

1. *Nucleophilic Displacement*

Substituents on the benzenoid ring of indoles are less reactive toward nucleophilic displacement than similar substituents on ordinary benzene rings. This deactivation is due to the electron releasing effect of the indole nitrogen. The chlorine atom of 4-chloro-7-nitroindole (**928**) could be displaced by secondary amines such as piperidine and morpholine to give **929**, but vigorous conditions (140° for 15 hr) were required[581] (Eq. 154). In contrast,



928; R = H
930a; R = $CO_2C_2H_5$
930b; R = $CONHC_4H_9$

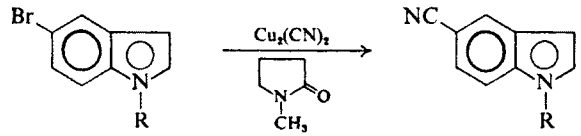
929; R = H
931a; R = $CO_2C_2H_5$
931b; R = $CONHC_4H_9$

(154)

the corresponding 2-carboxamido and 2-carboxylic ester derivatives (**930a** and **930b**, respectively) underwent nearly quantitative displacement of chloride by these amines at room temperature in ethanol to give **931a** and **931b**.[581] Evidently the additional electron-withdrawing groups of these derivatives are able to overcome the deactivating effect of the indole nitrogen. The sodium salt of 4-chloro-7-nitroindole-2-carboxylic acid, with a full negative charge on the carboxylate group, was less active toward nucleophilic substitution than other carboxylic acid derivatives.[581]

2. *Other Reactions*

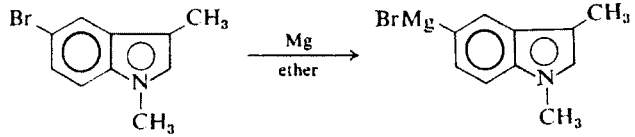
Displacement of substituents from the benzenoid ring of indoles by free radical reactions appears to proceed as readily as in the corresponding simple benzene derivatives. Thus 5-bromoindole (**932**) was converted into 5-cyanoindole (**933**) by cuprous cyanide in *N*-methylpyrrolidone in 70%



932; R = H, CH_3 **933**

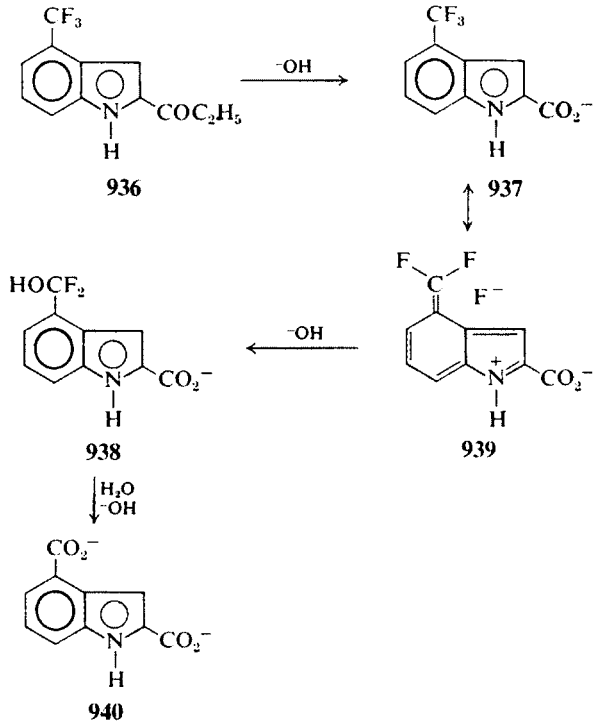
(155)

yield[582] (Eq. 155). The *N*-methyl homolog of **932** underwent a similar transformation.[583] Preparation of Grignard reagent **935** from 5-bromo-1,3-dimethylindole (**934**) was relatively easy[584] (Eq. 156).



934 **935** (156)

In the saponification of ethyl-4-trifluoromethylindole-2-carboxylate (**936**) (Scheme 114), it was found that not only the ester group, but also the tri-



940

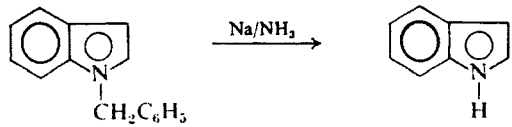
Scheme 114

fluoromethyl group, was converted to a carboxylate anion (**940**).[385] Ordinarily trifluoromethyl groups on benzene rings are stable to hydrolysis; however, when hydroxyl or amino groups are *ortho* or *para* to these functions, alkaline hydrolysis is possible. In **936** the electron-releasing nitrogen is *meta* to the trifluoromethyl group, but is in direct conjugation with it by way of alternative structure **939**, hence reactivity toward nucleophilic attack by hydroxide

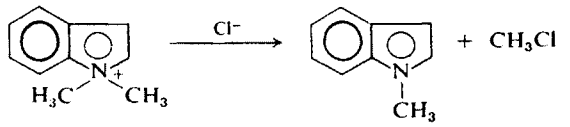
ion is promoted. The trifluoromethyl group of ethyl-6-trifluoromethylindole-2-carboxylate is similarly activated toward hydrolysis.[585] Trifluoromethyl groups on the benzene rings of indoles may be hydrolytically cleaved by heating in hydrochloric acid.[586]

D. Substituents on $N_{(1)}$

Since the two π electrons on indole nitrogens are part of the aromatic system of the nucleus, they are not readily available for conjugation with substituents on this nitrogen. Consequently $N_{(1)}$ acyl indoles possess little amide character and may be readily hydrolyzed. Alkyl substituents on the nitrogen are difficult to remove; however, *N*-benzyl indoles (e.g., **941**) may be readily cleaved with sodium in liquid ammonia to the indoles and toluene[587] (Eq. 157). 1,1-Dimethylindolium ion (**942**) is a moderately active methylating



941 (157)



942 (158)

agent, transferring a methyl group even to chloride ion in its conversion to 1-methylindole[35] (Eq. 158).

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CHAPTER II

Synthesis of the Indole Nucleus

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I. Introduction

Several articles have been written reviewing the various methods of synthesizing indoles up to 1953.[1–5] Since their publication, a large volume of work has appeared in the literature, amplifying the known methods of synthesis and in addition providing new routes for the preparation of the indole ring system. The Fischer indole synthesis has received particular attention since it is no doubt the most versatile and widely applicable method of obtaining indoles. Of the reviews that deal only with the Fischer indole synthesis,[6–10] those of B. Robinson[9, 10] are the most comprehensive and up-to-date.

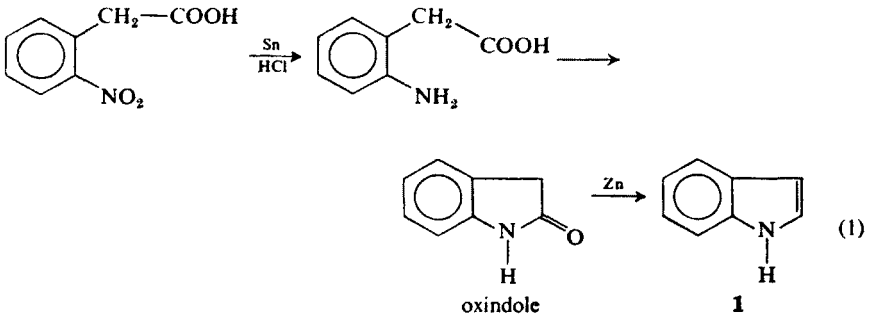
The purpose of the present chapter is to provide a compilation of the methods of preparing indoles, primarily emphasizing the work that has appeared since 1953. The approach will be in terms of modern electronic and structural concepts, and mechanisms of reaction will be provided for those methods in which they have been established or reasonably presented.

No attempt has been made to cover every published article wherein indole preparation has been described. It is hoped, however, that all significant articles have been included as well as a sufficiently good representation of those dealing merely with the utility and application of methods of synthesis, so that the reader will be provided with adequate background and information.

II. The Structure of Indole

In a study of the structure of indigo, Baeyer and Knop[11] reduced isatin, a product of the nitric acid oxidation of indigo.[12, 13] first to a substance $C_8H_7NO_2$ by use of sodium amalgam in alkaline solution and then under acidic conditions with tin, or preferably sodium amalgam, to C_8H_7NO. These two substances were considered to be oxygen derivatives of the parent

substance C_8H_7N, which was named indole,[14] and hence they were named dioxindole and oxindole, respectively. The complete reduction of oxindole to indole was accomplished by distillation of a mixture of oxindole and zinc dust.[14] Because indole could be made by the fusion of a mixture of *o*-nitrocinnamic acid with iron filings and potassium hydroxide, or by the action of lead peroxide on azocinnamic acid,[15] Baeyer proposed structure **1** for indole. This was substantiated by the reductive cyclization of *o*-nitrophenylacetic acid to oxindole, the lactam of *o*-aminophenylacetic acid[16] which could then be reduced to indole by distillation with zinc dust (Eq. 1). More recently[17]

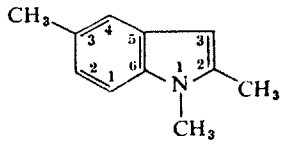


(1)

it has been shown that $LiAlH_4$ is a satisfactory agent for the reduction of *N*-alkyloxindoles (but not oxindole itself) to the corresponding *N*-alkylindoles. That **1** is indeed the correct structure of indole has been fully supported by all the work that has appeared since Baeyer's first proposal.[15]

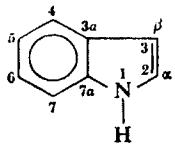
III. Nomenclature

The system of nomenclature first proposed by Baeyer[18] and employed and amplified by Fischer[19] was unwieldy and soon lost favor. In this method the benzene ring portion was labeled B and the hetero ring labeled Pr (an abbreviation for pyrrole). Each ring was numbered separately, the hetero ring anticlockwise away from the benzene ring, beginning with the atom adjacent to the bridgehead carbon as number 1 (in this case the nitrogen atom), while the benzene ring was numbered clockwise with the carbon atom adjacent to the bridgehead carbon nearest the nitrogen atom as number 1. The position of the nitrogen atom in the heterocyclic ring was indicated by the superscript *n* following the position number. By the appropriate combination of the ring label and position number it was possible to name substituted indoles as shown in the following example.

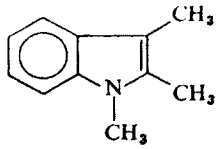


B3-Pr1", 2-trimethylindole

A method of nomenclature that emphasizes the atoms of the pyrrole ring labels the two carbon atoms which are not part of the benzenoid ring as α and β (Structure **1a**). Only those compounds with substituents at either of



1a



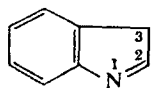
2

these two positions or attached to the nitrogen atom are readily named by this method. For example, Structure **2** is *N*,α,β-trimethylindole.

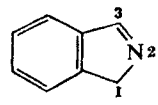
The modern and most popular method, which permits naming of compounds substituted in the benzenoid ring as well, is to number the bicyclic system consecutively anticlockwise starting with the nitrogen atom as number 1 and label the bridgehead carbon atoms as 3*a* and 7*a* (Structure **1a**). Structure **2** by this method is termed 1,2,3-trimethylindole.

Although the trivial name, *indole*, is used almost exclusively to designate Structure **1a**, the following names have also been employed: 1*H*-benzo[*b*]pyrrole(systematic name),[20] 1-benzazole, α,β-benzopyrrole, 1-azaindene, ketole.

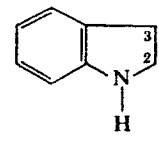
The isomer of indole wherein the nitrogen atom is attached to the double bond (Structure **3**) is called 3*H*-benzo[*b*]pyrrole (systematic name),[20] 3*H*-indole, 3-pseudoindole, or indolenine, while the isomer **4** in which the



3



4

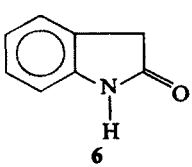


5

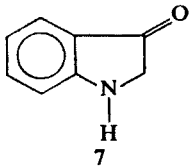
nitrogen atom is not directly attached to the benzeneoid ring is named 1*H*-benzo[*c*]pyrrole (preferred systematic name),[20] 1*H*-isoindole, or pseudoisoindole. Structure **5**, saturated at positions 2 and 3, is named indoline. The

names and structures of the oxygenated derivatives of indole are indicated by Structures **6–9**.

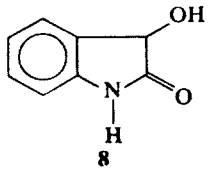
For interesting accounts of the history and naturally occurring sources of indole and indole derivatives, the reader is referred to reviews cited above.[1, 2, 4, 5]



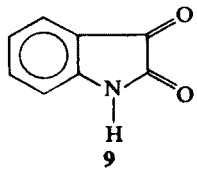
6
oxindole



7
indoxyl



8
dioxindole

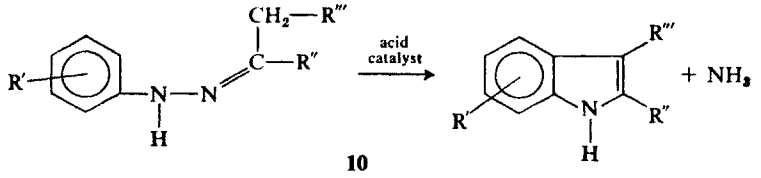


9
isatin

IV. Methods of Preparing the Indole Ring System

A. The Fischer Indole Synthesis

By heating the unsymmetrical methylphenylhydrazone of pyruvic acid in dilute hydrochloric acid, Fischer and Jourdan[21] obtained in small yield a substance $C_{10}H_9NO_2$ which[22] proved to be 1-methylindole-2-carboxylic acid. It was found later that the low yields obtained with dilute hydrochloric acid, presumably due to hydrolysis of the hydrazone, could be avoided by using zinc chloride as catalyst. A mixture of acetone phenylhydrazone with a 5-fold excess of zinc chloride heated to 180° gave 2-methylindole (methylketol) in 60% yield.[23, 24] Since that time the arylhydrazones obtained from the reaction of many carbonyl compounds, such as aldehydes, ketones, keto acids and esters, and diketones, with arylhydrazines in which the mononuclear or polynuclear aryl group is either unsubstituted or substituted in various positions of the ring, have been converted by a wide variety of acids, or metal halides which can coordinate with organic molecules, to compounds containing the indole structural unit. This conversion of arylhydrazones to the indole, accompanied by the elimination of ammonia, is known as the Fischer indole synthesis and is represented by Eq. (2). The modification discovered by Arbuzov and Tikhvinskii[25] in which many arylhydrazones



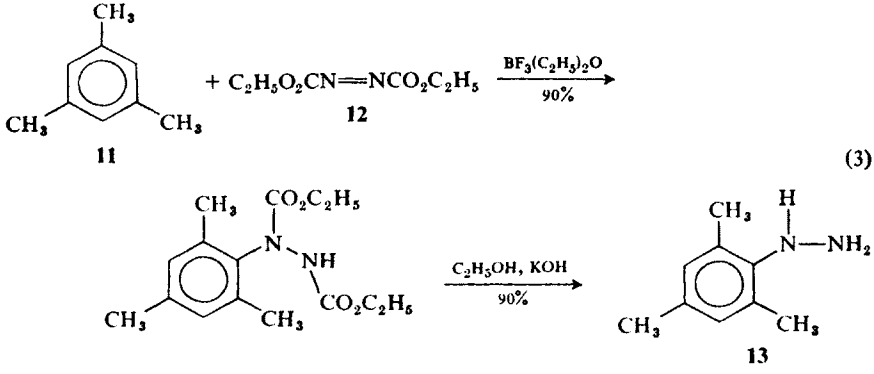
10 (2)

could be converted to the corresponding indoles by the use of only catalytic (1%) amounts of the Lewis acid has been termed the "Fischer-Arbuzov" reaction.[26]

1. *Preparation of Arylhydrazines and Hydrazones*

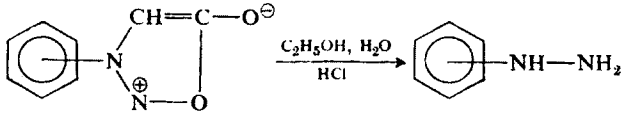
The preparation of arylhydrazines and their conversion to hydrazones has been accomplished by a variety of methods and techniques. The arylhydrazines are usually prepared either by reduction of the *N*-nitrosoarylamines[22, 27-31] or by the reduction of the diazonium salts.[29, 32-34] These arylhydrazines can be isolated as such or, in cases where they are susceptible to decomposition, can be preserved as the hydrochloride.[32, 34] In some cases where the hydrazine is unstable it has been produced by the reduction of the *N*-nitrosoarylamine in the presence of the carbonyl compound and then immediately converted *in situ* by the addition of an acid catalyst via the hydrazone to the indole.[27, 28] Frequently the solution of the arylhydrazine, obtained by the reduction of the aryldiazonium salt, is treated with the carbonyl compound and the resulting hydrazone, without isolation, is converted directly to the indole.[25, 29] This procedure was found to be particularly useful where the arylamines contained an electron-withdrawing group such as the nitro group or a *t*-amino group (quaternized in acid solution) and where the indole decomposed quickly on exposure to heat or light.[29]

A method of arylhydrazine production which appears to have considerable potential has been illustrated in the production of mesitylhydrazine (**13**) in

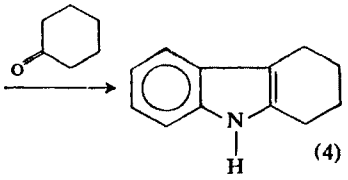


high yield by the reaction of mesitylene (**11**) with ethyl azodicarboxylate (**12**)[35] (Eq. 3). This reaction was based on the reported preparation of 1,2-dicarbalkoxy-1-arylhydrazines by the acid-catalyzed electrophilic reaction of azodicarboxylic esters with alkylbenzenes.[36]

Another potentially useful method of producing arylhydrazines involves the acid-catalyzed hydrolysis of *N*-arylsydnones (**14**).[37, 38] The addition of cyclohexanone to the solution of the hydrazone so obtained was found to give 1,2,3,4-tetrahydrocarbazole (**15**) although in small yield[33] (Eq. 4).



14

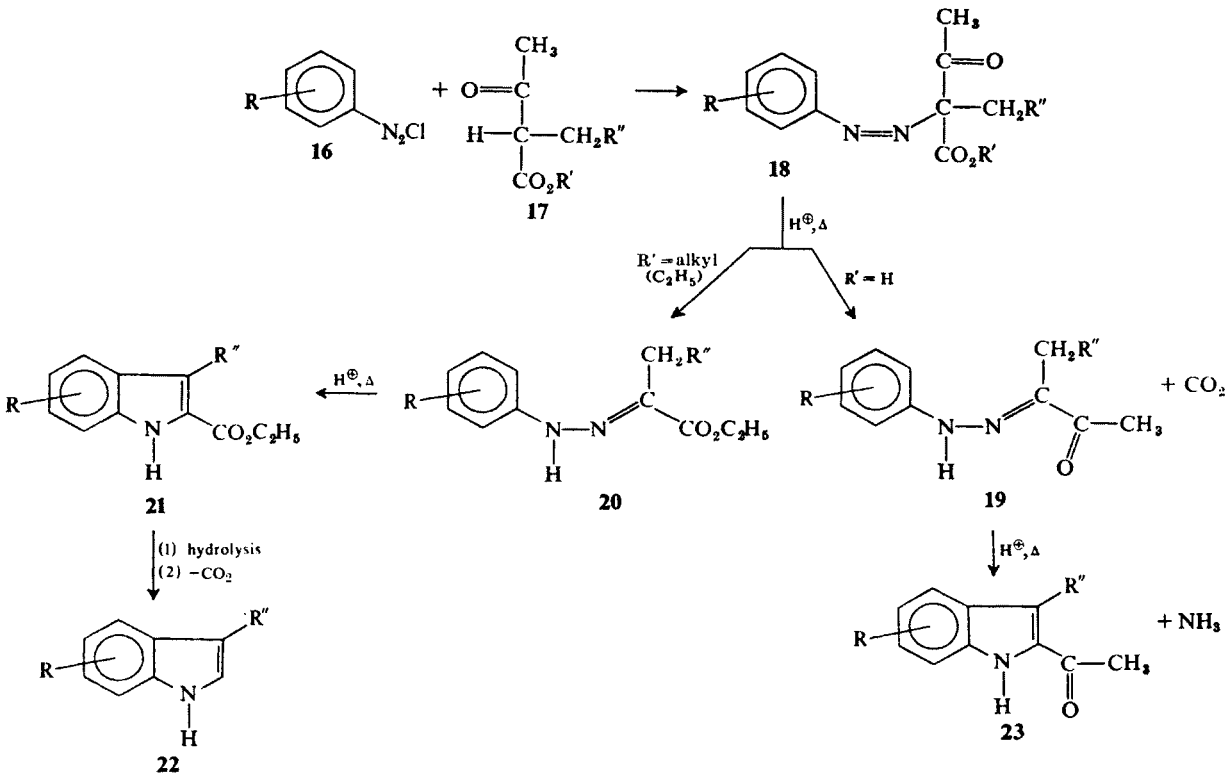


(4)

15

Generally, equimolar quantities of the hydrazine and carbonyl compound are heated in a suitable solvent (ethanol or acetic acid) and are thus converted to the hydrazone. Treatment of the hydrazone, frequently without its prior isolation, with a strong acid catalyst or a metal halide provides the indole. Use of the acetal derivative of the carbonyl compound frequently is preferred since better yields of the indole are thus obtained.[39, 40]

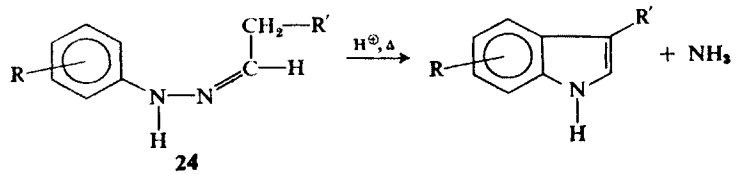
The *Japp-Klingemann reaction*[41] provides an excellent alternative method of preparing a large variety of arylhydrazones. This reaction has been reviewed up to 1959 with respect to its broader applications.[42] It has also been examined and discussed in connection with the preparation of arylhydrazones for the production of indoles.[43–48] This reaction involves an electrophilic attack, under neutral,[49–52] slightly acidic,[48] but usually alkaline conditions[53–59], of an aryldiazonium salt **16** on a compound that possesses a reactive methylene or methine hydrogen (e.g., **17**) to produce, first, the intermediate azo compound **18** which, when subjected to heat, alkaline, or better still, acidic conditions, is converted to the hydrazone **19** or **20**. The product obtained, **19** or **20**, from the decomposition of the azo compound **18** depends upon the composition of the active hydrogen species **17**. If it contains an acyl group


16
17
18
19
20
21
22
23
R′ = alkyl (C2H5)
R′ = H
H⊕, Δ
(1) hydrolysis
(2) −CO2
+ CO2
+ NH3

Scheme 1

and a free carboxylic acid group, both attached to the methine carbon (**17**; R′ = H), then the carboxyl group is lost thus forming the arylhydrazone of an α,β-diketone **19** which will provide, upon cyclization, a 2-acylindole **23** unsubstituted or substituted at the β(C-3) position in the pyrrole ring depending upon whether R″ in **17** is H or an alkyl or aryl group. If the carboxyl group is esterified (**17**; R′ = C_2H_5), then loss of the acyl group occurs on decomposition of the azo intermediate (**18**; R′ = C_2H_5), thus providing the arylhydrazone of an α-keto carboxylic acid ester **20** which upon cyclization gives an indole with a carbalkoxy group attached to the α(C-2) position (**21**). Hydrolysis of **21**, followed by decarboxylation, produces an indole unsubstituted at the α position of the pyrrole ring (**22**) (Scheme 1).

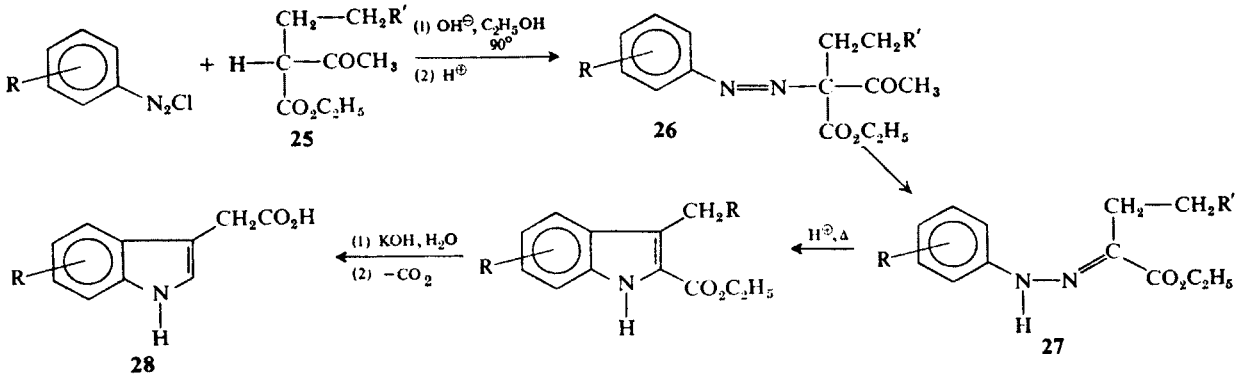
The latter route permits the synthesis of indole itself from **16** (R = H) and **17** (R″ = H, R′ = alkyl) as well as a large variety of indoles either substituted only on the aromatic ring [Ref. 57 (CH_3O, n-C_3H_7); Ref. 59 (CH_3, Cl, Br); Ref. 60 (CH_3O); Ref. 61 (CO_2H, $CO_2C_2H_5$); Ref. 62 (CH_3O); Ref. 63 (F); Ref. 64 ($PhCH_2O$); Ref. 65 (CH_3O, NO_2)], or substituted only at C-3 (β position) [Ref. 58 (R = H, R″ = 2-pyridylmethyl in **22**)], or substituted in both the aromatic ring and the β position of the pyrrole ring [Ref. 52 (5-$PhCH_2O$, 3-$CH_2CH_2NH_2$); Ref. 57 (5,6-di-CH_3O, 7-n-C_3H_7, 3-CH_3)]. Indoles unsubstituted at C-2 are otherwise obtained by use of the arylhydrazone of the appropriate aldehydes **24** [39, 40, 66, 67] (Eq. 5).



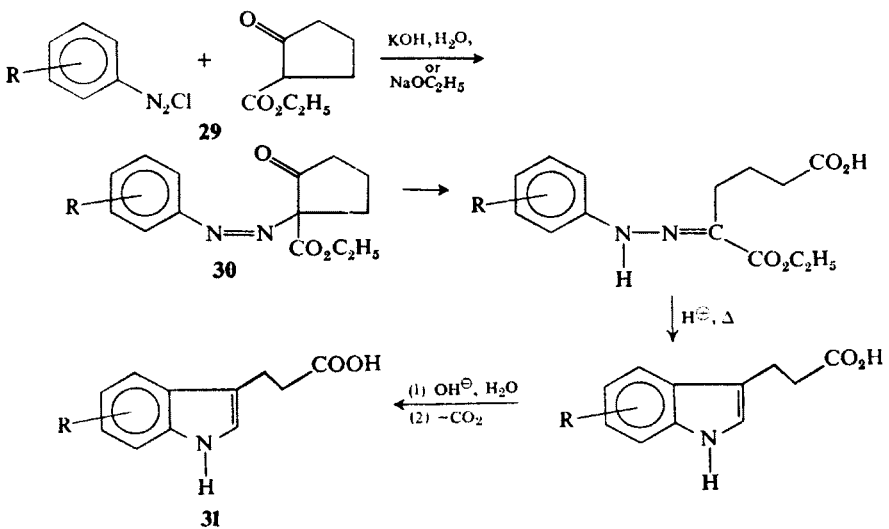
24 (5)

The Japp-Klingemann reaction is particularly advantageous for the preparation of unsubstituted or substituted 3-indolylacetic, -propionic, or -butyric acids. 3-Indolylacetic acids (**28**) are readily prepared by the reaction of the aryldiazonium salt with either diethyl α-acetoglutarate (**25**, R′ = $CO_2C_2H_5$),[53, 68] or with ethyl α-(2-cyanoethyl)acetoacetate (**25**, R′ = CN)[46] (Scheme 2). Similarly 3-indolyl-β-propionic acids can be prepared by the reaction of the appropriate aryldiazonium salts with 2-carbethoxycyclopentanone **29** [Ref. 54 (R = H); Ref. 69 (R = H); Ref. 70 (R = $PhCH_2O$); Ref. 71 (R = NO_2, I, CH_3O); Ref. 72 (R = OH)]. The reaction proceeds through **30** and other intermediates shown in Scheme 3.

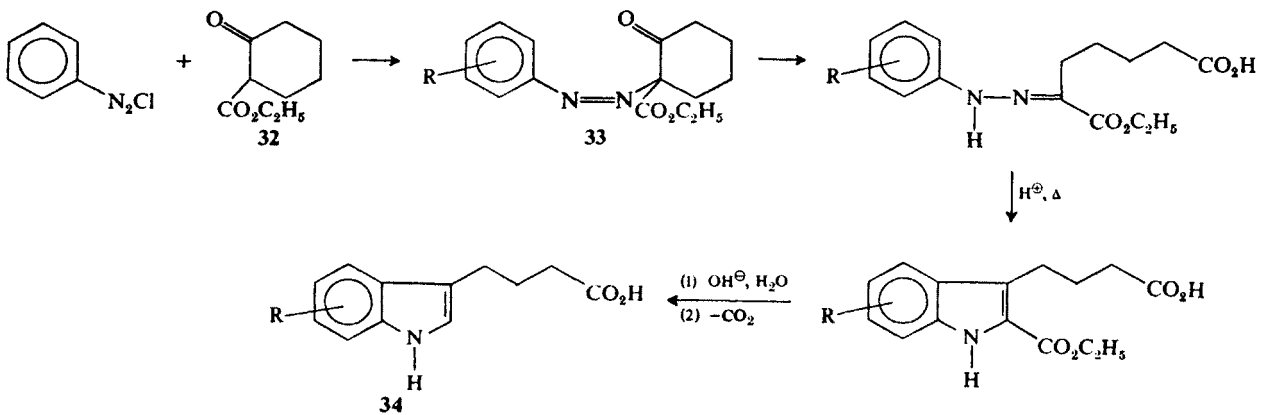
The reaction of aryldiazonium salts with 2-carbethoxycyclohexanone (**32**) provides a useful route to 3-indolyl-γ-butyric acids **34** [Ref. 55 (R = CH_3 or H); Ref. 72 (R = OH, I)] (Scheme 4). In connection with this reaction, if



Scheme 2

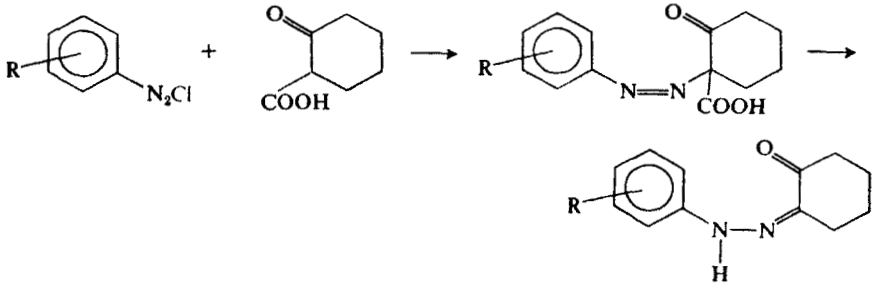


Scheme 3


N2Cl
CO2C2H5
32
R
N=N
CO2C2H5
33
CO2H
N
H
CO2C2H5
H⊕, Δ
(1) OH⊖, H2O
(2) −CO2
34

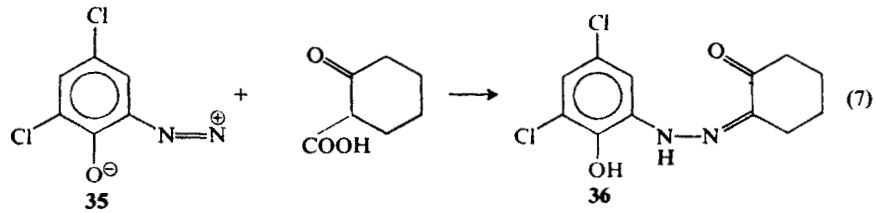
Scheme 4

cyclohexanone-2-carboxylic acid was used rather than the ester **32**, loss of CO_2 was found to occur when coupling took place under neutral or weakly acidic conditions to provide the monophenylhydrazone of cyclohexanone-1,2-



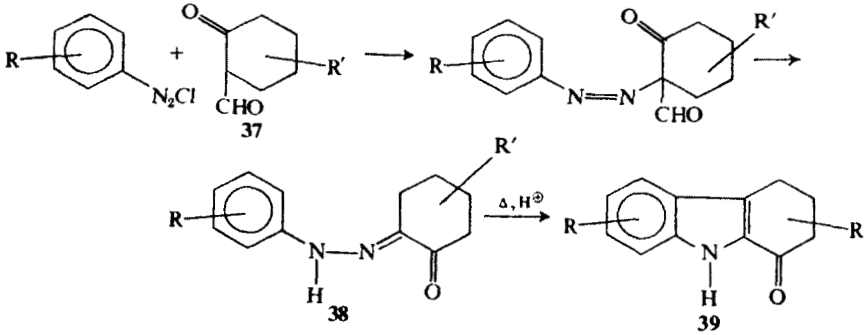
(6)

dione (Ref. 51; R = H) (Eq. 6). The same phenomenon was observed[72] when 4,6-dichloro-1,2-benzoquinone-2-diazide (**35**) reacted with cyclohexanone-2-carboxylic acid to provide **36** in 30% yield (Eq. 7). The reaction



(7)

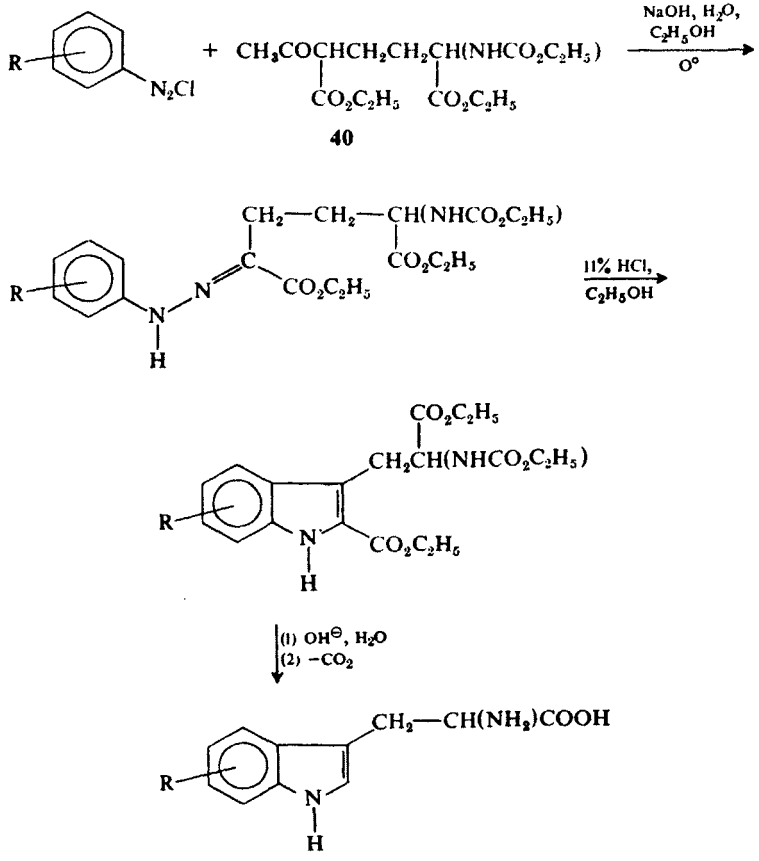
of aryldiazonium salts with 2-formylcyclohexanone (**37**) also provides the monoarylhydrazone of cyclohexanone-1,2-diones **38** which are cyclized to



(8)

1-keto-1,2,3,4-tetrahydrocarbazoles **39** and then dehydrogenated to methyl carbazoles[73] (Eq. 8).

The Japp-Klingemann reaction also provides a convenient route to tryptophans **41**, illustrated by the reaction of diazonium salts with diethyl α-acetyl-α′-(carbethoxyamino)adipate (**40**) (Scheme 5).

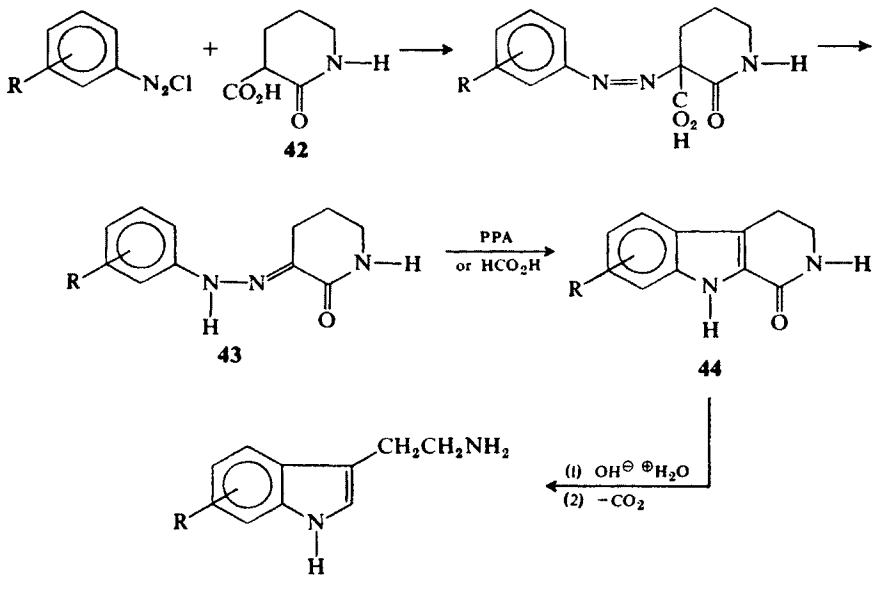


40

41

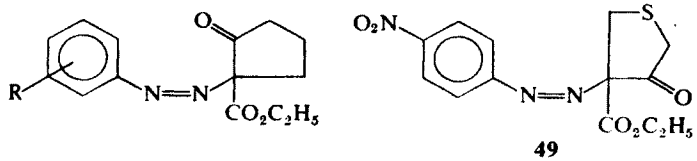
Scheme 5

The discovery[49, 56] that diazonium salts can react with 2-oxopiperidine-3-carboxylic acid (**42**) with subsequent loss of CO_2 to yield 2,3-dioxopiperidine-3-phenylhydrazone (**43**, R = H), which can be cyclized by polyphosphoric acid (PPA) or formic acid to 1-keto-1,2,3,4-tetrahydro-β-carboline (1-keto-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole; **44**), which in turn can be hydrolyzed and decarboxylated to tryptamine (**45**, R = H) (Scheme 6), has led to much work in which substituents have been introduced into the tetrahydropiperido ring (and thus in the aminoethyl group of **45**),[74, 75] the benzene ring,[45, 76–78] or in both the benzene ring and the C-3 side chain.[75, 79, 80]



Scheme 6

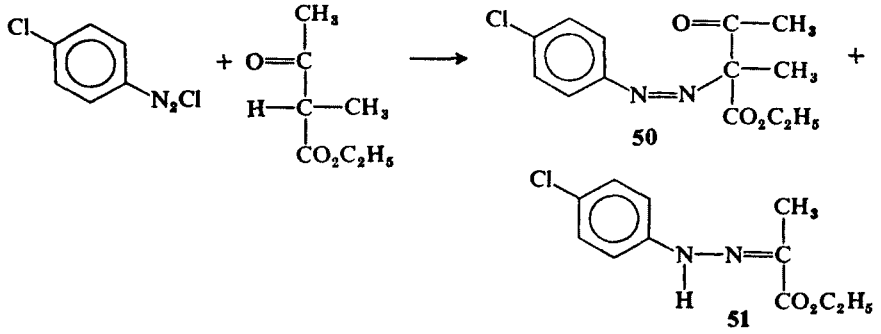
Under the conditions employed for most of the Japp-Klingemann reactions, the intermediate azo compound **18**, **26**, **33** is unstable and readily decomposes to the hydrazone, which then requires more stringent conditions for its indolization. The "red oil" reported in several cases, and assumed to be the hydrazone,[54, 81, 82] may in fact have been the azo intermediate. Isolation of the azoester (**30**; R = H) has been reported[46, 48] from the reaction of phenyldiazonium chloride with ethyl cyclopentanone-2-carboxylate (**29**). There is also reported the isolation and purification of the three substituted azoesters **46**, **47**, and **48** from the reaction of the appropriate diazonium salt with ethyl cyclopentanone-2-carboxylate[70] and the azoester **49** from the



46; R = 4-NO_2
47; R = 3,4,5-tri-I
48; R = 3,4-di-I-4-OCH_3

reaction of *p*-nitrobenzenediazonium chloride with ethyl 4-thiacyclopentanone-2-carboxylate.[47] An intensive study has been made recently[48] of the reaction of diazonium salts with ethyl α-methylacetoacetate under mild

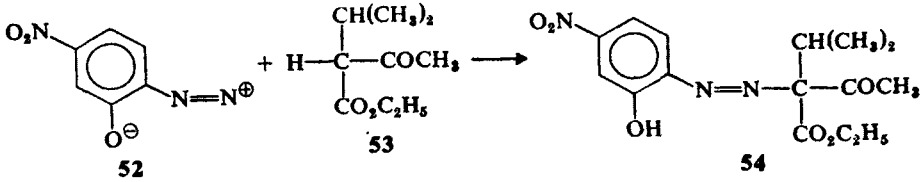
conditions (pH 5, 0°), permitting the isolation of the azoester, frequently as the only product, and which in several cases could be successfully distilled under vacuum. Under these conditions *p*-chlorobenzenediazonium chloride gave the azoester **50** along with the hydrazone **51** in the approximate proportion of 7:1 (Eq. 9). Since the diazoester but not the hydrazone is soluble in petroleum



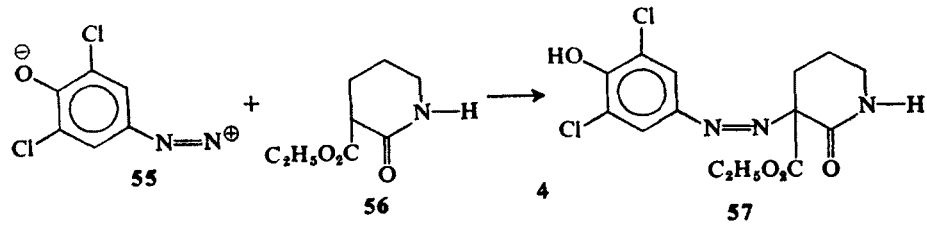
(9)

ether, these two products can be readily separated. The azoesters under neutral or slightly acidic conditions could be converted, with loss of the acetyl group, to the hydrazone. Under more vigorous conditions (hot ethanolic HCl) both the azoester and the hydrazone were cyclized to the indole-2-carboxylate.

A stable azoester **54** has been obtained[72] from the reaction of 5-nitro-1,2-benzoquinone-2-diazide (**52**) with ethyl α-isopropylacetoacetate (**53**) (Eq. 10), and the azoester **57** has been isolated from the reaction of 2,6-dichloro-1,4-benzoquinone-4-diazide (**55**) with ethyl 2-oxopiperidine-3-carboxylate (**56**)[72, 79] (Eq. 11).

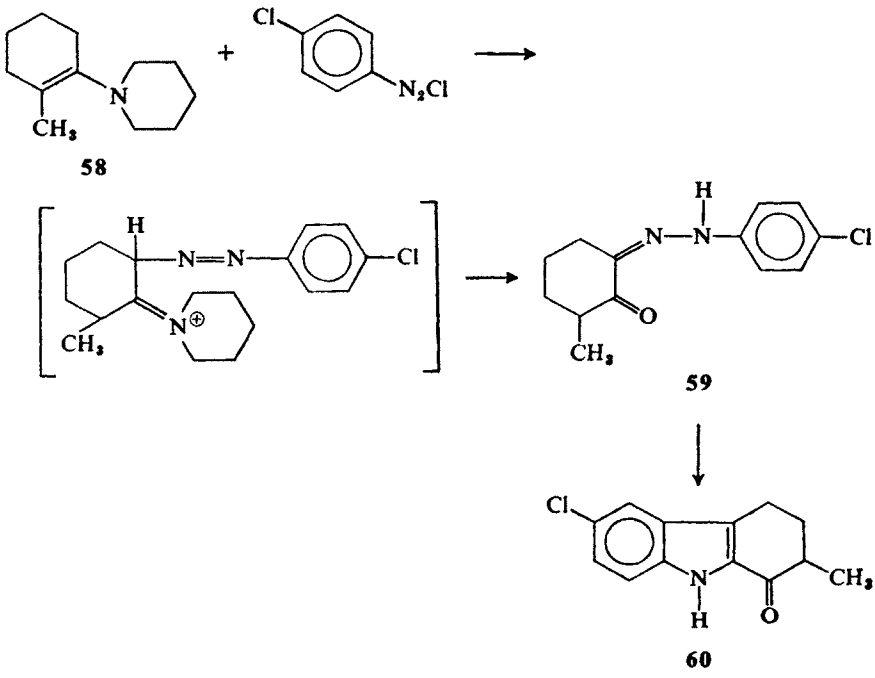


(10)



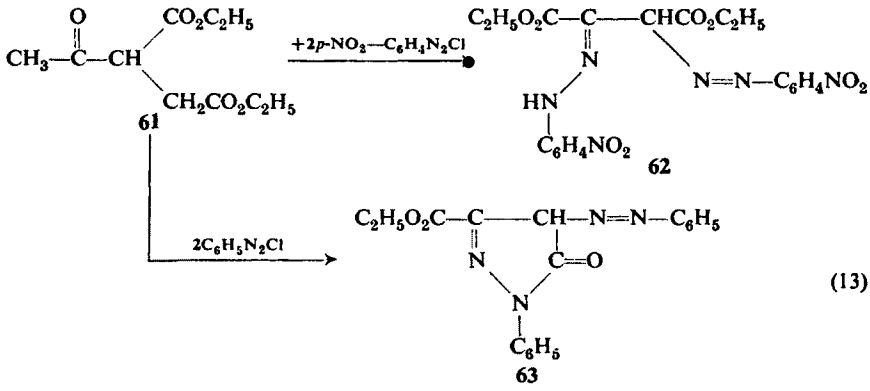
(11)

An interesting extension of the Japp-Klingemann method has been reported[83] in the reaction of *p*-chlorobenzenediazonium chloride with piperidine 2-methylcyclohexanone enamine (**58**) at pH 5–6, which forms the monochlorophenylhydrazone of 3-methylcyclohexane-1,2-dione (**59**) in 76% yield. The hydrazone is readily indolized with hot ethanolic sulfuric acid to 6-chloro-2-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**60**) (Eq. 12).



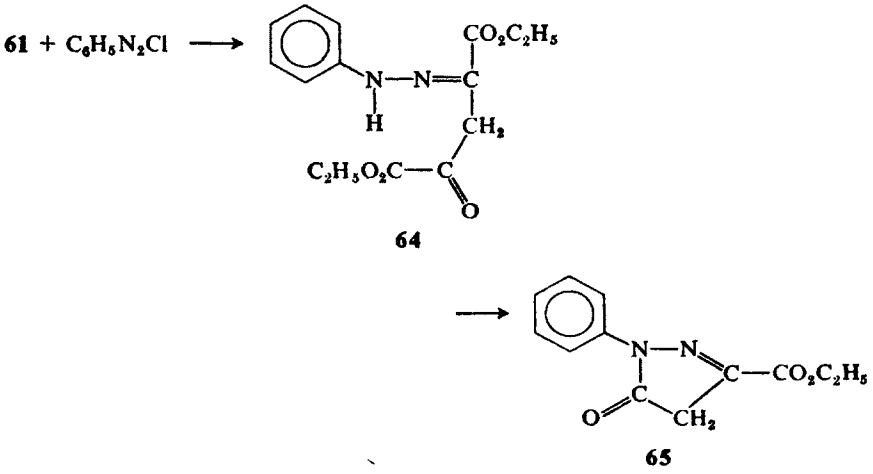
(12)

Some precaution must be used in the choice of the active hydrogen compound used for reaction with the diazonium salt. It has been reported[84] that diethyl acetosuccinate (**61**) reacts with two molecules of *p*-nitrobenzenediazonium chloride to produce a red solid regarded as diethyl *p*-nitrobenzeneazooxalacetate *p*-nitrophenylhydrazone (**62**). On the other hand, **61** reacts with two molecules of benzenediazonium chloride to form 3-carbethoxy-1-phenyl-4-phenylazopyrazole-5-one (**63**) (Eq. 13). The pyrazolone **63** no doubt arises via the normal Japp-Klingemann reaction, first with one molecule of the diazonium salt to form the monophenylhydrazone **64** of a 3-ketoester which readily forms the pyrazolone **65** as expected[42] (Eq. 14). The pyrazolone **65** then undergoes a second Japp-Klingemann reaction at the



(13)

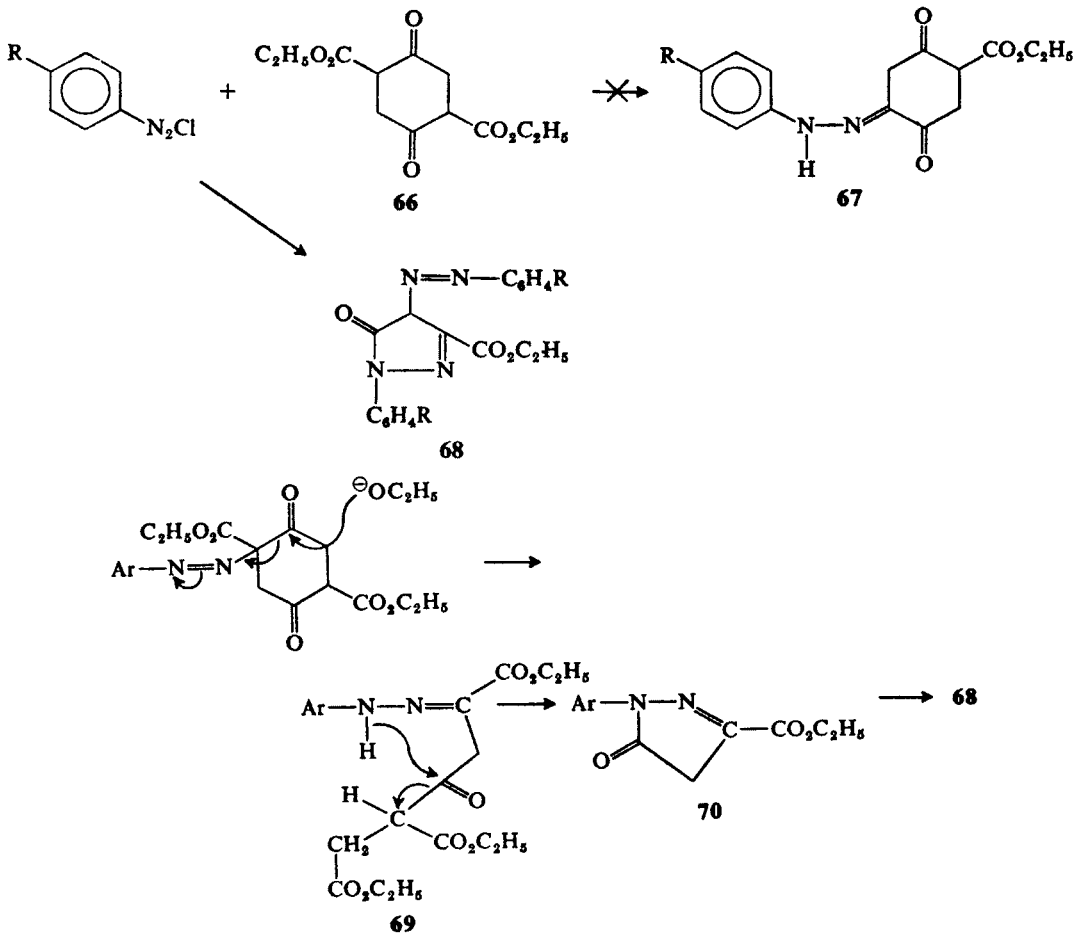
active methylene site to produce the azo compound **63**. Alternatively, Compound **64** could first react with the second molecule of diazonium salt



(14)

and the product then cyclize to form **65**. Compound **62** is formed similarly by two successive reactions with the diazonium salt. In this case, cyclization to the pyrazolone appears to be hindered by the presence of the *p*-nitro substituent.

Another example has been reported[85] in the reaction of an aryldiazonium salt with 2,5-dicarbethoxycyclohexane-1,4-dione (**66**). The product is not the expected compound **67**, but instead is 1-aryl-4-arylazo-3-carbethoxy-pyrazol-5-one (**68**). This also could arise by a twofold Japp-Klingemann reaction via the intermediates **69** and **70** (Scheme 7).



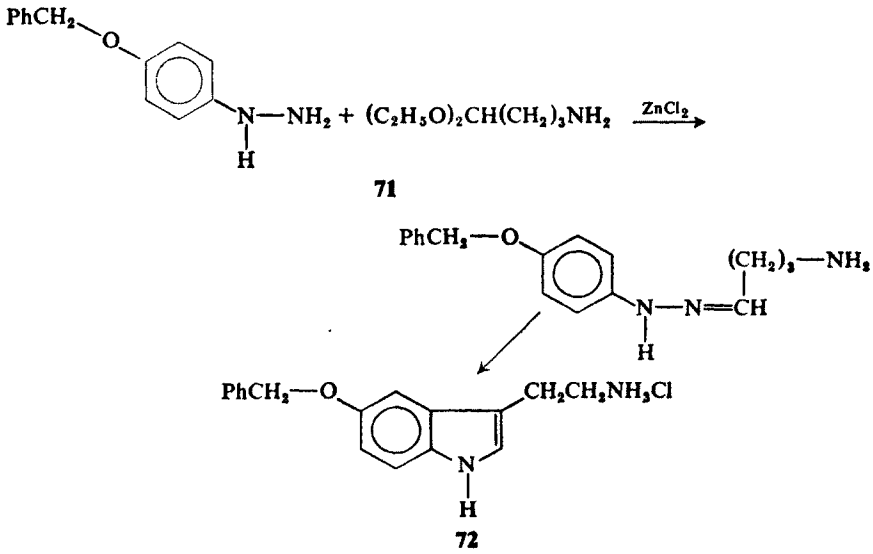
Scheme 7

2. *Cyclizing Agents for the Fischer Indole Synthesis*

Since the discovery by Fischer and Jourdan that dilute hydrochloric acid promotes the formation of 1-methylindole-2-carboxylic acid from the methylphenylhydrazone of pyruvic acid[21] and that zinc chloride was a more effective catalyst than dilute hydrochloric acid,[23, 24] a wide variety of catalysts have been tested and used.[4, 5, 9] Generally, acids and metal salts capable of complex formation with organic ligands[9] are found to promote indolization. However, of the large number so examined, only a few have proven to be sufficiently useful and conveniently available for general adoption. Reports have appeared in which the relative effectiveness of a number of catalysts have been examined.[49, 86–91] These have been compared on the basis of yield of isolated material or the rapidity with which the product is obtained. However, since no careful rate studies were made, and the conditions of the reactions varied greatly, and also since there was no assurance that all the product had been obtained from the reaction mixture, the results quoted are only qualitative, although quite useful. The ease of cyclization depends on the nature of the substituents in the arylhydrazone, the catalyst, the solvent, the temperature, and the type of carbonyl component of the hydrazone. Combinations of these have varied considerably. No one catalyst or set of conditions can be chosen as best for all arylhydrazones or even for all which are closely related. Experience is necessary to obtain the best combination of solvent, catalyst, and temperature because some hydrazones and some indoles are unstable at higher temperatures and under the influence of acid catalysts. Frequently the more vigorous catalysts required to effect indolization also cause more severe decomposition of reactants or products. Those catalysts that have proven to be generally useful are $ZnCl_2$, H_2SO_4, HCl, H_3PO_4, polyphosphoric acid, BF_3, formic acid, acetic acid, and more recently cation exchange resins, sulfosalicylic acid, and polyphosphate ester.

Pulverized fused zinc chloride has been widely used and found to be one of the most, if not the most, vigorous catalysts. It is mixed intimately with the hydrazone and the mixture is heated either without a solvent[61, 62, 92–97] or in solvents such as anhydrous ethyl alcohol,[87, 98, 99] nitrobenzene,[97] acetic acid,[100, 101] xylene,[95, 102] or cumene.[90] Originally a large excess of zinc chloride was used at temperatures above 150°,[23, 24] and this procedure has been followed widely.[61, 92–97, 101] However, the use of equal weights of hydrazone and zinc chloride in boiling cumene was found to be more effective than other proportions of zinc chloride or than other acidic catalysts examined for the cyclization of acetone 4-chlorophenylhydrazone.[90] This proportion of reagents in xylene as solvent had been employed previously[102] to condense 4-aminobutanal diethylacetal (**71**) with *p*-benzyloxyphenylhydrazine and

cyclize the resulting hydrazone to 5-benzyloxytryptamine hydrochloride (**72**) in 40% yield, although later workers[103] could not repeat the results but found that milder conditions (dilute aqueous hydrochloric acid in ethanol) afforded the product in 68% yield (Eq. 15). When equal amounts of zinc chloride and the *o*- or *p*-methoxyphenylhydrazone of acetone were heated to 180° with or without tetrahydronaphthalene as solvent, no isolable indole was obtained,[60] but by heating equal amounts of zinc chloride and the hydrazone

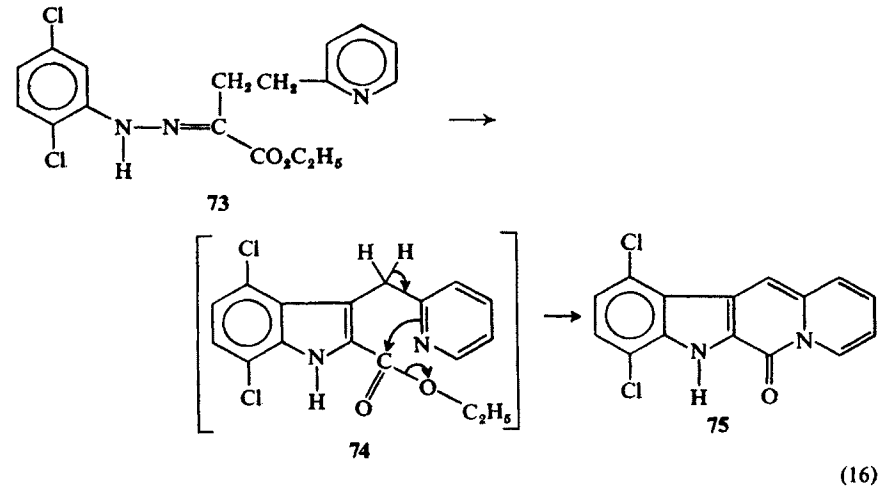


(15)

to only 110° and under vacuum, a method reported previously,[104] a 20% yield of 2-methyl-5-methoxyindole was obtained from acetone *p*-methoxyphenylhydrazone.

Zinc chloride in ethanol was preferred to zinc chloride alone, and to other acidic catalysts such as alcoholic or aqueous hydrogen chloride or sulfuric acid, for the conversion of the *p*-bromo- and *p*-nitrophenylhydrazones of levulinic acid to the corresponding indole.[87, 99] When two halogen atoms are present in the benzene ring of the hydrazone, indolization appears to be inhibited since ethanolic zinc chloride at 125° failed to cyclize the 2,5-dichlorophenylhydrazone of 2-keto-4-(2-pyridyl)butyrate (**73**) whereas ethanolic zinc chloride at 150° provided 4′,7′-dichloro-4-oxoindole[3′,2′-2,3]pyridocoline (**75**), no doubt by conversion, under the more vigorous conditions, of the expected product, ethyl 4,7-dichloro-3-(2-pyridylmethyl)-indole-2-carboxylate (**74**) to **75**[58] (Eq. 16).

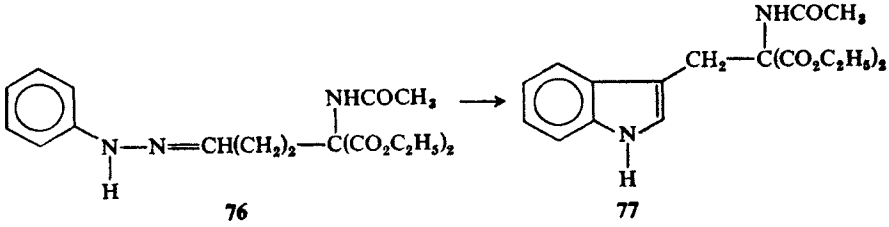
In the preparation of thioethers of indole by cyclizing arylhydrazones of β-oxythioethers, it was found that zinc chloride caused decomposition with



(16)

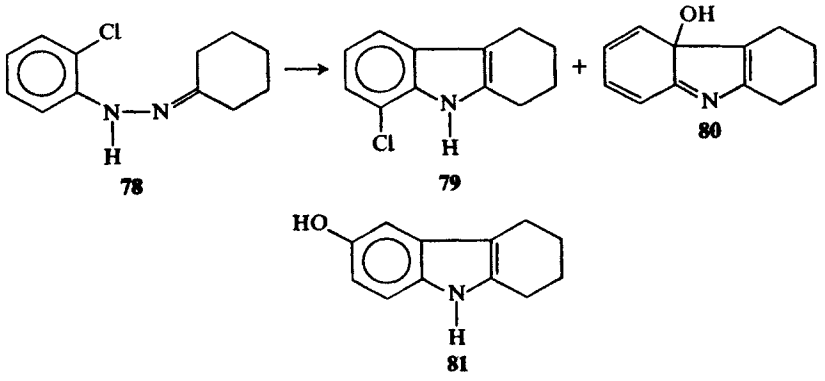
loss of sulfur, whereas good results were obtained by the milder reagent hydrogen chloride in alcohol.[105]

Sulfuric acid appears to be somewhat less potent than zinc chloride, and has been used (*1*) as a dilute aqueous solution to prepare substituted tetrahydrocarbazoles[106, 107] and tryptophans[108, 109]; (*2*) as a mixture of concentrated sulfuric acid in anhydrous ethyl alcohol[69, 84, 86, 95, 107, 108, 110–113] for the preparation of substituted tryptophans,[108] benzoindoles,[84, 110] 3-indolylacetic acids,[69, 95, 111] 3-indolyl-γ-butyric acids,[86, 112, 113] and nitroindoles[84]; and (*3*) as a mixture of concentrated sulfuric acid in methanol[86] as a somewhat less effective agent than is ethanolic sulfuric acid (probably because of the lower boiling point) for the preparation of 3-indolyl-γ-butyric acid. A 10% solution of sulfuric acid in ethanol failed to convert acetone *o*- and *p*-methoxyphenylhydrazone to the corresponding 2-methyl-5(and 7)-methoxyindoles, whereas zinc chloride at 110° provided these indoles in ~20% yield.[60] Refluxing aqueous sulfuric acid cyclized γ-acetamido-γ,γ-dicarbethoxybutyraldehyde phenylhydrazone (**76**) to the corresponding indole **77** in 90% yield while with alcoholic sulfuric acid the yield was 40–50% and boron trifluoride etherate in glacial acetic acid gave much lower yields of



(17)

77[108] (Eq. 17). Ethanol—sulfuric acid was preferred to zinc chloride for the preparation of ethyl 6,7-benzindole-2-carboxylate,[84] and gave excellent yields of ethyl 2-methyl-3-indolylacetate[95]; but when substituents were in the aryl ring of the hydrazone, incomplete reaction occurred, hence a refluxing solution of zinc chloride in xylene was employed.[95] It has been reported that the reaction of cyclohexanone *o*-chlorophenylhydrazone (**78**) in dilute sulfuric acid[106] gave as the major product 8-chloro-1,2,3,4-tetrahydrocarbazole (**79**) along with a minor product considered to be 12-hydroxy-1,2,3,4-tetrahydroisocarbazole (**80**). The minor product was later[114] found to be 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**81**), which illustrates a case wherein the solvent moiety was incorporated in the product, replacing the halogen atom (Eq. 18).

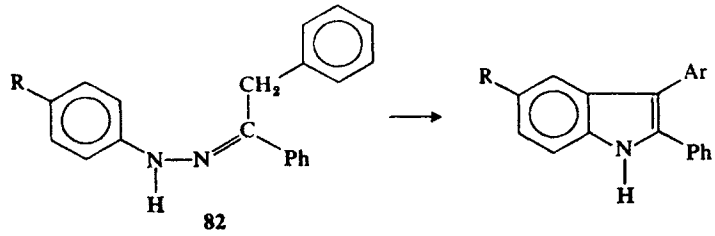


(18)

Hydrogen chloride has proven to be an effective catalyst and has been used in the form of concentrated hydrochloric acid[89, 115–119] for the preparation of a variety of indoles substituted by nitro groups in the benzene ring.

It has been found[89] that concentrated hydrochloric acid is best for preparing mononitroindoles from the appropriate arylhydrazones of several dialkyl ketones, and tetrahydrocarbazoles from the mono- or dinitrophenylhydrazones of cyclohexanone and 4-methylcyclohexanone, but that concentrated sulfuric acid is preferred when two nitro substituents are present in the aryl ring. On the other hand, 2-phenacylpyridine *p*-nitrophenylhydrazone (**82**, R = NO_2) could not be indolized, by concentrated hydrochloric acid, to 5-nitro-2-phenyl-3-(2′-pyridyl)indole (**83**), whereas if R = H or CH_3, a high yield of **83** (R = H or CH_3) was obtained under these conditions.[93] Since the *m*- and *p*-nitrophenylhydrazone of deoxybenzoin could be readily cyclized to **84** by a 1 : 1 mixture of concentrated hydrochloric acid and glacial acetic acid (omission of the glacial acetic acid resulted in extensive hydrolysis and tar formation),[120] the lack of success in obtaining **83** (R = NO_2) was believed

due to protonation of the pyridine nucleus[93] (Eq. 19). It is interesting that *p*-nitrophenylhydrazones of aliphatic aldehydes have failed to yield the expected 3-alkyl-5-nitroindoles[84, 116, 121] with a variety of catalysts. Since propionaldehyde *p*-nitrophenylhydrazone when treated with hydrochloric

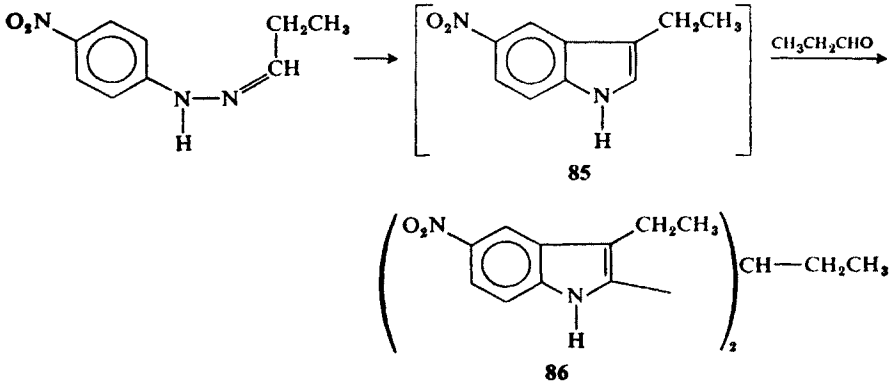


(19)

82

83; R = 5-NO_2; Ar = α-pyridyl
84; R = 4- or 5-NO_2; Ar = C_6H_5

acid gave a propylidene di-2,2′-indole **86**, presumably the 3-ethyl-5-nitroindole **85** did form, but condensed rapidly with propionaldehyde, which must have been formed by hydrolytic decomposition of the hydrazone (Eq. 20). By use of a two-phase system of benzene and concentrated hydro-



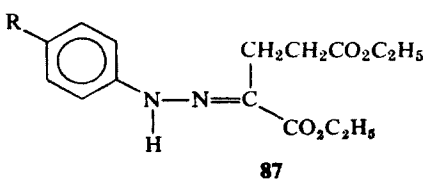
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86

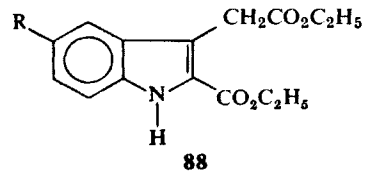
(20)

chloric acid, it has been possible to extract the indole into the benzene layer away from the aldehyde and thus minimize the condensation with the aldehyde produced by hydrolysis of the hydrazone.[118, 119]

Hydrogen chloride in anhydrous ethanol has been widely used[53, 57, 60, 86, 105, 121a, 122] and appears to be a somewhat milder system than is concentrated hydrochloric acid. Better results are obtained with 8–11% than with 15–20%[121a, 122] hydrogen chloride in ethanol in the conversion of diethyl α-ketoglutarate *p*-methoxyphenylhydrazone (**87**, R = CH_3O) to ethyl 2-carbethoxy-5-methoxy-3-indolylacetate (**88**, R = CH_3O), but the reaction fails if R = Cl, even if $ZnCl_2$ is also added (Eq. 21). Similar results have been noted in the failure of alcoholic hydrogen chloride to cyclize the



87

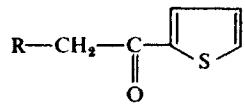


88

(21)

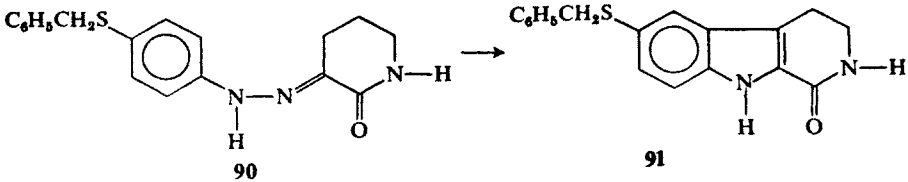
p-chlorophenylhydrazone of ethyl pyruvate, although the *p*-methoxy and *p*-benzyloxy analogs were readily indolized.[48] This inhibitory effect of the halogen substituent is overcome by the use of polyphosphoric acid.[48] In general, the presence of electron-donor substituents (*o-p* directors) in the aromatic ring of the arylhydrazine permit indolization by hydrogen chloride in alcohol, of the hydrazones of carbonyl compounds such as ethyl methyl ketone,[123] the ethyl esters of α-ketopropionic and butyric acids,[57] ethyl α-keto-γ-cyanobutyrate,[50] and δ-formylvaleric acid,[86] although in the last case concentrated sulfuric acid is better, while zinc chloride in refluxing xylene is preferred.

A solution of hydrogen chloride in glacial acetic acid has also been used frequently[92, 124, 125] with results somewhat like those obtained with hydrogen chloride in ethanol. This is useful for the indolization of arylhydrazones of structures such as **89** where R = alkyl or aryl, but quite unsatisfactory if



89

R = H.[92] This is similar to the failure of alcoholic hydrogen chloride to effect the cyclization of acetone *p*-methoxyphenylhydrazone.[60] Hydrogen chloride in glacial acetic acid has given good conversion[125] of 2,3-diketopiperidine-3-(*p*-benzylthiophenylhydrazone) (**90**) to 6-benzylthio-1,2,3,4-tetrahydro-1-oxo-β-carboline (**91**), required for the preparation of 5-mercaptotryptamine (Eq. 22).



90 91

(22)

Polyphosphoric acid (PPA; $H_3PO_4 + P_2O_5$) was first examined[126] as an indolization catalyst for those compounds which require "drastic conditions" for their cyclization. It was found to be widely applicable and to give good yields of indoles, though negative results were obtained with aldehyde

phenylhydrazones.[126] Since that time it has been found to be quite satisfactory and often superior to other agents for the preparation of nitroindoles obtained by cyclizing the nitrophenylhydrazones of ethyl pyruvate[88, 127, 128] and ethyl α-keto-γ-diethylaminobutyrate,[129] and for the preparation of chloroindoles from the chlorophenylhydrazones of pyruvic acid[130] and ethyl pyruvate.[59] Either 9% PPA in methanol or PPA itself satisfactorily converts succinaldehydic acid *p*-methoxyphenylhydrazone to 5-methoxy-3-indolylacetic acid.[131, 132] Some limitations of the utility of PPA, in addition to that mentioned above, have been noted. Although PPA satisfactorily converted the 3-phenylhydrazone of 2,3-diketopiperidine (**43**; R = H) in small quantities,[133] on a large scale it caused extensive charring and decomposition,[49, 134] hence formic acid was employed instead. While PPA was quite unsatisfactory for indolization of **43** (R = *m*- and *p*-CH_3O), it successfully indolized the nitro analog (**43**; R = *p*-NO_2) whereas formic acid did not.[49, 134] The *m*-nitrophenylhydrazone of isobutyl methyl ketone gave much lower yields of the indole with PPA than with concentrated hydrochlorie acid or hydrogen chloride in acetic acid.[117] Indolization of acetone *p*-chlorophenylhydrazone was quite unsuccessful with PPA, but could bc satisfactorily accomplished by $ZnCl_2$ in cumene.[90] Excellent conversion of α-ketoglutaric acid phenylhydrazone to ethyl 2-carbethoxy-3-indolylacetate occurred with 5% PPA in dry ethanol saturated with hydrogen chloride, thus assuring an anhydrous medium and a reasonably high boiling solvent.[135] A 7% solution of phosphoric acid in methanol has been used to cyclize succinaldehydric acid *p*-benzyloxyphenylhydrazone to the 3-indolylacetic acid.[136] The presence of the *p*-benzyloxy substituent led to extensive decomposition when sulfuric acid, hydrochloric acid, or zinc chloride was used as cyclizing agent. Such decomposition by these three agents does not occur when the substituent is the *p*-CH_3O group.[111] Phosphoric acid alone has been used to cyclize acetophenone phenylhydrazone to 2-phenylindole in excellent yield.[137]

Boron trifluoride has frequently been used as a mild cyclization catalyst, sometimes in alcohol solution[86] but usually as a mixture of boron trifluoride etherate in glacial acetic acid.[93, 100, 108, 138, 139] It appears to be most successful for those carbonyl compounds whose arylhydrazones are easily indolized such as cyclohexanone, ethyl methyl ketone,[139] methyl β-phenylethyl ketone,[93] and pyruvic acid,[101] probably because decomposition of the hydrazones or products is minimized under such mild conditions. However, in many cases poor results are obtained with boron trifluoride, and therefore other cyclizing agents are much to be preferred.[86, 93, 108, 111] Boron trifluoride with or without glacial acetic acid failed to indolize succinaldehydic acid phenylhydrazone whereas concentrated sulfuric acid in absolute ethanol (under nitrogen) gave good results.[111]

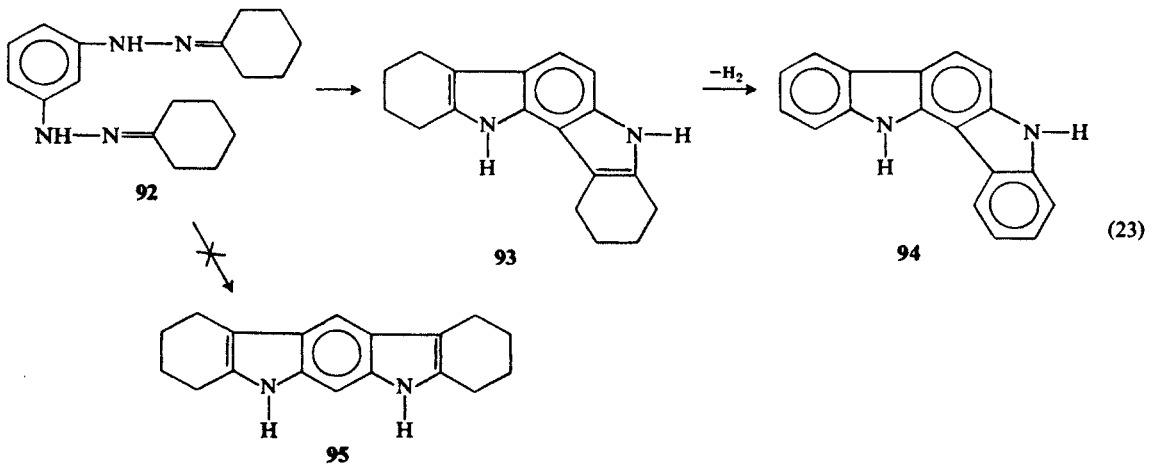
In several cases acetic acid alone has been sufficient to cause cyclization of the arylhydrazone to the indole. Cyclohexanone *o*-chlorophenyl- and 2-chloro-5-methylphenylhydrazone have given good yields of the indole under these conditions.[106] Glacial acetic acid has converted pyruvic acid *N*-methyl-*p*-ethoxyphenylhydrazone in 41% yield to 1-methyl-5-ethoxy-2-indolecarboxylic acid.[140] In the preparation of indolo-(3',2'-1,2)carbazole (**94**) from biscyclohexanone *m*-phenylenedihydrazone (**92**), the only catalyst that gave satisfactory results was acetic acid since other acidic catalysts (H_2SO_4, etc.) gave only small amounts of the indole due to decomposition of the hydrazone[141] (Eq. 23).

In this case it is interesting that although two products are possible, **93** and **95**, only the angular product **93** is obtained. Generally the use of acetic acid alone is successful for those carbonyl compounds whose arylhydrazones are easily indolized. The nature of the substituent in the aromatic ring influences the ease of cyclization[142] and possibly the stabilities of the hydrazone and the products, since yields of isolated material varied from 4 to 70% when glacial acetic acid was employed to obtain substituted thianaphtheno[3,2-*b*]indoles **96**[143] (Eq. 24). Recently the use of acetic acid as cyclizing agent has been examined and found advantageous for the preparation of *N*-acylindoles from a mixture of the *N*-acylated hydrazine, containing an electron-donor group (CH_3O) in the aryl ring, and an unsymmetrical dialkyl ketone.[144, 145]

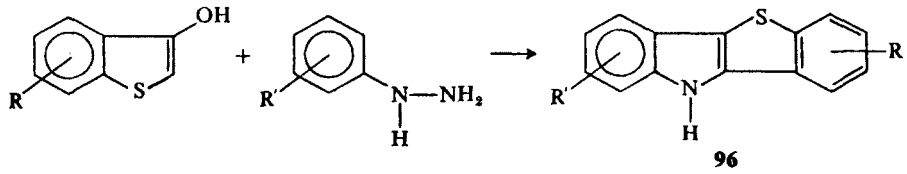
Formic acid has become a popular mild reagent, particularly since it effected conversion of 2,3-dioxopiperidine-3-phenylhydrazone (**43**) to 1-keto-1,2,3,4-tetrahydro-β-carboline (**44**) (a precursor for the synthesis of tryptamine) in good yield, whereas PPA caused extensive decomposition and charring.[49] Excellent yields of substituted β-carbolines **97** have been obtained with formic acid; **97**, R = H or OCH_3 and R' = R'' = CH_3[75]; R = halogen (F, Cl, I) and R' = H, R'' = CH_3[80]; R = I, R' = R'' = H.[77] However, formic acid failed to effect cyclization when R = NO_2 was in **43**[134] and PPA was required to bring about satisfactory conversion in this case. In a study of the effectiveness of a number of acidic catalysts in promoting the cyclization of the phenylhydrazones of several ketones,[146] it was found that formic acid was the most satisfactory.

Cation exchange resins (Amberlite IR-120) have also given good results as indolization catalysts when used in boiling water,[147, 148] but acetone phenylhydrazone could not be converted to 2-methylindole this way.[147] Best results were obtained with the acidic resin when 99% ethanol was the solvent.[149]

The discovery that hydrogen chloride in dry ethanol failed to cyclize succinaldehydic acid *p*-benzyloxyphenylhydrazone (**98**; R = $C_6H_5CH_2O$, R' = COOH) and gave only the hydrochloric acid salt of the hydrazine, while sulfosalicylic acid in ethanol gave the indole **99** (R = $C_6H_5CH_2O$, R' = COOH)

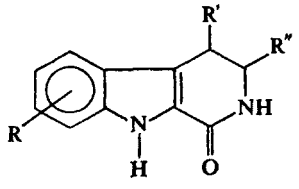


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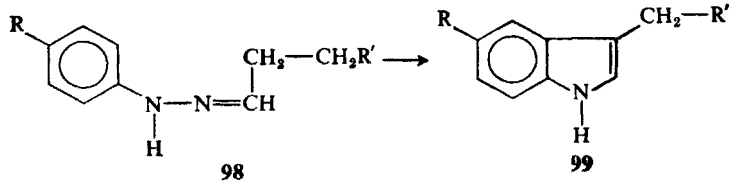
96

(24)



97

in excellent yield[150] (Eq. 25), led to several experiments wherein this reagent was used as catalyst[74, 151–155] to obtain good to excellent yields of the indoles from arylhydrazones of Structure **98** in which R = $C_6H_5CH_2O$, R′ = $C(NHCOCH_3)(CO_2C_2H_5)_2$ [151]; R = $C_6H_5CH_2O$, R′ = $C(CH_3)(NO_2)\cdot(CO_2C_2H_5)$[153]; and of 1-oxo-1,2,3,4-tetrahydro-β-carbolines of Structure **97** where R = R′ = H, R″ = CH_3,[74] and R = 6-benzyloxy, R′ = R″ = H.[154]

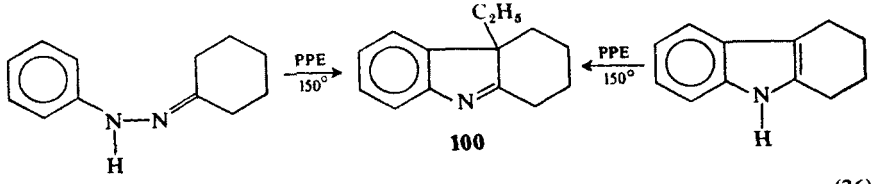


98 99

(25)

Recently polyphosphate ester (PPE) has been introduced as a catalyst,[155–157] often as a homogeneous solution in chloroform,[156, 157] which permits indolization under very mild conditions. This reagent is particularly advantageous for the conversion of phenylhydrazones of aldhydes, such as propionaldehyde, to 3-substituted indoles since poor results are usually obtained with other cyclizing catalysts including PPA.[126] Using this method the rate of cyclization of the phenylhydrazones of five- and seven-membered cyclic ketones has been found to be slower than that of cycylohexanone. Since the phenylhydrazones of both acetaldehyde and acetophenone failed to indolize, it was concluded that this reagent was incapable of involving the carbon atom of a methyl group of a methyl ketone in the formation of the pyrrole ring of indole. Since there was no attempt to indolize acetone phenylhydrazone, or the phenylhydrazones of pyruvic acid, or ethyl pyruvate, all three of which are known to form indoles under appropriate conditions,[60, 61] it is not known whether the above conclusion is quite general. The failure to cyclize acetaldehyde phenylhydrazone is not surprising since to date all attempts to do so

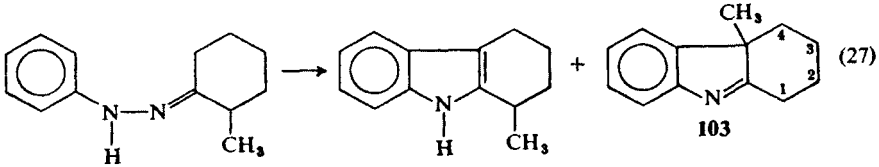
have failed.[4, 5, 9, 10] A drawback with PPE is its decomposition at higher temperatures (>100°) to produce ethylene, presumably stemming from a species such as an "ethyl carbonium ion," which introduces an ethyl group into the indole product. Thus, cyclohexanone phenylhydrazone treated with PPE at 150° gave 4*a*-ethyl-1,2,3,4-tetrahydrocarbazolenine (**100**) (Eq. 26). The same carbazolenine is produced by treating 1,2,3,4-tetrahydrocarbazole with PPE at 150°.



100

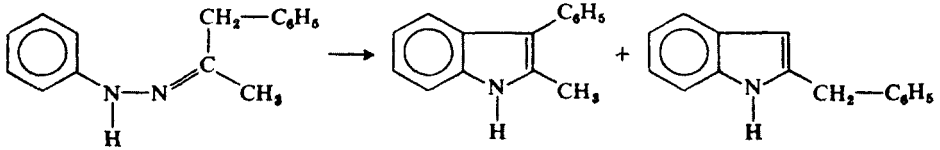
(26)

Certain of the above catalysts have been found to exert a specific directional or selective influence in the cyclization of arylhydrazones. In the indolization of 2-methylcyclohexanone phenylhydrazone (**101**) two products are possible. They are 1-methyl-1,2,3,4-tetrahydrocarbazole (**102**) and 4*a*-methyl-1,2,3,4-tetrahydrocarbazolenine (**103**). Both isomers are usually produced, but



101 **102** **103** (27)

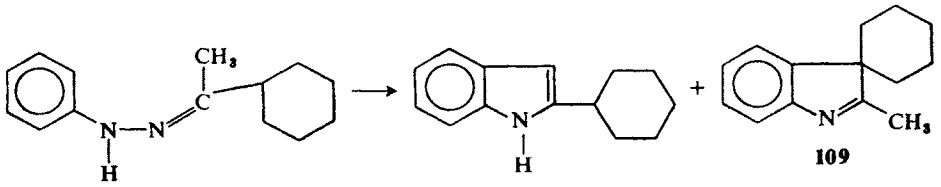
alcoholic or aqueous sulfuric acid favors the formation of the tetrahydrocarbazole **102** while glacial or aqueous acetic acid or hydrogen chloride in benzene favors the carbazolenine **103**[107] (Eq. 27). The cyclization of phenylacetone phenylhydrazone (**104**) can provide the two products 2-methyl-3-phenylindole (**105**) and 2-benzylindole (**106**). The catalysts hydrogen chloride in glacial acetic acid, zinc chloride, boron trifluoride, or hydrogen chloride each cause cyclization of **104** to **105** in 86% yield whereas PPA converted **104** into both **105** and **106** in the relative proportion of 1:5 (Eq. 28). Since under the conditions of the reaction these two products do not isomerize, it is clear that PPA causes preferential cyclization towards the methyl group in



104 **105** **106**

(28)

104. Unfortunately, no report was made concerning the phenylhydrazone of ethyl methyl ketone to determine whether this effect of PPA in promoting preferential reaction with the methyl group is more general. However, a second case of this directive effect has been found in the cyclization by PPA of cyclohexyl methyl ketone phenylhydrazone (**107**) preferentially to 2-cyclohexylindole (**108**) while zinc chloride or acetic acid catalysts gave only the 3*H*-indole **109**[158] (Eq. 29). This directive effect is unexpected since it is

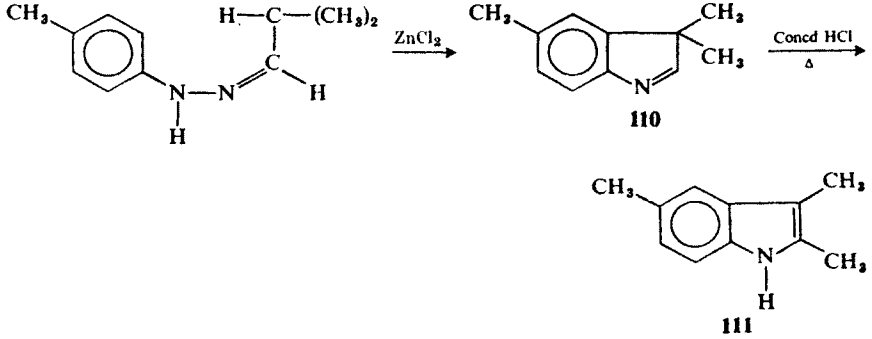


107 **108** **109**

(29)

generally observed that the methylene group or methine group of unsymmetrical alkyl methyl ketones reacts practically exclusively in the cyclization reaction.[9, 10]

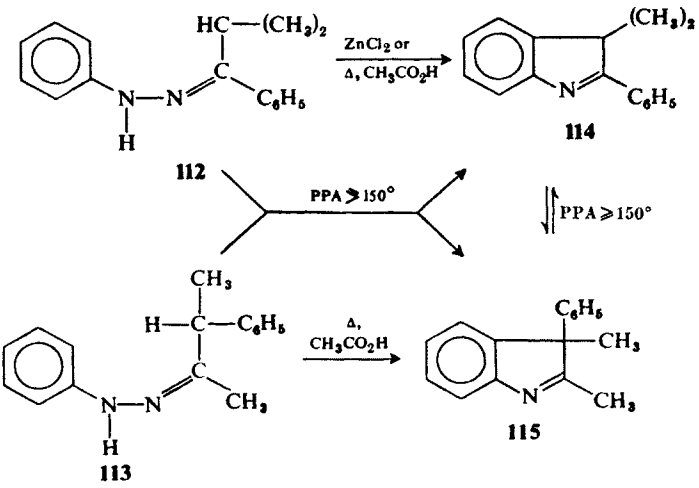
Indolenines, first prepared by Fischer,[67] are known to isomerize in the presence of acids. Thus 3,3,5-trimethylindolenine (**110**), when heated with concentrated hydrochloric acid, isomerizes to 2,3,5-trimethylindole (**111**)



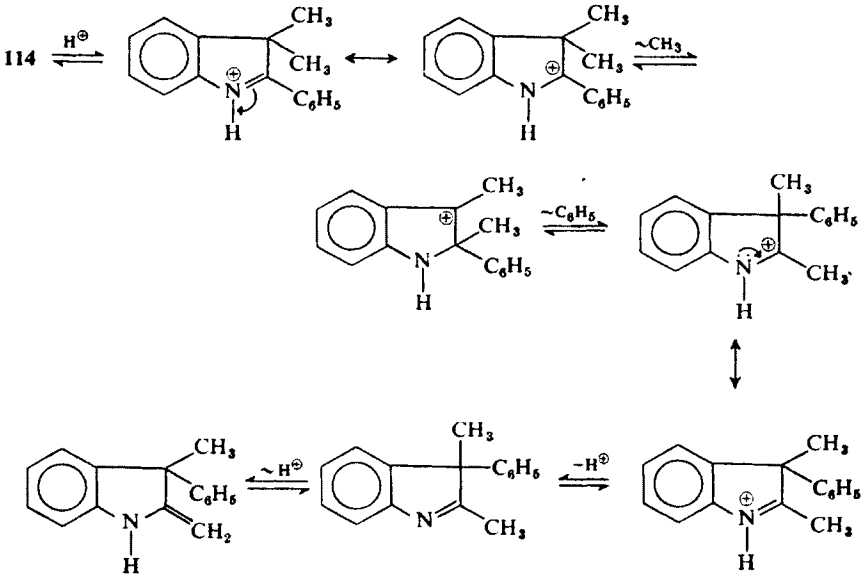
110 **111**

(30)

(Eq. 30). A detailed study[159] of the cyclization of the phenylhydrazones of isopropyl phenyl ketone **112** and 3-phenyl-2-butanone **113** has shown that hot acetic acid will indolize **112** and **113** to 3,3-dimethyl-2-phenylindolenine (**114**) and 2,3-dimethyl-3-phenylindolenine (**115**), respectively, and under these conditions both **114** and **115** are stable (Scheme 8). In PPA at elevated temperatures ($\geqslant$ 150) both **112** and **113** form the respective indolenines which are isomerized to an equilibrium mixture of **114** and **115** in the proportion **114**/**115** = 3:7. It is likely that this isomerization proceeds by a twofold Wagner-Meerwein rearrangement as shown in Scheme 9. Other acidic



Scheme 8

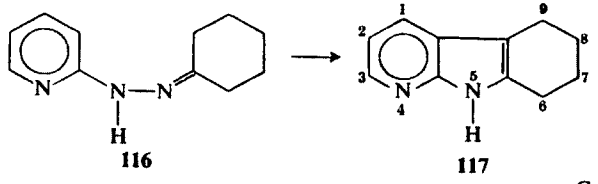


Scheme 9

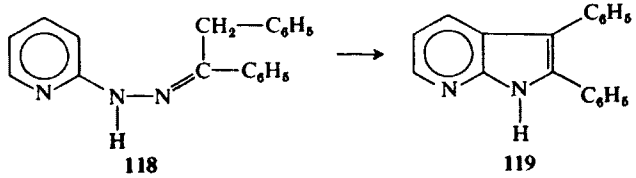
catalysts, boiling 48% hydrobromic acid, zinc chloride, or boron trifluoride can also cause isomerization of **114** but only if the temperature of reaction is greater than 100°. Such isomerizations of indolenines require caution and careful establishment of structure of products obtained under isomerizing conditions.

3. *Thermal Indolization*

Since Fischer's discovery of the cyclization of arylhydrazones to indoles by dilute hydrochloric acid[21] or zinc chloride,[23, 24] it had been tacitly assumed that this conversion required an acid catalyst. The mechanism of indole formation developed by Robinson and Robinson[160] was based in part on this view. However, following the recognition of the discovery that acetophenone phenylhydrazone upon distillation gave 2-phenylindole, though in low yield,[161] it was shown that 30–70% yields of indoles could be obtained by simply heating arylhydrazones in a high boiling solvent such as ethylene glycol, diethylene glycol, or tetralin in the absence of an acidic catalyst.[162] Yields were comparable in either the glycols or tetralin, hence polarity of the solvent apparently had no significant effect under these conditions. Since no careful rate studies were made under identical conditions, the relative yields obtained must be considered only as qualitative. Because it was found that the thermal cyclization could occur even in the presence of a small amount of alkali, it was concluded that the Robinson mechanism[160] did not appear to be adequate for the thermal indolization reaction. However, it should be pointed out that the alkali may just be an artifact with no bearing whatsoever on the thermal cyclization, which probably would have given the same results without the alkali. This point had not been considered.[162] A subsequent detailed study of this thermal indolization[163] corroborated these findings and showed that this procedure was particularly advantageous for the preparation of indoles that have marked acid sensitivity. Furthermore, whereas cyclization of pyridylhydrazones by the Fischer acid-catalyzed method has met with little success and could be accomplished in moderate yield[164] only with those carbonyl compounds whose phenylhydrazones cyclize with extreme ease, such as cyclohexanone or deoxybenzoin, the thermal reaction generally gave satisfactory results. The 2-pyridylhydrazones **116** and **118** could be converted to 6,7,8,9-tetrahydro-α-carboline (**117**) and 2,3-diphenylpyrrolo[2,3-b]pyridine (2,3-diphenyl-7-azaindole; **119**) in 70 and 50% yield, respectively (Eqs. 31 and 32). In contrast, the yields with PPA were 53 and 12%, respectively. The improved results were attributed to the fact that in the Fischer reaction, the pyridine ring, normally resistant to electrophilic substitution, was further deactivated by protonation by the acid catalyst, while such additional deactivation by acid is absent in the thermal reaction. This thermal cyclization has been extended successfully to several other 2-pyridylhydrazones[165] and to 4-pyridylhydrazones as well as 4-pyrimidylhydrazones[166] giving, respectively, 7-aza-, 5-aza-, and 5,7-diazaindoles. As in the case of acid-catalyzed cyclization, wherein it is found that electron-attracting groups in the aryl ring reduced the ease of indolization of these

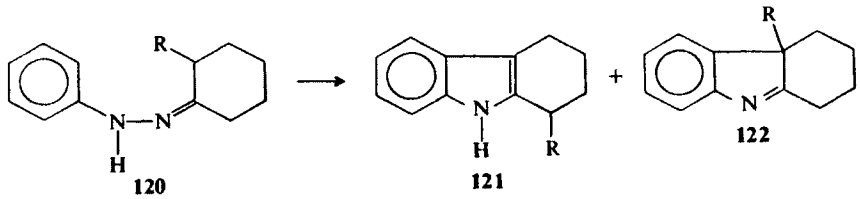


116 117 (31)



118 119 (32)

substituted arylhydrazones,[9, 10, 89] only a poor yield of 6-nitro-1,2,3,4-tetrahydrocarbazole was obtained upon thermal cyclization of cyclohexanone *p*-nitrophenylhydrazone.[163] It is interesting that in this latter reaction, the addition of cuprous chloride, advocated as a catalyst,[25] failed to give any increase in yield of the 6-nitro-1,2,3,4-tetrahydrocarbazole although ammonia evolution did increase. Another observation made[163] was that thermal cyclization of cyclohexanone phenylhydrazone **120**, R = H, gave 1,2,3,4-tetrahydrocarbazole **121**, R = H, in 83% yield while 2-substituted cyclohexanone arylhydrazones produced both of the possible isomers **121** and **122** with the



120 121 122 (33)

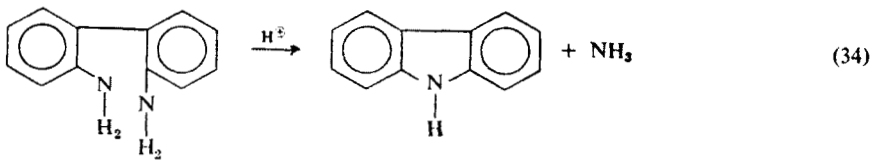
proportion of **122**/**121** decreasing as the substituent R changed from methyl to *n*-propyl to phenyl (Eq. 33). If R is benzyl, then none of the indolenine **122** is formed.[10] These observations show that steric factors are important in determining the relative amount of indolenine formed.

4. *The Mechanism of the Fischer Indole Synthesis*

Four different mechanisms have been advanced to explain the course of the Fischer indole synthesis. These were proposed respectively by Reddelien, by Bamberger and Landau, by Cohn, and by Robinson and Robinson.[5] Only

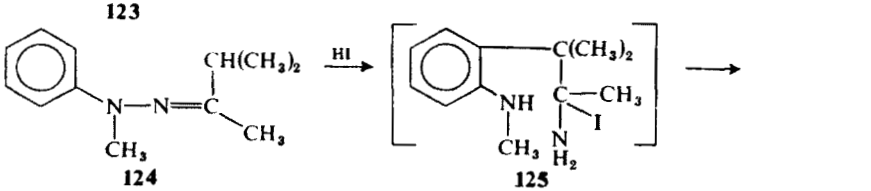
that of the Robinsons[160] has survived because it is in agreement with the mass of accumulated information. Accordingly, it alone will be considered here. For a brief but adequate description of the other three proposals as well as the Pausacker modification of the Robinson mechanism and the reasons for their early elimination from serious consideration, the review by Sumpter and Miller[5] should be consulted.

Brunner in 1898[167] compared the acid-catalyzed indolization of the *N*-methylphenylhydrazone of methyl isopropyl ketone **124** with the conversion of 2,2′-diaminobiphenyl (**123**) to carbazole under acidic conditions[168] (Eq. 34), and suggested that the indolization reaction leading to **126** could involve an intermediate **125** of structure similar to that of the diamine **123** (Eq. 35).

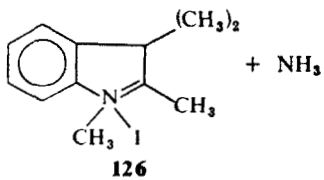


(34)

123



124 **125**

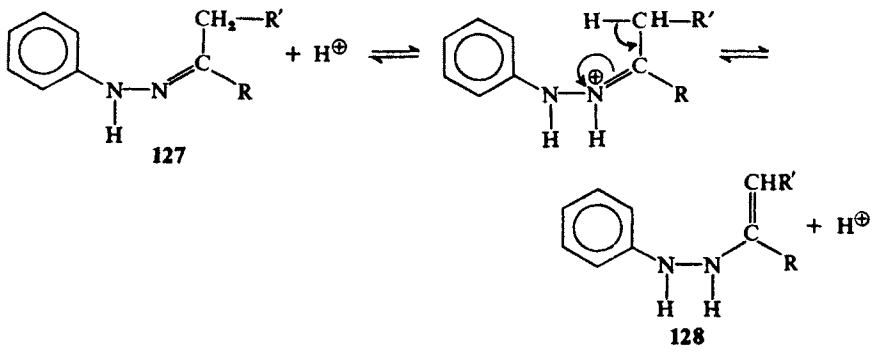


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(35)

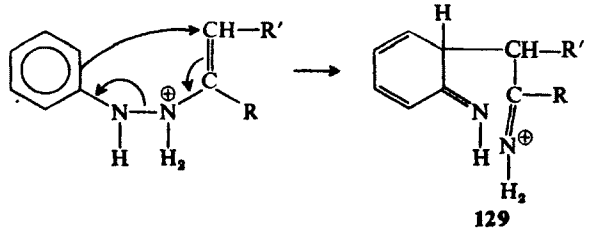
This observation remained unnoticed until 1957.[169] In 1918, Robinson and Robinson[160] considered the Fischer reaction in relation to the *o*-benzidine rearrangement and proposed a mechanism which they divided into three distinct stages, the latter two of which were similar to the Brunner proposal. Analogies were provided to support these three stages.[160] The nitrogen tracer studies of Allen and Wilson[170] supported the mechanism, hence it was accepted by them though with some minor modification. Carlin and Fisher[171] noted the strong resemblance between the Robinson mechanism and the *o*-Claisen rearrangement.[172] The three stages of the Robinson mechanism have been clearly described in a recent review of the Fischer indole synthesis[9] and are shown below.

Stage 1. Hydrazone–ennehydrazine tautomerism (Eq. 36).



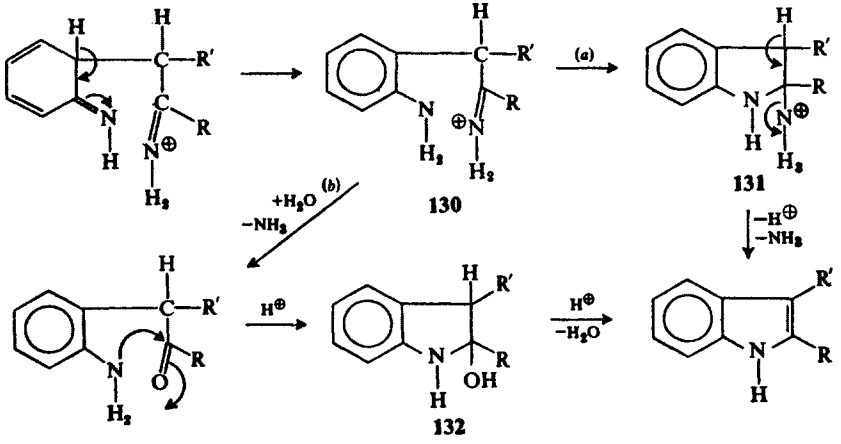
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Stage 2. Formation of the new C—C bond (*o*-benzidine rearrangement) (Eq. 37).



(37)

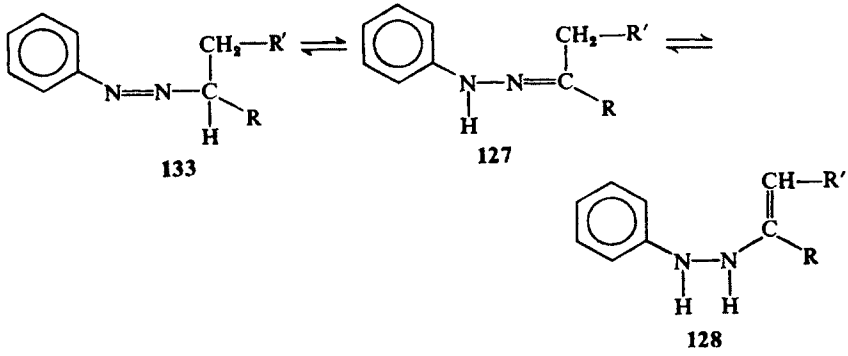
Stage 3. Cyclization and loss of ammonia by either of the routes (*a*) or (*b*) (Eq. 38).



(38)

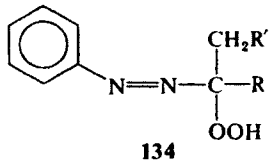
The evidence accumulated to support the concept of these three stages of the reaction leaves little doubt that it is indeed correct. It can be discussed conveniently in relation to each of three stages.

a. Evidence for Stage 1. Conversion of the Hydrazone to the Enehydrazine. Robinson and Robinson had shown[160] that those aldehydes or ketones which enolized readily formed hydrazones which also indolized readily, thus supporting the view that the first requirement is conversion of the hydrazone **127** to the enehydrazine **128**, under the influence of an acidic catalyst (Eq. 36). A study of the addition of Grignard reagents to aryl-



(39)

hydrazones led to the postulation that arylhydrazones might tautomerize to the enehydrazine.[173] Results of attempts to find evidence to support the existence of the enehydrazine by ultraviolet (uv) spectral studies[174] indicated that the azo **133** and hydrazone **127** tautomers exist in equilibrium in neutral organic solution, but no evidence was found for the enehydrazines **128** (Eq. 39). Nevertheless, this work was considered to provide evidence for the formation of **128**[175] and indeed, under Fischer conditions, the enehydrazine might actually be formed as expected. O'Connor's uv, infrared (ir), and nuclear magnetic resonance (nmr) studies of arylhydrazones[176, 177] also failed to reveal evidence for the presence of the enehydrazine **128**, but in neutral, nonpolar media it appeared from his work that the hydrazone **127** rapidly changed to the azo tautomer **133**. A repetition of this work[178] revealed that the azo compound observed by O'Connor was really the hydroperoxide **134** which was formed only when atmospheric oxygen was available to the solution of the hydrazone. Neutral solutions of arylhydrazones, from which oxygen was rigorously excluded, gave no evidence of either the azo **133** or the enehydrazine **128** tautomers. Recent studies[179] support the latter observation and point out that in both the solid state or in solution only the thermodynamically more stable hydrazone **127** is present. It has also been shown[180] that mild acid or alkaline conditions, as well as the presence of radicals, will

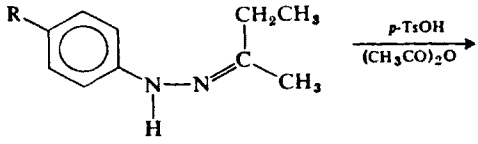


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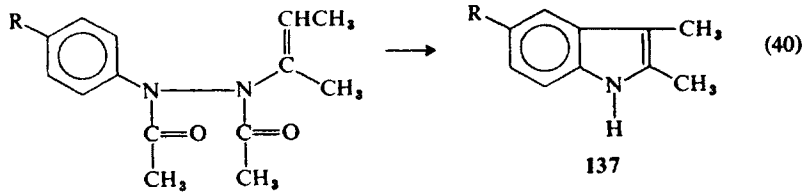
convert the azo compounds **133** to the hydrazones **127**, and that vigorous acidic conditions can convert both the azo compounds and hydrazones to indoles. The observation by other workers[181] that hydrazones autoxidize readily emphasizes the desirability of conducting indolization experiments in an atmosphere of nitrogen.

Polarographic studies[182] indicated that in alcohol solution the phenylhydrazones of aliphatic and alicyclic ketones have the enehydrazine structure in the free state while the phenylhydrazones of aldehydes and aliphatic–aromatic ketones retain the hydrazone structure. This supports the view that in polar media arylhydrazones can be converted to the enehydrazine. Subsequent polarographic work also supported the concept that the azo, hydrazone, and enehydrazine tautomers can exist in equilibrium.[183]

More direct evidence in support of the enehydrazine **128** is the isolation[184] of its *N*,*N*′-diacetyl derivative, 2-(*N*,*N*′-diacetyl-β-phenylhydrazino)-2-butene (**136**; R = H) in good yield from the reaction of ethyl methyl ketone phenylhydrazone (**135**, R = H) (Eq. 40). The diacetyl compound **136** when



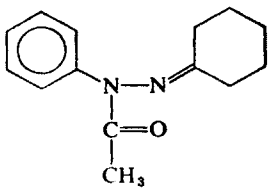
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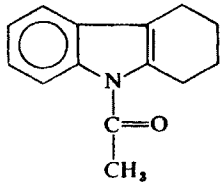
136 137 (40)

heated with diluted sulfuric acid could be converted to 2,3-dimethylindole (**137**; R = H). In a similar manner the *N*,*N*′-diacetyl derivatives of the enehydrazine tautomer of the arylhydrazones of several aldehydes and ketones having in some cases either a methyl, a methoxy, or a nitro group in the *para* position of the benzene ring were prepared.[185] The ethyl methyl ketone

N-methylphenylhydrazone (**135**; R = H, NH replaced by N—CH_3) under similar conditions did not provide the corresponding *N*-acetyl compound but instead was converted directly to a mixture of 5-, 6-, and 7-monoacetyl-1,2,3-trimethylindoles along with substantial quantities of two other substances, *N*-methylacetanilide and β-acetyl-α-methyl-α-phenylhydrazine.[186, 187] The inability to obtain the *N*-acetyl derivative of the enehydrazine in this case, while the hydrazones lacking a methyl group on the nitrogen atom readily provided the *N*,*N*′-diacetyl compound **136**, was attributed to the presence of the acetyl groups on the nitrogen atoms, which decreased the ability of the nitrogen atom's lone electron pair to participate in the next step (Stage 2) of the Fischer reaction. It has long been known that the yields of indoles from unsymmetrical phenylalkylhydrazones are higher than those obtained from the phenylhydrazones with no alkyl substituent on the nitrogen atom.[186, 188] Suvorov observed[185] that in a repetition of the experiment in which it was claimed[189] that dilute sulfuric acid converted cyclohexanone *N*-acetylphenylhydrazone (**138**) to *N*-acetyl-1,2,3,4-tetrahydrocarbazole (**139**), he obtained 1,2,3,4-tetrahydrocarbazole rather than its *N*-acetyl derivative **139**. This led him to conclude that cyclization to indole



138

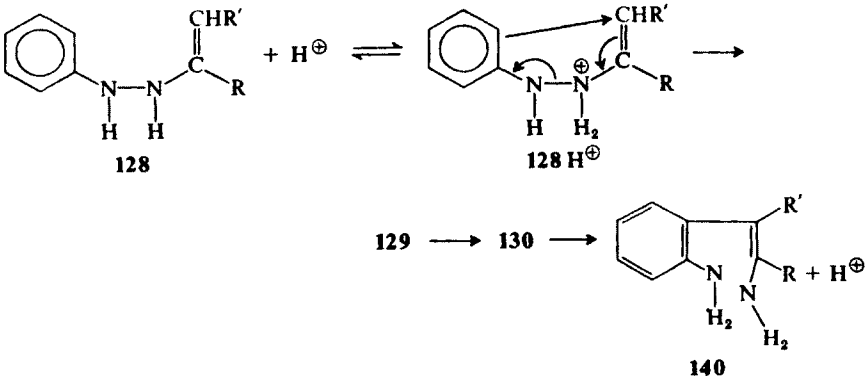


139

was preceded by removal of the acetyl group from the nitrogen atom of **138**, and this supported his view stated above. However, Yamamoto[190] substantiated the previous claim[189] and obtained a *mixture* of both the tetrahydrocarbazole and *N*-acetyl-1,2,3,4-tetrahydrocarbazole (**139**). Further work showed that milder cyclizing agents such as hydrogen chloride in acetic acid[190] and acetic acid alone[144, 145] converted *N*-acyl arylhydrazones readily and in high yield directly to the *N*-acylindoles. A mixture of the hydrochloric acid salt of the *N*-acylated phenylhydrazone and levulinic acid could be readily converted in warm acetic acid to the corresponding *N*-acylated indole. Solvents such as formic, propionic, butyric, and lactic acids, as well as cyclohexane and hexane, also gave satisfactory results, whereas benzene, toluene, dioxane, and butanol gave only poor yields.[145] These *N*-acylated indoles are very easily hydrolyzed at pH < 1 and > 9,[144] an observation that may explain the failure[185] to obtain **139** from **138**. Yamamoto's work[144, 145, 190] does show that *N*-acylation of the arylhydrazones offers no serious barrier to indolization.

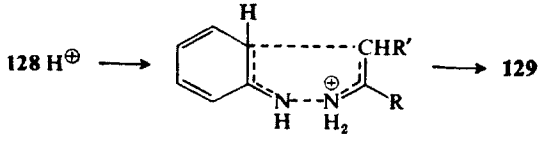
The work of Suvorov[184] and of Arbuzov and Kitaev,[182, 183] as well as the analogy pointed out by the Robinsons,[160] does support the view that the first step of the mechanistic sequence of the Fischer indole synthesis is the formation of the enehydrazine **128** from the hydrazone **127** (Eq. 36).

b. Evidence for Stage 2. Formation of the C—C Bond (*o*-Benzidine Rearrangement). Possible details of Stage 2 of the Fischer indole synthesis are shown in the structures **128** → **130** and **140** (Eq. 41). Arbuzov and Kitaev[169] have discussed the conjugation and polarization of the enehydrazine **128** and



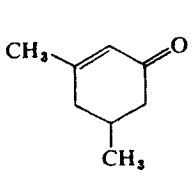
(41)

state that in the presence of acidic catalysts the polarization of the enehydrazine is increased (as in **128H⊕**). The partially charged atoms of this 1,6-dipolar structure are spacially situated quite advantageously for mutual reaction with consequent bond breaking and bond formation to produce **129**.

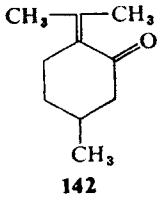


These authors[169] consider the Fischer reaction, the *o*-Claisen rearrangement, and the *o*-benzidine rearrangement as three examples of the reactions of polarized 1,6-conjugated systems. The failure to observe *para* rearrangement in the Fischer reaction has raised some opposition[1, 3] to the Robinson mechanism based on the analogy to the benzidine rearrangement. This has been countered by the statement that *ortho* rearrangement is spatially favored,[169] and subsequent cyclization to indole products occurs much more readily than does further rearrangement to the *para* position. If indeed *para* rearrangement occurs at all, one would expect to obtain *p*-alkylamino acids or *p*-aminophenylacetaldehydes or *p*-aminobenzyl ketones which are very reactive species and would form tars under the usual conditions of the

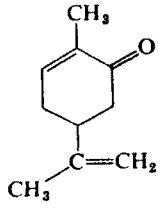
Fischer reaction.[9] The *para* rearrangement should be more likely in the arylhydrazones of α,β-unsaturated aldehydes or ketones since these have the structural requirements for *para* rearrangement. It is interesting that indoles could not be obtained from the *m*-nitrophenylhydrazones of the α,β-unsaturated ketones 3,5-dimethylcyclohex-2-enone (**141**), pugelone (**142**), and *d*-carvone (**143**),[191] though his may have been due to the presence of the *m*-nitro group and/or the mild conditions used.[9] Also, attempts to indolize 3-phenylcyclopent-2-ene-1-one *N*-methylphenylhydrazone (**144**) by thermal means have been unsuccessful.[10, 163]



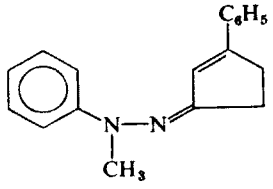
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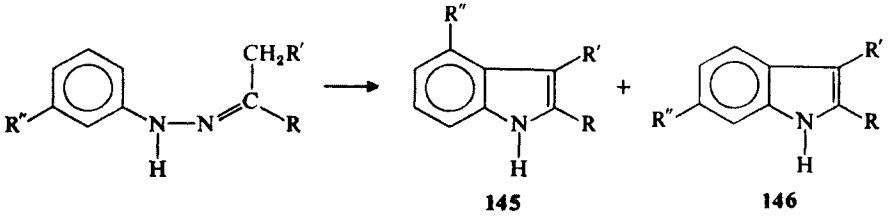


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144

Arguments to support Stage 2 of the Robinson mechanism have been based on the view that the conversion of the enehydrazine **128** to the dienone-imine **129** is a case of electrophilic substitution (cf. Structure **128H**$^{\oplus}$). A study of the indolization of *m*-substituted phenylhydrazones,[192] which give both the 4- and the 6-substituted indoles, **145** and **146**, revealed that the ratio of the yield of the 6-isomer to the 4-isomer generally is greater than 1 if the substituent R″ is an *ortho-para* directing (electron-donor) group whereas the reverse is true if R″ is an *ortho-meta* director (electron-attracting group)



145 **146**

(42)

(Eq. 42). These observations agree with the view expressed in Structure **128H**$^{\oplus}$ that Stage 2 involves an electrophilic attack on the aromatic ring. However, a report of the indolization of a series of *o*-, *m*-, and *p*-nitrophenylhydrazones of several ketones[193] states that in all cases, except for the phenylhydrazone of ethyl methyl ketone, higher yields of indoles were obtained from *m*-nitrophenylhydrazones than from the corresponding *ortho* or *para* isomers. This indicates that the nitro group deactivates the *ortho* and *para* positions to electrophilic attack in Stage 2 and accordingly, to accommodate these observations, the new C—C bond formation should occur by intramolecular *nucleophilic* attack of the enehydrazine on the aromatic ring. But, as has been pointed out,[9, 194] it is not known which step in the Fischer indole synthesis is rate controlling, and furthermore it is incorrect to assume that the yield of product obtained is directly proportional to the velocity of the rate-determining step. In many instances only the isolated yield is reported and this may not be equivalent to the true yields.

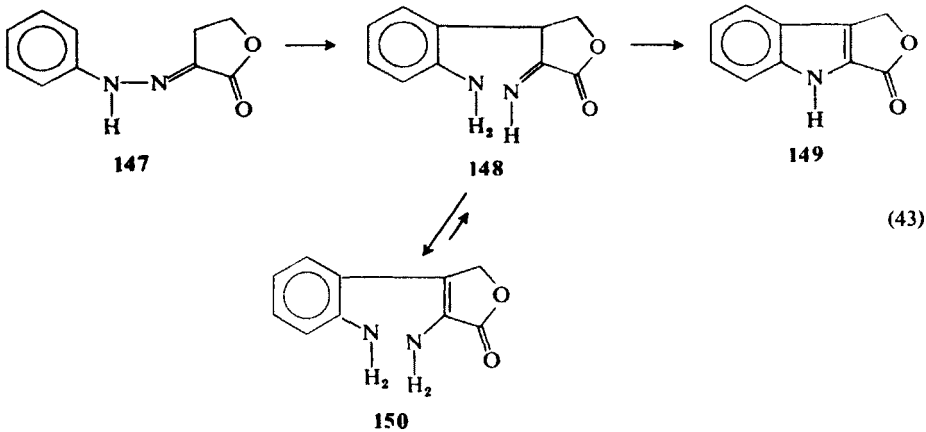
It has been observed that under mild conditions (25% acetic acid at 50–80°) the reaction between *m*-benzyloxyphenylhydrazine hydrochloride, or phenylhydrazine hydrochloride, and 4-aminobutanal diethyl acetal failed to provide an indole whereas the *ortho*- and *para*-benzyloxyphenylhydrazine salts both gave indoles, the *para* isomer to a greater extent than the *ortho* isomer.[195] Under these same conditions arylhydrazone hydrochlorides with electron-withdrawing groups attached at any position in the aryl ring did not indolize at all.[142] This generally agrees with the view that Stage 2 involves an electrophilic attack on the aromatic ring. However, the fact that the *m*-benzyloxy isomer gave little or no indolization whereas the *p*-benzyloxy isomer gave the largest yield of the cyclized product is the reverse of what is expected if Stage 2 is the rate-determining step. Pausacker and Schubert have also shown that cyclohexanone 4-methoxyphenylhydrazone cyclizes very much faster than does the 3-methoxy isomer.[196] These observations have been explained[195] by assuming that it is Stage 1 that is involved in rate determination and that the affinity of the acid for the β-nitrogen is increased by the electron donor in the *para* position via a mesomeric effect. The *meta* isomer does not provide this enhancement of basicity and hence the protonated enehydrazine is in relatively low concentration, resulting in a lower rate of reaction.

The greater amount of indole obtained from the *para* isomer compared with that obtained from the *ortho* isomer is considered to be due to the steric interference of the *ortho* substituent in the formation of the new C—C bond.[195] This steric effect of the *ortho* substituent has been noted previously.[197]

It has been observed many times that electron-donor substituents (alkyl, alkoxy) in the aromatic ring of the arylhydrazone usually aid the polarization[142] and promote indolization, whereas electron-attracting groups

(NO_2, CN, COOH, halogens) retard cyclization to indoles and therefore in the latter case more stringent conditions are required to effect indolization.[9, 58, 61, 89, 185, 195, 196, 198–201] The ease of cyclization of arylhydrazones containing electron-withdrawing groups in the aromatic ring can be increased markedly by the choice of a carbonyl moiety, such as cyclohexanone or deoxy benzoin, whose arylhydrazones are known to form indoles very easily.[29b, 202] In contrast, the nature of the substituent in the carbonyl moiety has a much smaller effect on the ease of cyclization.[195] Only two reports of rate studies of the Fischer synthesis have appeared,[196, 201] but in neither case was the rate-determining step established. Studies based on the rate of evolution of ammonia[196] showed that in glacial acetic acid the reaction was first order (in hydrazone) while in dioxane–aqueous sulfuric acid the reaction was second order (first order in hydrazone and in acid). Careful rate studies under a variety of catalytic conditions are still required.[9]

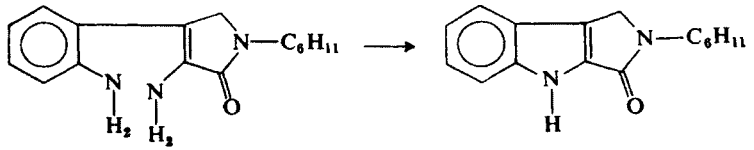
The work of Plieninger[203, 204] provided the first clear support for Stage 2. Plieninger used a milder catalyst, hydrogen chloride in acetic acid rather than concentrated hydrochloric acid in acetic acid,[205] in an effort to obtain a better yield of the indole **149** from α-keto-γ-butyrolactone phenylhydrazone (**147**) (Eq. 43). However, he first obtained the hydrochloric acid salt of a product whose structure was considered to be α-imino-β-(*o*-aminophenyl)-γ-butyrolactone (**148**). The dry hydrochloride of **148** when heated gave the indole **149**. Later,[206] nmr studies showed that the compound was the enamine **150**, the lactone of 2-amino-3-(*o*-amino phenyl)-4-hydroxy-2-butenoic acid, rather than **148**. This finding stemmed from the preparation[206] of the pyrrol-



147 **148** **149** **150** (43)

idine analog **151** of the Plieninger intermediate by an indirect route not involving an arylhydrazone. Compound **151**, 3-amino-4-(*o*-aminophenyl)-1-cyclohexyl-3-pyrrolin-2-one, when heated in a mixture of methanol and

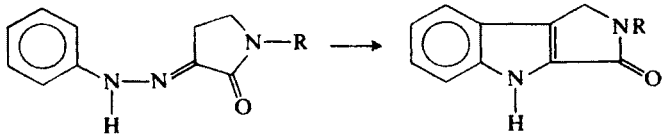
acetic acid, was easily converted to **152** (Eq. 44) whereas **150** required more vigorous conditions for its conversion to **149**. This facile conversion of **151** to **152** explains the failure to obtain an intermediate similar to **151** from the



(44)

151 **152**

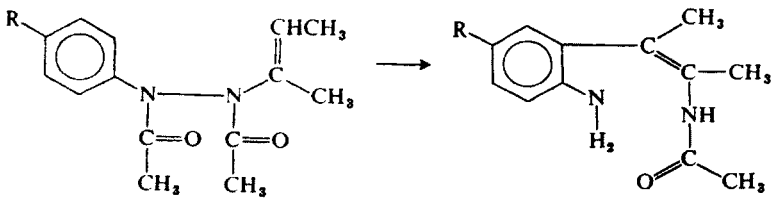
reaction of 1-substituted-2,3-dioxopyrrolidine-3-phenylhydrazones **153** when they were indolized under Plieninger conditions.[207] Only the final indoles **154** were obtained (Eq. 45).



(45)

153 **154**

The work of Suvorov et al.[186] provided further support for Stage 2. The *N,N'*-diacetyl compound **136** (R = H) when heated in dilute sodium

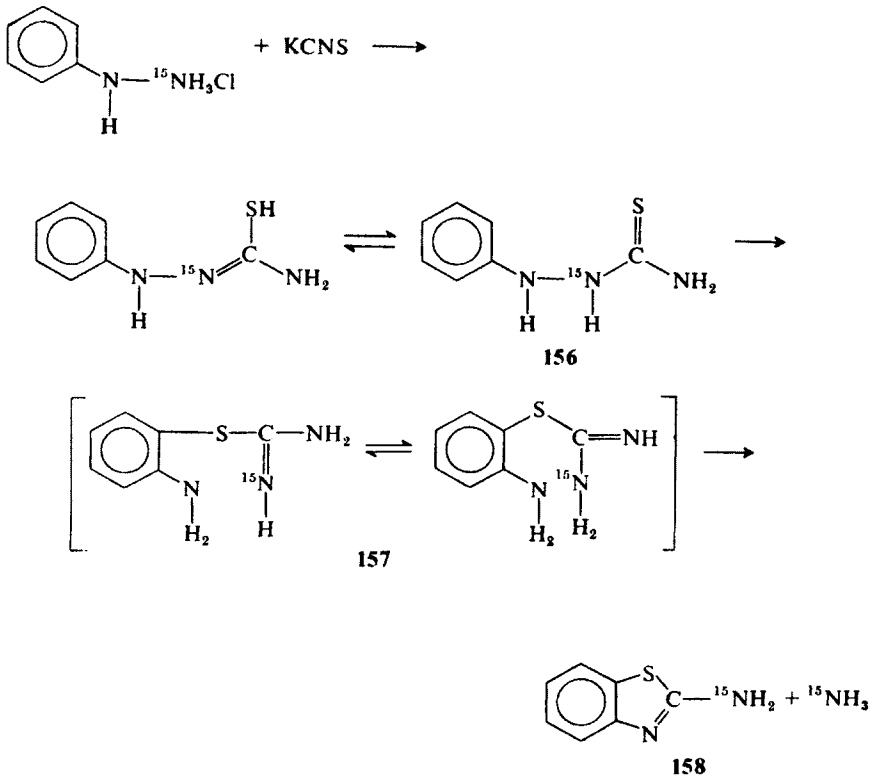


(46)

136 **155**

hydroxide gave 3-acetylamino-2-(*o*-aminophenyl)-2-butene (**155**; R = H) (Eq. 46). The same results were obtained[186] when the substituent R in **136** was methyl. Subsequent work[186] showed that the *formation* of the *N,N'*-diacetyl compounds **136** was easily accomplished when R is CH_3O, CH_3, H, or NO_2. However, when these *N,N'*-diacetyl compounds were heated with dilute aqueous potassium hydroxide, the *p*-nitro compound **136** (R = NO_2) was hydrolyzed to ethyl methyl ketone and *p*-nitrophenylhydrazine while the *p*-methoxy derivative **136** (R = CH_3O) gave only 6-methoxy-2,3-dimethylindole.

Clusius and Weisser[208] also gave evidence for enehydrazine **128** and diamine **130** intermediates. Their synthesis of 2-aminobenzothiazole by heating ^{15}N-labeled *N*-phenylthiosemicarbazide **156** with concentrated hydrochloric acid gave two products, 2-aminobenzothiazole **158** and ammonia, each containing half the activity (Scheme 10). This is in agreement with the



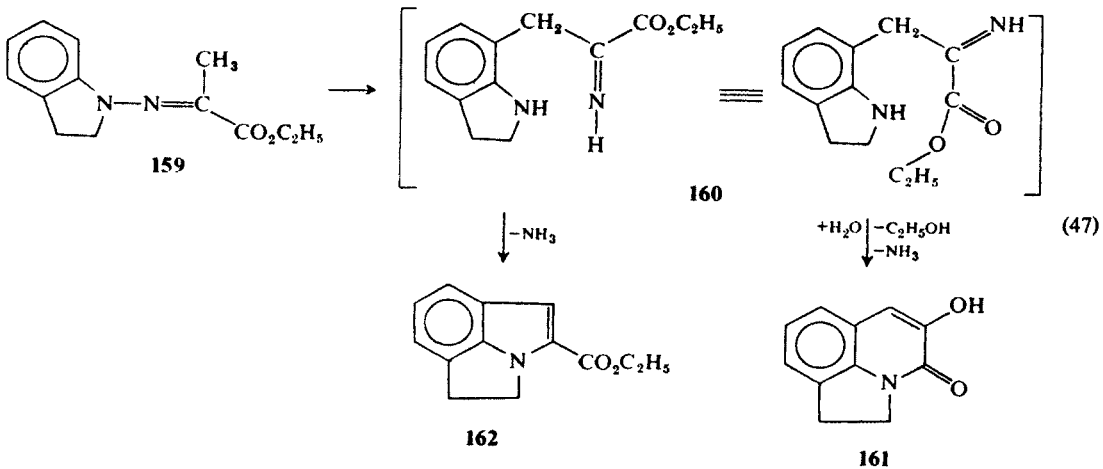
Scheme 10

postulated diamine intermediate **157** in which proton transfer occurs rapidly *before* cyclization takes place.

The condensation product **159** of 1-aminoindoline and ethylpyruvate, when heated with absolute alcohol containing 10% sulfuric acid,[209] gave 3-hydroxypyrrolo[3′,2′,1′-*i*,*j*]quinolin-2-one (**161**) as the major product along with a small amount of the expected product **162**, ethyl pyrrolo[3′,2′,1′-*h*,*i*]indole-2-carboxylate (Eq. 47). The easier cyclization to **161** is preferred to that involving the formation of a structure **162** containing two fused five-membered rings. Other examples of such preferential ring closure are quoted in Ref. 10.

The formation of the two products **161** and **162** can be explained satisfactorily only if it is accepted that a diimine **160** (cf. **129**) is first formed and then reacts according to the routes available to it.

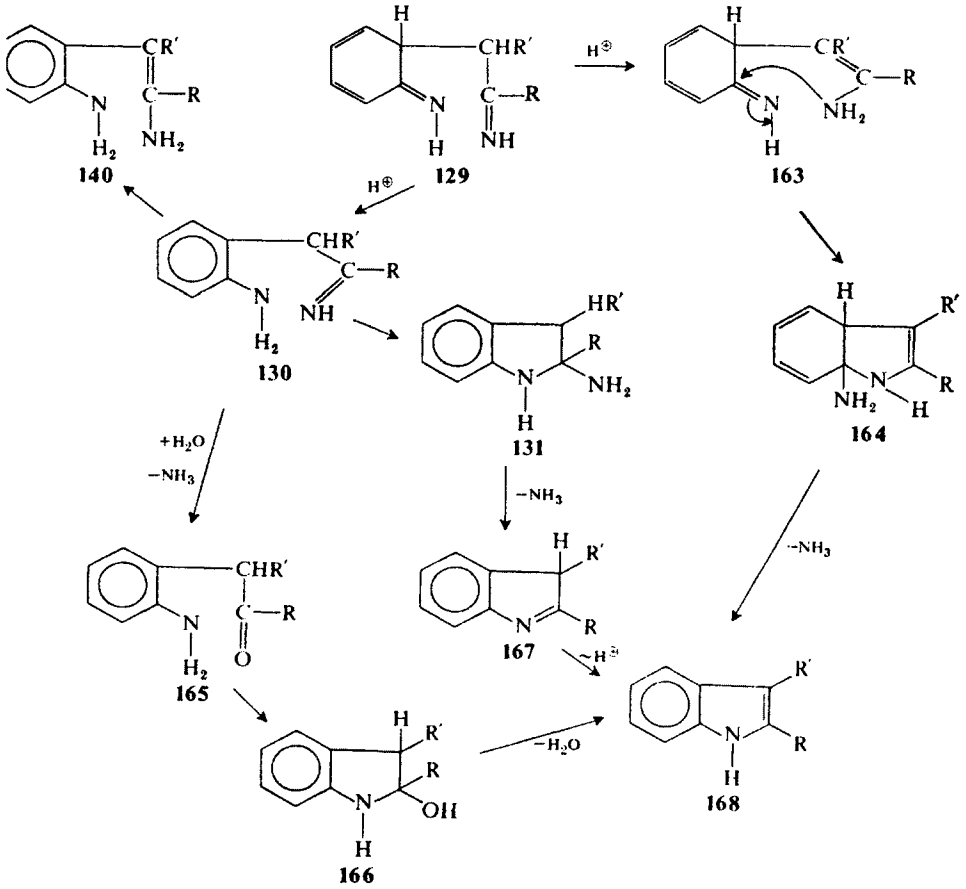
Although the work of Plieninger,[203, 204] Owellen et al.[206] and Suvorov[186] has clearly supported the existence of the diamine **140** as an intermediate, in


CH3
N
N
C
CO2C2H5
159
CH2
CO2C2H5
C
NH
N
H
160
CH2
NH
C
NH
C
O
O
C2H5
−NH3
+H2O
−C2H5OH
−NH3
N
CO2C2H5
162
OH
N
O
161

(47)

the Fischer indole synthesis by the actual isolation of the products **150** and **155**, evidence for the precursor to **140**, the diimine **129**, or the amino-imine **130** has been only indirect.[208, 209] Recent work has provided direct evidence for such a diimine as an intermediate in the Fischer synthesis. However, this is best considered in connection with Stage 3, which involves cyclization and loss of ammonia.

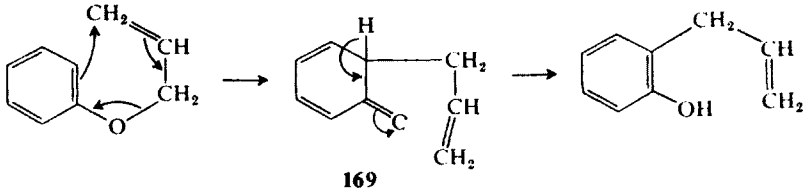
c. Evidence for Stage 3. Cyclization and Loss of Ammonia. The possible paths of reaction of the first product **129** expected from the reaction



Scheme 11

of the enehydrazine **128** in forming the new C—C bond are shown in Scheme 11.

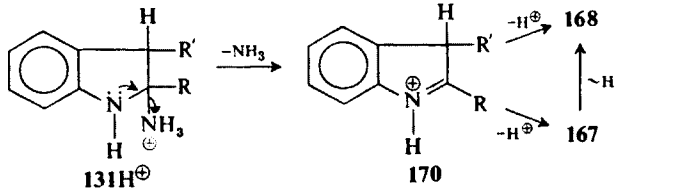
Carlin's anlogy[171] between the *o*-Claisen rearrangement and the Fischer indole synthesis can be clearly seen when one considers structure **129** and the



169 (48)

corresponding structure **169** from the rearrangement of allyl phenyl ether (Eq. 48). Some objection has been raised[9] regarding the correctness of the analogy with the Claisen rearrangement, since it has been demonstrated that the rate of the latter reaction is independent of the type and position of substituents in the aryl ring[172] and that it is thermally initiated requiring no acid catalyst, whereas the rate of indolization of arylhydrazones definitely depends upon the nature of the substituents and their location in the aromatic ring (see previous section for references). However, there are recorded instances where the Claisen rearrangement is definitely accelerated by the presence of acids.[210–213] The Fischer reaction can also be initiated by thermal means alone,[161–166] and in some cases the addition of acid catalysts improve the reaction. Thermal cyclization of cyclohexanone *p*-nitrophenylhydrazone gives a poor yield of 6-nitro-1,2,3,4-tetrahydrocarbazole,[163] but when the hydrazone is heated in the presence of an acid, a good yield of the product is obtained.[89] Hence it is likely that protonation of the hydrazone is generally not essential in the Fischer reaction but is definitely of assistance, and may even be necessary when indolization is difficult.[9]

The dienone-imine **129** will rearrange spontaneously to **130** rather than to **163** because of the strong tendency for aromatization. The labile allylic hydrogen in **129** allows this to occur. Subsequent addition of the aryl amino group to the conveniently situated imino double bond of **130** would provide the intermediate compound **131** (2-aminoindoline). This is a nitrogen hemiacetal and accordingly should lose the amino group as ammonia very readily, particularly so in the presence of an acid catalyst **131**H^+, to provide a positively charged species **170** which in turn, simultaneously or subsequently, loses a proton to form either the indolenine **167** or the indole **168** (Eq. 49).



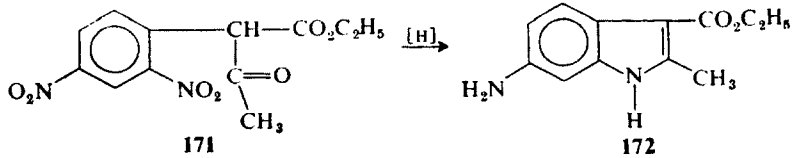
131$H^{\oplus}$ 170 (49)

The latter is preferred because of its greater aromaticity. The work of Hinman[214, 215] shows clearly that protonation of indole occurs at the β-carbon, thus supporting the species **170** and **167**.

The preference for route **129** → **130** → **131** → **167** or **168** (Scheme 11)

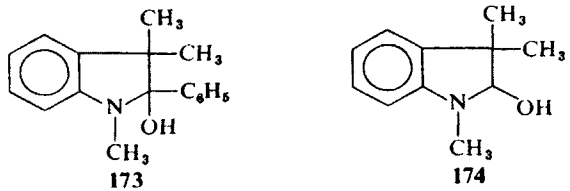
clearly shows that it is the β-nitrogen (more remote from the aromatic ring) which is lost as ammonia. That the β-nitrogen is indeed the one which *usually* emerges as ammonia has been verified several times. The formation of 1-methylindole from the hydrazones obtained from unsymmetrical methylphenylhydrazine[22, 216] provided early evidence for this. Allen and Wilson's[170] finding that acetophenone α-^{15}N-phenylhydrazone gave labeled 2-phenylindole and unlabeled ammonia provided additional support. Final confirmation was obtained by Clusius and Weisser[208] who found that acetone β-^{15}N-phenylhydrazone gave unlabeled 2-methylindole and labeled ammonia. The small amount of activity found in the 2-methylindole[208] was attributed to the presence of ~0.37% ^{15}N in ordinary nitrogen.

The view[175] that indole formation occurs by hydrolysis of the imine **130** to the carbonyl compound **165** which then cyclizes to **166** and then by loss of water forms the indole **168** is not shared by Allen and Wilson[170] who favor the route **130** → **131** → **168**. Pausacker and Schubert[175] find support for the hydrolysis route in the report[217] that ethyl α-(2,4-dinitrophenyl)acetoacetate (**171**) gives ethyl 6-amino-2-methylindole-3-carboxylate (**172**) (Eq. 50) which



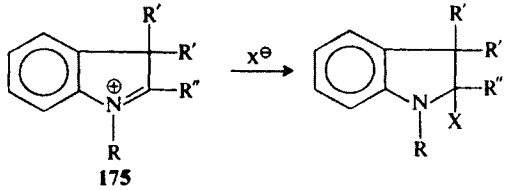
171 **172** (50)

must involve species such as **165** and **166**. However, this is a peculiarity of the structure of **171** and does not prove that hydrolysis of the imine **130** must precede cyclization. A second item given in support of the hydrolysis route[175] is the observation that the α-methylphenylhydrazones of phenyl isopropyl ketone and isobutyraldehyde give 2-hydroxy-1,3,3-trimethyl-2-phenylindoline (**173**)[218] and 2-hydroxy-1,3,3-trimethylindoline (**174**),[219] respectively. But it is

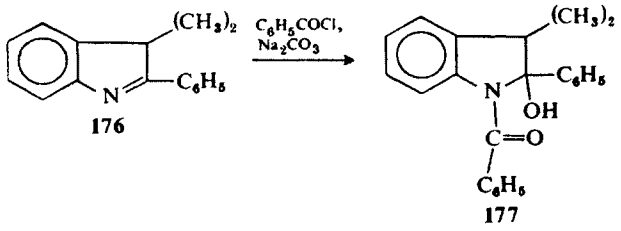


173 **174**

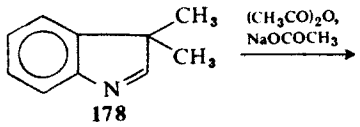
now known[9] that these 2-hydroxy indolines are the result of the reaction of base with the indoleninium salts **175** (cf. **170**) (Eq. 51). Leuchs et al.[220] found

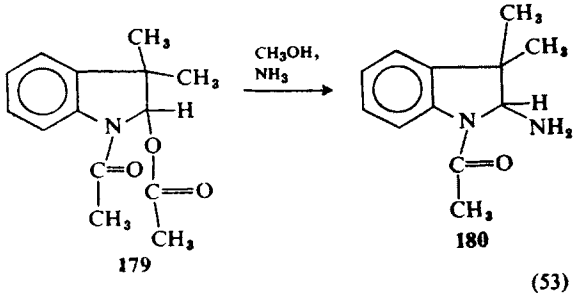


175 (51)



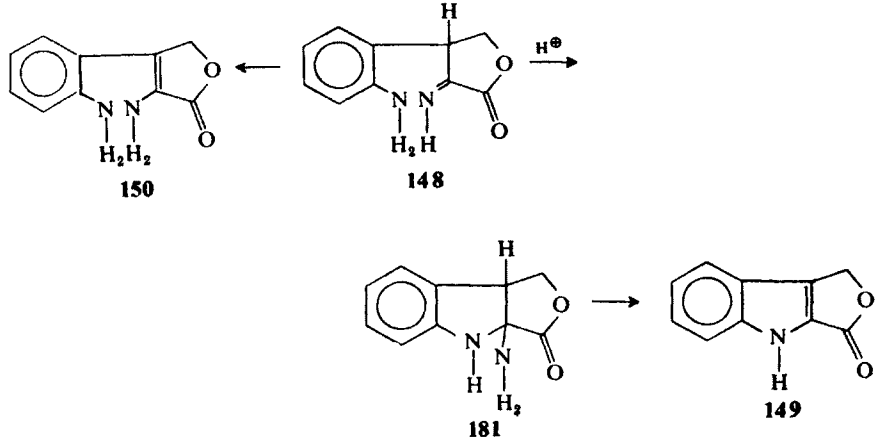
(52)





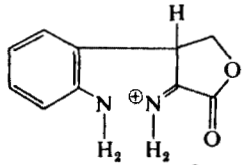
(53)

that 3,3-dimethyl-2-phenylindolenine (**176**) could be converted to 1-benzoyl-2-hydroxy-2-phenyl-3,3-dimethylindoline (**177**) by treatment with benzoyl chloride and sodium carbonate (Eq. 52), and that the reaction of 3,3-dimethylindolenine (**178**) with acetic anhydride and sodium acetate gave 1-acetyl-2-acetoxy-3,3-dimethylindoline (**179**) which could be converted to 1-acetyl-2-amino-3,3-dimethylindoline (**180**) (Eq. 53).



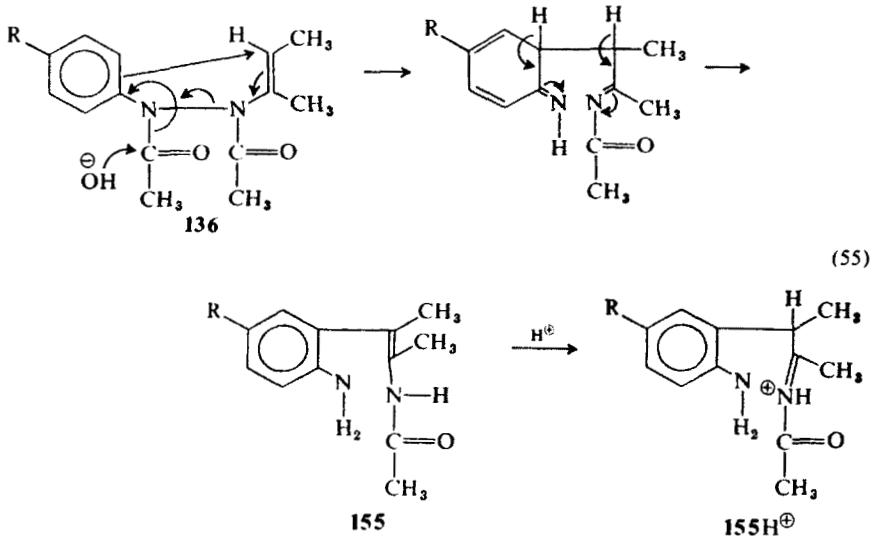
(54)

In compounds where the cyclization of **130** to **131** could be hindered due to development of structural strain, such as in the Pleininger intermediate where addition of the arylamino group to the imino double bond in **148** would require fusion of two five-membered rings **181** (cf. **131**), the alternate route to **150** (cf. **140**) involving a 1,3-proton shift to form a structure stabilized by conjugation of the α,β-double bond with the aromatic ring is preferred (Eq. 54). The view[206] that, because of the requirement of acid to cyclize the Plieninger intermediate **150** to the indole **149**, it is the immonium ion species **148H**$^{\oplus}$ which is involved in the cyclization step, may be correct. It also agrees with the views of Allen and Wilson[170] and of the author.



148H$^{\oplus}$

The explanation for the formation and stability of the Suvorov intermediate **155**[186] may have a similar basis. The presence of the acetyl group on the β-nitrogen as well as the stability achieved by conjugation of the double bonds would promote the 1,3-shift of the proton to form **155**. In order for **155** to cyclize, the immonium ion **155H**$^{\oplus}$ must be formed (Eq. 55).

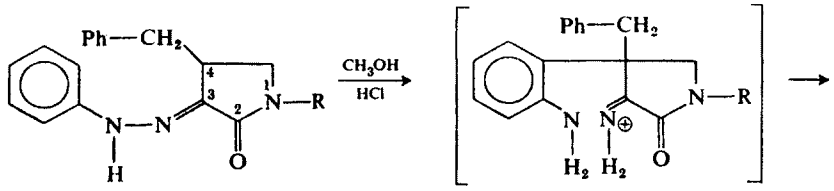


136 **155** **155H**$^{\oplus}$

(55)

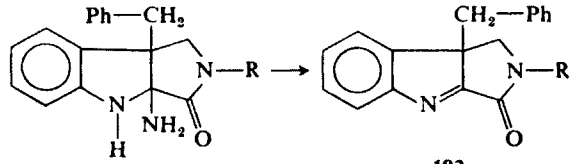
The cyclization[221] by methanolic hydrochloric acid of several 1-substituted-4-benzyl-2,3-dioxopyrrolidine-3-phenylhydrazones **182** to obtain first the intermediate **183** and then **183a** supports the view that the immoniun ion is

the species involved in the cyclization step (Eq. 56). When **182** was heated for a short time in a solution of methanol and hydrochloric acid, compounds



182

(56)

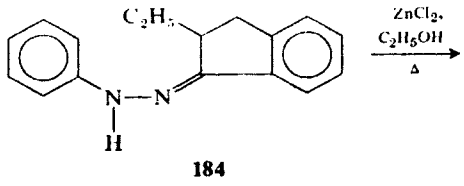


183 **183a**

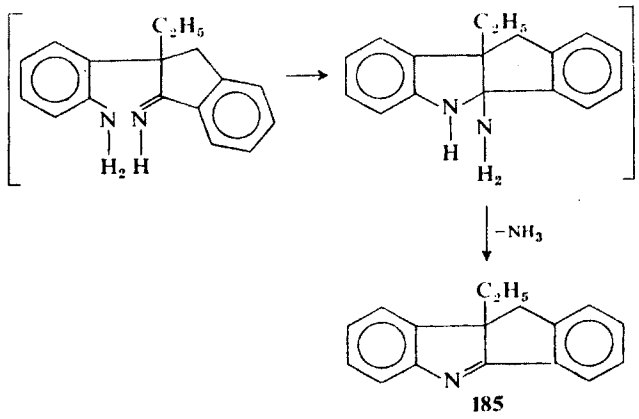
of structure **183**, 2-substituted-3*a*-amino-8*b*-benzyl-1,3*a*,4,8*b*-tetrahydropyrrolo[3,4-*b*]indole-3(2*H*)-ones, were formed. Further heating in aqueous acid or with sodium ethoxide converted **183** to the indolenine **183a** (2-substituted-8*b*-benzyl-1,8*b*-dihydropyrrolo[3,4-*b*]indolenine). This is an interesting example of arrested deamination in the Fischer indole synthesis, and the resistance to form **183a** is believed due to the increase of strain which occurs in the accommodation of the double bond in the two fused five-membered ring system. Such a strain appears to be minimal or absent if a six-membered ring is fused to the pyrrole moiety.

The reaction of 2-ethyl-1-hydrindone phenylhydrazone (**184**) with zinc chloride in hot ethanol gave 3-ethyl-3,2-(*o*-benzylene)-indolenine (**185**)[222] (Eq. 57) while *β*-benzyl-*α*-tetralone phenylhydrazone (**186**) was converted to 4*a*-benzyl-1,2-benzo-3,4-dihydrocarbazolenine (**187**)[220] (Eq. 58). Decahydro-3,4-dioxoisoquinoline-4-phenylhydrazone (**188**) was readily converted by boiling 90% formic acid to a substance tentatively assigned the structure **189**[223] (Eq. 59). In none of these three experiments was an attempt made to arrest the reaction at an intermediate stage.

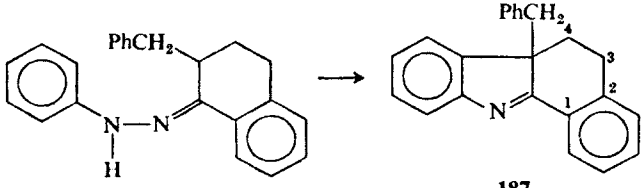
Some attempts have been made to isolate or trap the dienone-imine **129** and thus verify it as an intermediate in the Fischer sequence. Conroy and Firestone[224] isolated the dienone **190** (cf. **169**) as the Diels-Alder adduct by heating allyl 2,6-dimethylphenyl ether with maleic anhydride, and this dienone was shown to be a true intermediate in the Claisen rearrangement[225, 226] (Eq. 60). Accordingly an attempt was made[97] to trap the dienone-imine intermediate **192** (cf. **129**) expected from the zinc chloride-catalyzed



184



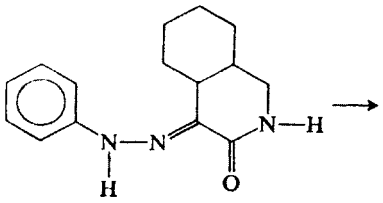
185 (57)



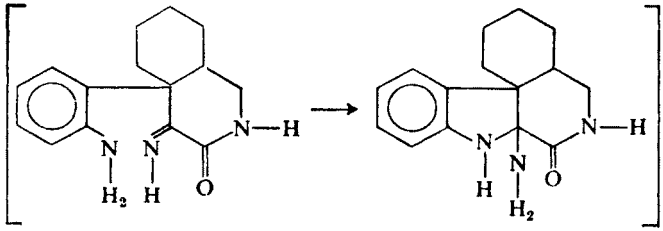
186 **187** (58)

indolization of ethyl pyruvate 2,6-dimethylphenylhydrazone **191** in the presence of maleic anhydride with or without nitrobenzene as solvent. No material was isolated indicative of such an adduct, and the only identifiable indolic material obtained was a small amount of ethyl 4,7-dimethylindole-2-carboxylate (**193**) (Eq. 61).

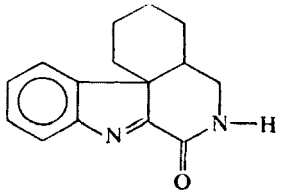
To avoid the stringent conditions employed as described above, Robinson and Brown allowed cyclohexanone to react with *N'*-methyl-2,6-dichlorophenylhydrazine **194** in benzene either at 80° or under vacuum at 20° in such a way as to remove, by azeotropic distillation, any water formed.[227] The rationale for the use of the *N'*-methyl dichloro derivative **194** was that the two chlorine atoms in the *ortho* positions of the aromatic ring would avoid the great susceptibility to decomposition which the 2,6-dimethylphenylhydrazine possesses, and in addition, the methyl group on the β-nitrogen



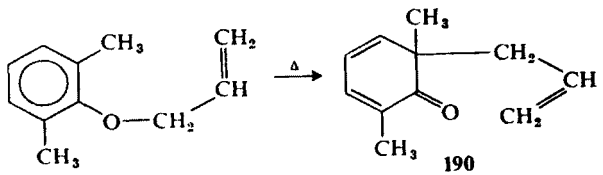
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(59)

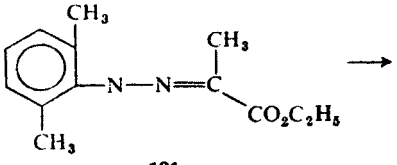


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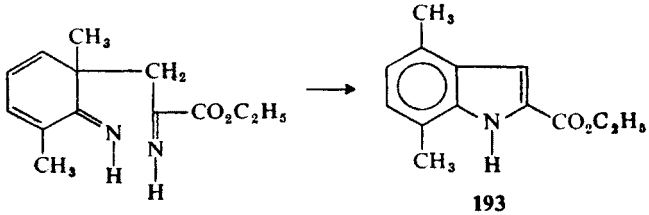


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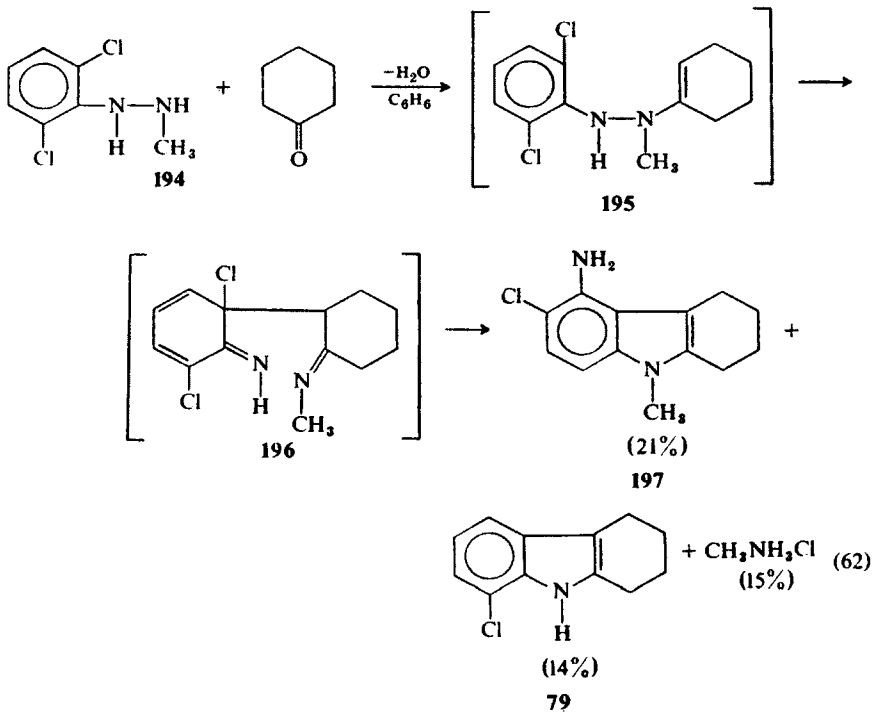


191



192 193

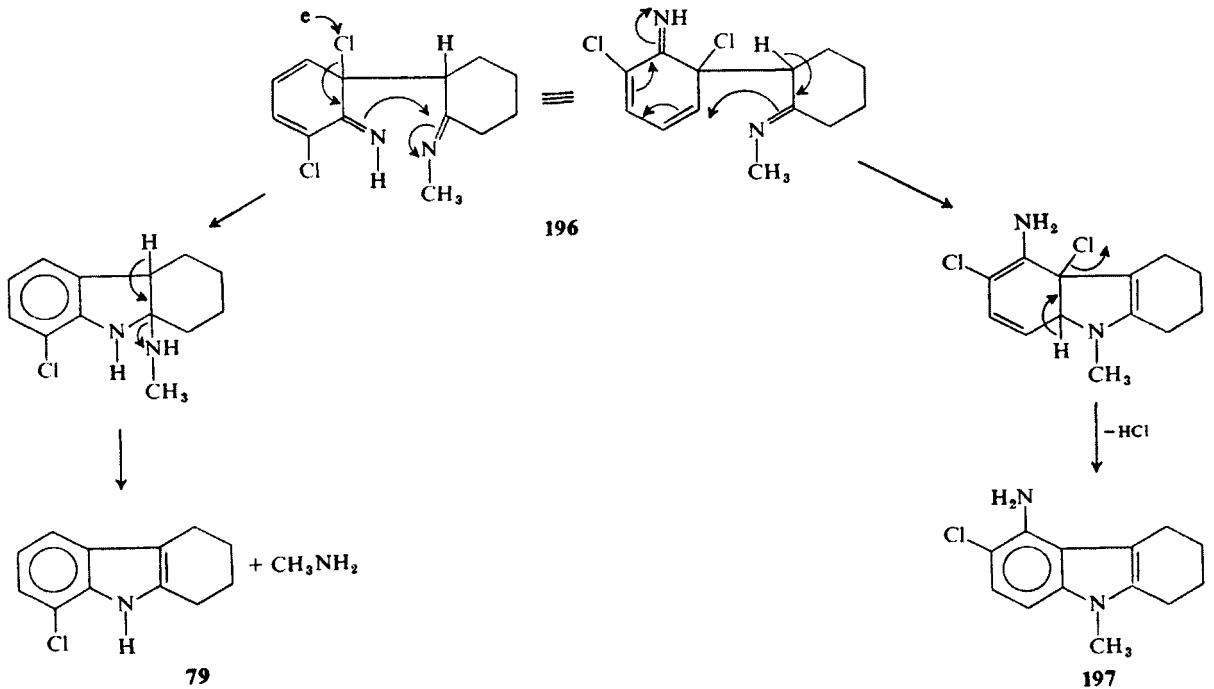
(61)



(62)

would compel direct formation of the enehydrazine **195**. Since Stage 1 of the Robinson sequence would thus be already completed and because Suvorov[184] had shown that acid catalysis was not necessary, though probably helpful, for Stage 2 of the Robinson scheme, it was anticipated that only very mild conditions would be required to form the dienone-imine **196** (cf. **129** and **190**). Under these mild conditions it might be possible to retain and isolate the dienone-imine **196**. A reaction did occur readily at room temperature, and water was obtained, but from the reaction mixture only three substances could be isolated in 21, 14, and 15% yield. These were, respectively, 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole (**197**), 8-chloro-1,2,3,4-tetrahydrocarbazole (**79**), and methylammonium chloride (Eq. 62). Neither the enehydrazine **195** nor the dienone-imine **196** could be obtained. The formation of **197** and **79** can be rationalized only if the intermediacy of the dienone-imine **196** is accepted. This is shown in Scheme 12.

The loss of halogen to form **79** was considered to be due to reduction by some (unidentified) readily oxidizable species in the reaction mixture. That the allylic halogen can be so lost had been shown in the preparation of 2-allyl-6-chlorophenol during the thermal rearrangement of allyl 2,6-dichlorophenyl ether in decalin[228] and by the isolation of 7-chloroindoles

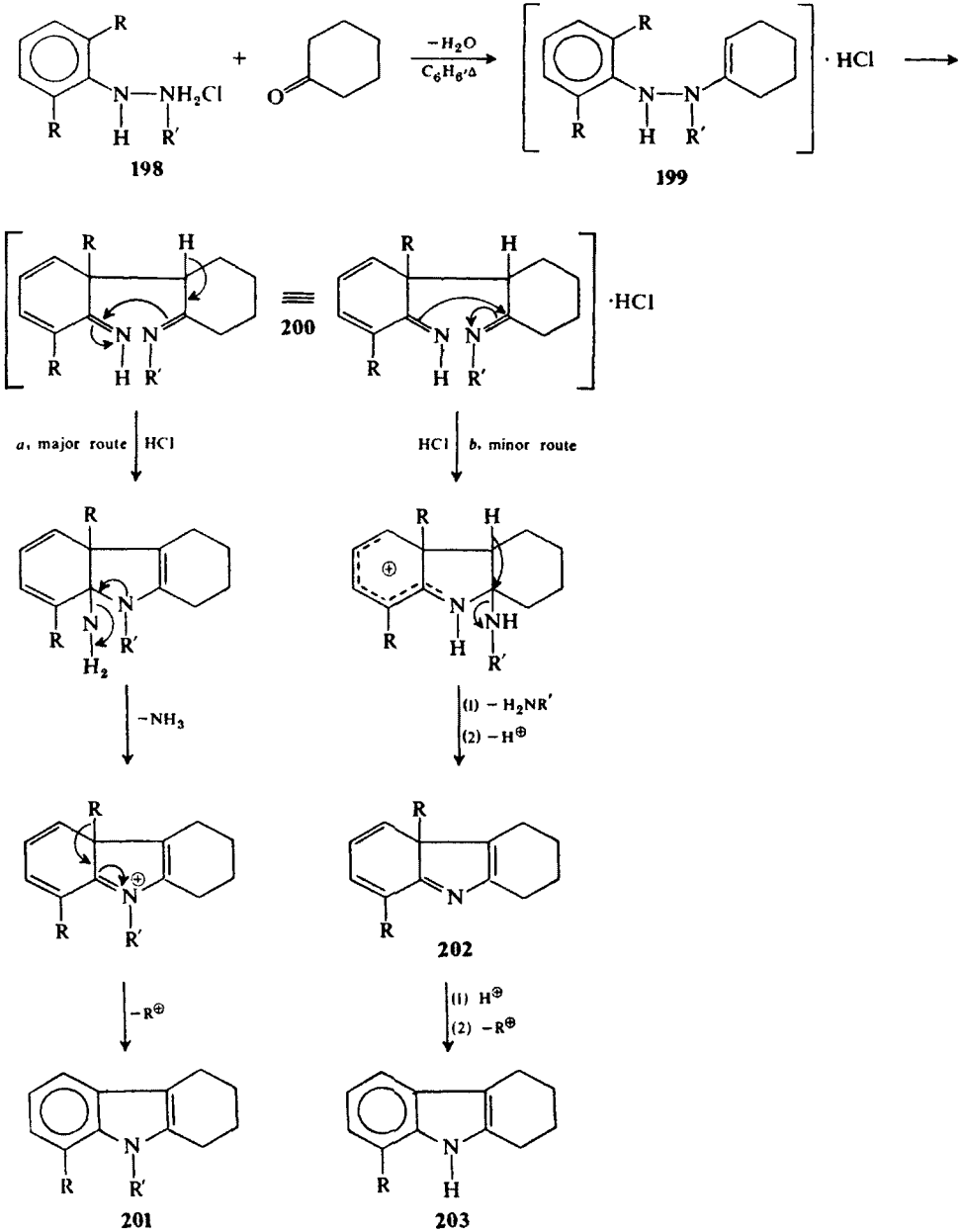

e
Cl
H
N
H
N
CH3
Cl
196
NH
Cl
H
N
CH3
H
NH
CH3
N
H
Cl
+ CH3NH2
79
NH2
Cl
Cl
H
N
CH3
-HCl
H2N
Cl
N
CH3
197

Scheme 12

from the stannous chloride-catalyzed cyclization of 2,6-dichlorophenylhydrazones.[229] The surprising ease of the conversion of the enehydrazine **195** to the dienone-imine **196** and then to products supports Suvorov's suggestion[184] that Stages 2 and 3 need not require acid catalysis. The formation of **197** shows clearly that the β-nitrogen can be retained in the pyrrole moiety of the indole structure. This reaction appears also to be the first case of a room temperature, nonacid-catalyzed Fischer reaction, at least in the first portion of the reaction.

Since the halogen substituent in *N'*-methyl-2,6-dichlorophenylhydrazine (**194**) was so easily lost when **194** reacted with cyclohexanone, this same reaction was extended to the *N'*-alkyl-2,6-dialkylphenylhydrazines **198**.[230] The use of the hydrochloric acid salts rather than the free hydrazines greatly reduced undesirable decomposition and gave a much cleaner reaction and better yields (Scheme 13).

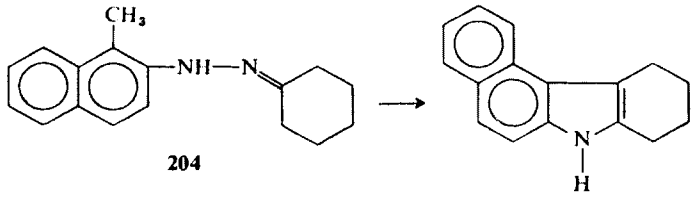
Here again, when the benzene solution was boiled, water was formed, indicative of condensation of **198** with cyclohexanone. However, no enehydrazine **199** nor dienone-imine **200** could be isolated. 8,9-Dialkyl-1,2,3,4-tetrahydrocarbazoles along with a considerable quantity of ammonium-chloride and a small amount ($\leqslant 6\%$) of alkylammonium chloride $R'NH_3Cl$ were obtained. It was shown that one of the two alkyl groups of the benzene ring was lost during the reaction. Its fate is unknown, but it was established that it did not provide the alkyl group on the nitrogen atom of **201** nor did it form the alkylammonium chloride. The results could be explained only by assuming the intermediacy of the dienone-imine **200** which reacted by the two competitive routes *a* and *b*. Route *a* should and did predominate because of the labile hydrogen atom which is lost to provide an enamine whose amino group will add to the ketimino moiety of the dienone-imine. Subsequent loss of the bridgehead amino group, particularly by protonation, leaves a resonance stabilized cation which is now a good "leaving group" and becomes neutral by loss of the cation $R^{\oplus}$. This is another example of preferential loss of the α-nitrogen atom of an arylhydrazine upon its conversion to an indole. The formation of the alkylammonium chloride $R'NH_3Cl$ can be explained by the less favorable attack of the dienone-imine nitrogen on the alternate imino group, the resonance stabilized cation being neutralized by elimination of a proton to give **202** which could, upon protonation, lose the alkyl group R and form the more stable 8-alkyl-1,2,3,4-tetrahydrocarbazole **203**. It is possible that the alkylammonium chloride could arise from decomposition of the arylhydrazine, since an arylamine in some cases has been obtained as a by-product from the indolization of arylhydrazones. It is known that phenyl hydrazine does decompose, when heated, to ammonia, benzene, N_2, and aniline. Since only unchanged 2,6-dialkylphenylhydrazine hydrochloride was recovered in a blank experiment containing no cyclohexanone, and no


R
N—NH2Cl
R
H
R′
198
+
O
−H2O
C6H6′Δ
R
N—N
R
H
R′
199
· HCl
200
·HCl
a, major route
HCl
HCl
b, minor route
−NH3
(1) − H2NR′
(2) −H⊕
202
(1) H⊕
(2) −R⊕
201
203

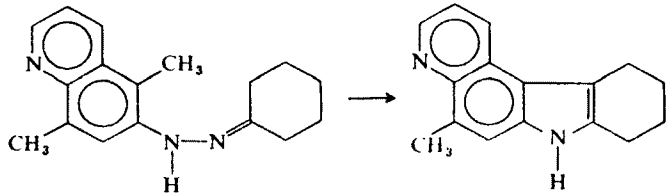
Scheme 13

ammonium chloride or alkylammonium chloride was detected, this alternative explanation for the formation of the alkylammonium chloride was considered to be unlikely.

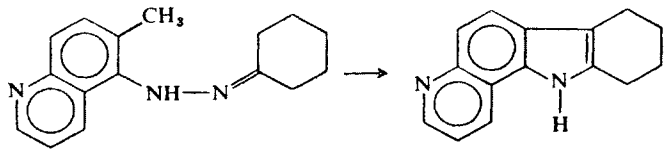
The loss of an alkyl group from the aromatic ring of an arylhydrazone has been noted before[231] in the indolization of cyclohexanone 1-methyl-2-naphthylhydrazone (**204**), cyclohexanone 5,8-dimethyl-6-quinolylhydrazone (**205**), and cyclohexanone 6-methyl-5-quinolylhydrazone (**206**) (Eqs. 63, 64, and 65).



204 (63)

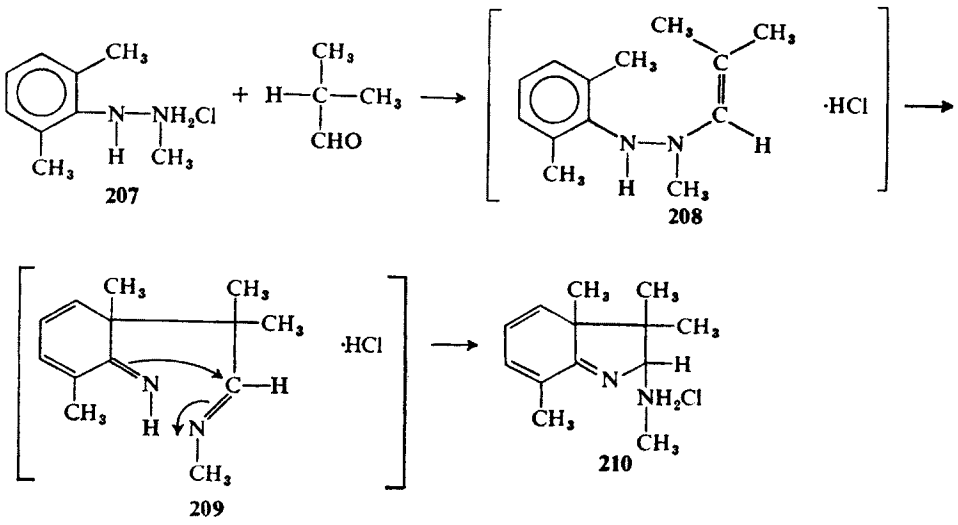


205 (64)



206 (65)

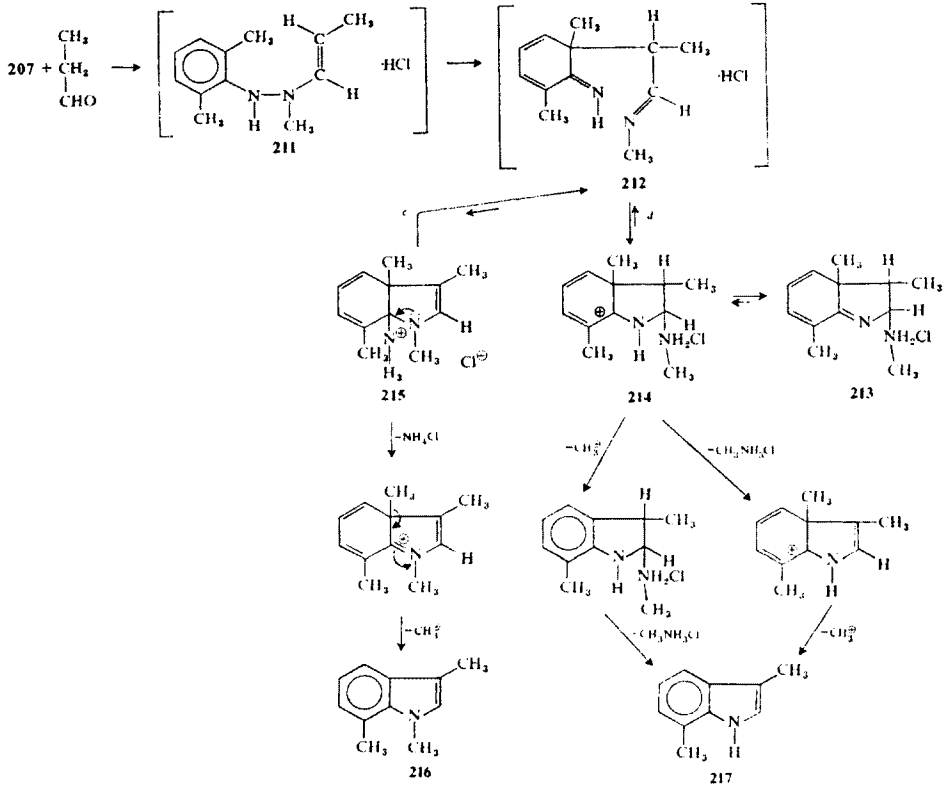
The work of Bajwa and Brown[232, 233] has provided conclusive evidence for the formation of a dienone-imine in the Fischer reaction. The reaction of *N'*-methyl-2,6-dimethylphenylhydrazine hydrochloride **207** with isobutyraldehyde in refluxing benzene[232] provided the hydrochloride of a dienone-imine **210** in 40% yield. Neither the enehydrazine **208** or the expected dienone-imine **209** could be obtained, although the isolation of **210** was good evidence that **209** had been formed (Scheme 14). It was expected that **209** would be sufficiently stable for isolation since there are no protons which by elimination could form an amino group which then would add to the imino double bond of the second nitrogen atom. However, that the dienone-imino nitrogen did in fact add to the aldimino moiety is no doubt due to the delocalization of the positive charge on the nitrogen throughout the conjugated triene system, and



Scheme 14

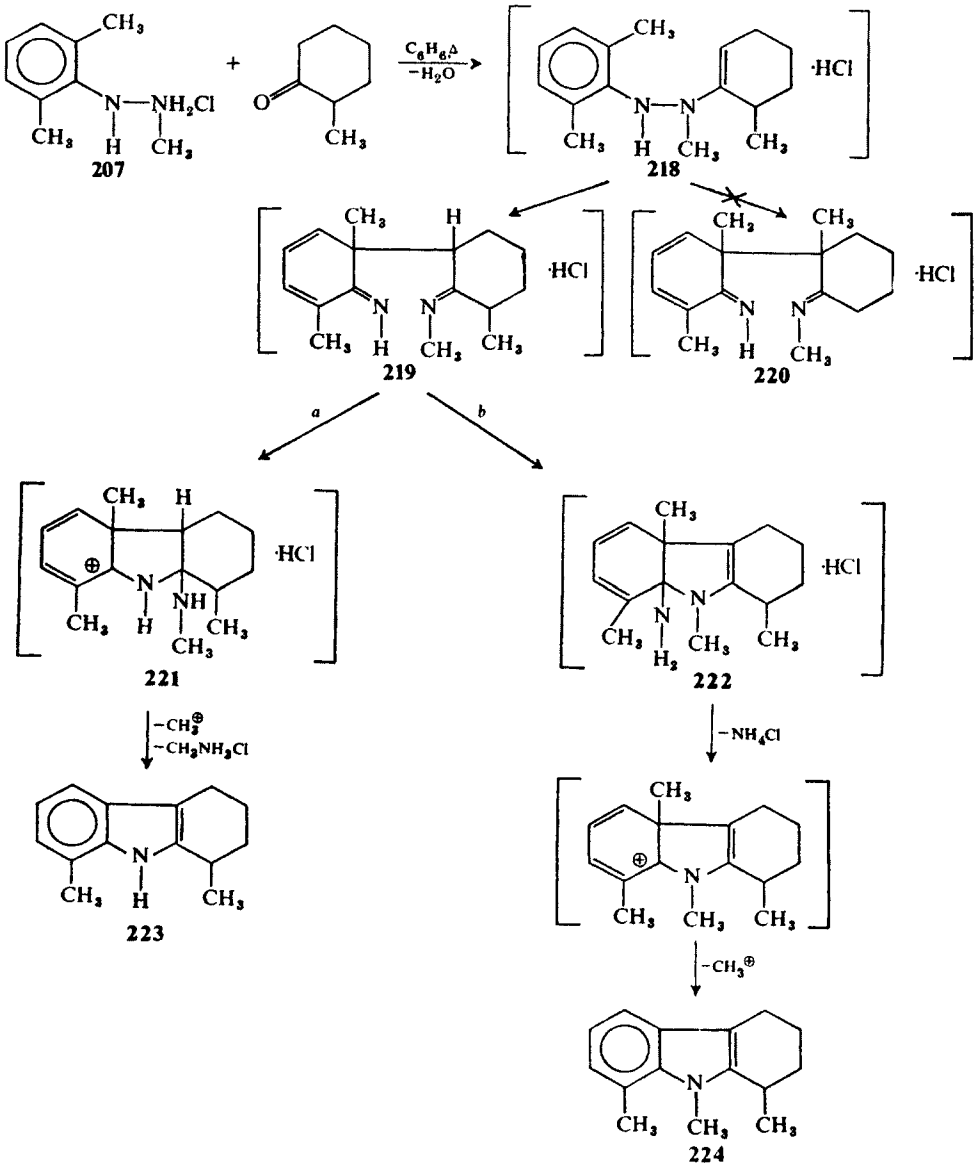
this is ultimately neutralized by elimination of the proton from the dienone-imino nitrogen. The isolation of **210** offers some support for the postulation that the small amount of alkylammonium chloride from the reaction of **198** with cyclohexanone[230] arises by the alternate Route *b* (see above) which is similar to that by which **210** is formed.

The reaction of **207** with propionaldehyde[233] under similar conditions gave, after 10–12 min of reaction time, a solid whose analytical and spectral data agreed with the dienone-imine structure **213**. When **213** was heated for an additional 20 hr a 3 : 1 mixture of ammonium chloride and methylammonium chloride was obtained along with a 36% yield (based on **213**) of 1,3,7-trimethyl indole (**216**). Infrared and nmr spectra of the crude residue left after removal of **216** showed strong evidence for the presence of 3,7-dimethyl-indole (**217**) but this could not be isolated (Scheme 15). The formation of both products **216** and **217** involves a loss of one of the methyl groups formerly attached to the aryl ring. Compound **217** is considered to arise from **213** by protonation followed by elimination of methylammonium chloride and the methyl cation by the path shown in Route *d*, whereas the formation of 1,3,7-trimethyl indole (**216**), the major product of the reaction, is considered to involve an equilibrium of the species **212–215**. The shift from **213** → **214** → **212** → **215** (Route *c*) occurs because there is more strain in Structure **215** than in Structures **213–214**. When heat is applied, **215** loses the amino group as ammonium chloride more readily than **214** loses methylammonium chloride or the methyl cation. This would account for the products obtained and would explain why the nitrogen atom adjacent to the aromatic ring is lost in preference to that more remote from the ring.



Scheme 15

From the reaction of **207** with 2-methylcyclohexanone in boiling benzene[234] there has been obtained from the tarry reaction mixture a 1:1 ratio of ammonium chloride and methylammonium chloride along with a 12% yield of 1,8,9-trimethyl-1,2,3,4-tetrahydrocarbazole (**224**) (Scheme 16). This compound **224** is believed to be formed by initial conversion of the ene-hydrazine **218** (nonisolable) to the dienone-imine **219** (nonisolable) which then can cyclize by the two routes indicated. Evidence for Route *b* has been obtained by the isolation of both ammonium chloride and **224**, a compound that crystallizes quite easily. The only evidence for Route *a*, and the formation of **223**, is the isolation of methylammonium chloride, which is not conclusive. It is unfortunate that attempts to isolate **223** were unsuccessful since it would have provided evidence that Route *a* is nearly as feasible as Route *b* (1:1 ratio of ammonium chloride and methylammonium chloride). Furthermore, it would have provided support for the view[233] that the steric strain developed in the initial cyclized products **221** and **222** due to the crowding about the amino or methylamino group is a prime factor which determines

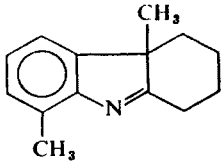


Scheme 16

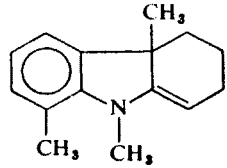
the direction of reaction (*a* or *b*) and which nitrogen atom is to be lost. The formation of **223** and **224** also involves loss of one of the methyl groups of the hydrazine **207**.

No evidence was obtained for the formation of the dienoneimine **220** that would ultimately provide a compound with a bridgehead methyl group of the

type **225** or **226**. It is known[175] that 2-methylcyclohexanone *o*-tolylhydrazone (**227**) upon indolization gives both 1,8-dimethyl-1,2,3,4-tetrahydrocarbazole

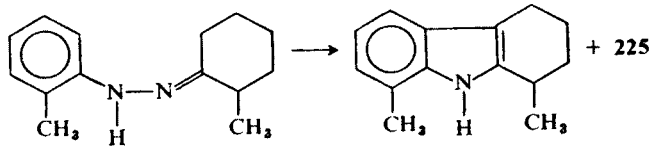


225



226

(**223**) and 8,11-dimethyl-1,2,3,4-tetrahydrocarbazolenine (**225**) (Eq. 66).

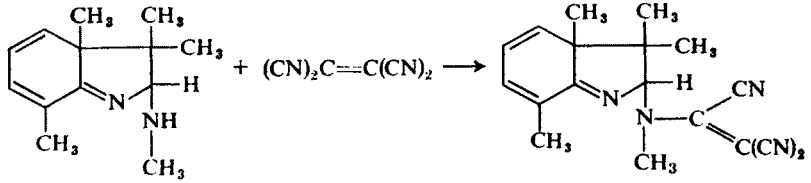


227 **223**

(66)

No compound such as **225** was isolable although it may have been present in the tarry reaction mixture. The fact that *N'*-methyl-2,6-dimethylphenylhydrazine hydrochloride (**207**) gave no reaction whatsoever with 2,6-dimethylcyclohexanone and was recovered in at least 90% yield indicates that both pairs of methyl groups situated in the 2,6-positions of both reactants prevented formation of the enehydrazine (cf. **218**), and if this is so, would support the view that **220** cannot be easily formed because of the opposing methyl groups.

The dienone-imine **210a** obtained from its hydrochloride **210** has been treated with the dienophile tetracyanoethylene[235] and gave compound **228** which resulted from the preferential reaction of the tetracyanoethylene with the secondary amino group, a type of reaction that is well-known[236] (Eq. 67).

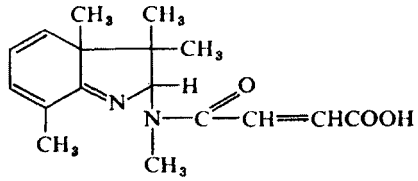


210a **228**

(67)

Evidence[235] indicates that maleic anhydride also reacts preferably with the amino group to give **229**. This reaction is of interest since it clearly points out that even if the dienone-imine **192** had formed as had been anticipated,[97]

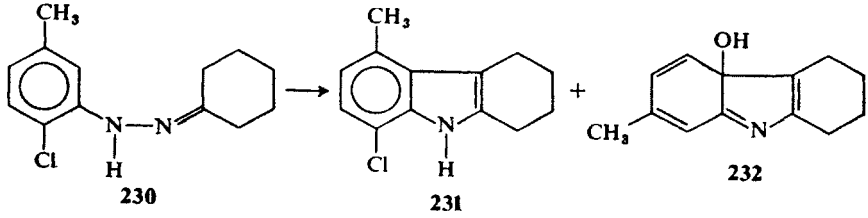
the maleic anhydride might react preferentially with the imino groups rather than undergo the Diels-Alder addition with the diene.



229

5. *Rearrangements which support the Robinson Mechanism*

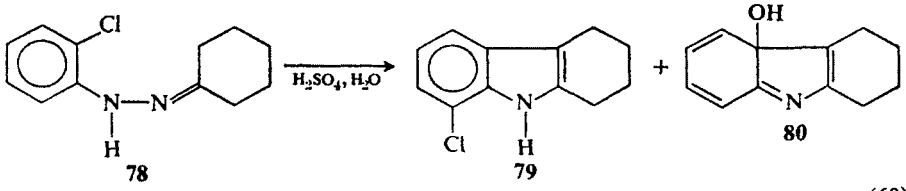
a. REARRANGEMENT OR DISPLACEMENT OF HALOGENS. Pausacker and Robinson[237] treated cyclohexanone 2-chloro-5-methylphenylhydrazone (**230**) with dilute sulfuric acid and obtained the expected material **231** along with a minor product whose structure was considered to be **232**, 12-hydroxy-7-methyl-1,2,3,4-tetrahydroisocarbazole (Eq. 68). Subsequently a number of



230 **231** **232**

(68)

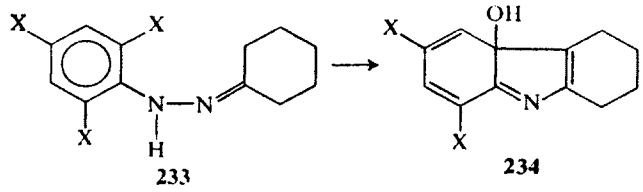
ortho-substituted phenylhydrazones were subjected to similar conditions[106] and it was found that cyclohexanone *o*-chlorophenylhydrazone (**78**) gave the "tetrahydroisocarbazole" **80** along with the major product **79** (Eq. 69), while cyclohexanone 2,4,6-trichloro- (and tribromo) phenylhydrazone



78 **79** **80**

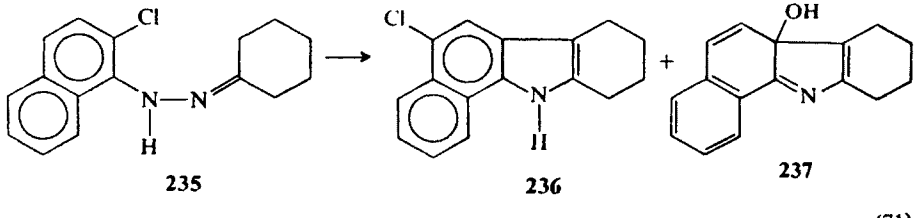
(69)

(**233**; X = Cl or Br) gave 6,8-dichloro(dibromo)-12-hydroxy-1,2,3,4-tetrahydroisocarbazole (**234**) (Eq. 70). *o*-Alkoxyphenylhydrazones gave similar results. A later paper[238] showed that cyclohexanone 2-chloro-1-naphthylhydrazone **235** in boiling glacial acetic acid produced the two

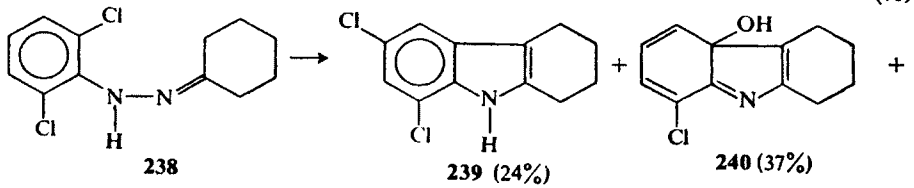


233 234 (70)

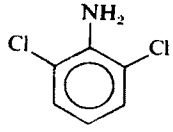
products 6-chloro-1,2,3,4-tetrahydro-7,8-benzocarbazole (**236**) and 1,2,3,4-tetrahydro-12-hydroxy-7,8-benzoisocarbazole (**237**) (Eq. 71). In addition, cyclohexanone 2,6-dichlorophenylhydrazone (**238**), treated with dilute aqueous sulfuric acid,[238] provided 6,8-dichloro-1,2,3,4-tetrahydrocarbazole (**239**), 8-chloro-12-hydroxy-1,2,3,4-tetrahydroisocarbazole (**240**) and 2,6-dichloroaniline (**241**) in the yields indicated (Eq. 72). It was subsequently



235 236 237 (71)



238 239 (24%) 240 (37%)

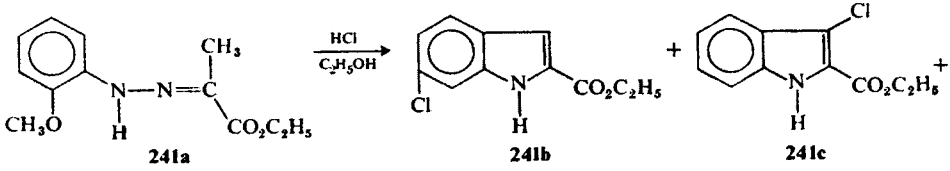


241 (5%) (72)

pointed out[114] that the by-product obtained from the cyclization of cyclohexanone *o*-chlorophenylhydrazone (**78**)[106] was not 12-hydroxy-1,2,3,4-tetrahydroisocarbazole (**80**) but really 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**81**). This discovery suggests that the structures of the other "tetrahydroisocarbazoles", e.g., **232**, **234**, and **237**,[106, 237, 238] require reexamination. The two products **236** and **239**[238] are interesting in that their formation requires a 1,3-migration of the halogen atom present in the original arylhydrazone.

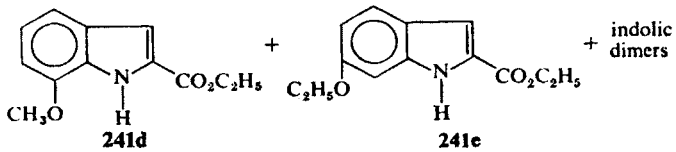
In this connection a recent report[238a] has shown that a repetition of the dilute sulfuric acid treatment of cyclohexanone *o*-methoxyphenylhydrazone[106] gave a 64% yield of 8-methoxy-1,2,3,4-tetrahydrocarbazole along with a 20% yield of a substance previously considered to be 12-methoxy-1,2,3,4-tetrahydroisocarbazole.[106] However, on the basis of elemental analysis and the parent peak of *m/e* 370 in the mass spectrum, the compound obtained in 20% yield is considered to be dimeric. Although its structure was not established, it certainly was not the structure 12-methoxy-1,2,3,4-tetrahydroisocarbazole previously suggested.[106] If the cyclization was carried out in ethanolic hydrogen chloride, only a 9% yield of the expected compound 8-methoxy-1,2,3,4-tetrahydrocarbazole was obtained, whereas the "dimeric substance" was isolated in 28% yield.[238a]

The same report[238a] showed that the *syn* and *trans* isomers of ethyl pyruvate *o*-methoxyphenylhydrazone (**241a**) heated in refluxing saturated ethanolic hydrogen chloride gave a mixture of indolic material containing ethyl 6-chloroindole-2-carboxylate (**241b**) as the main product (36%) along with quite minor amounts of ethyl 3-chloroindole-2-carboxylate (**241c**) and the expected ethyl 7-methoxyindole-2-carboxylate (**241d**) (Eq. 72a). Indolic



241a 241b 241c

(72a)

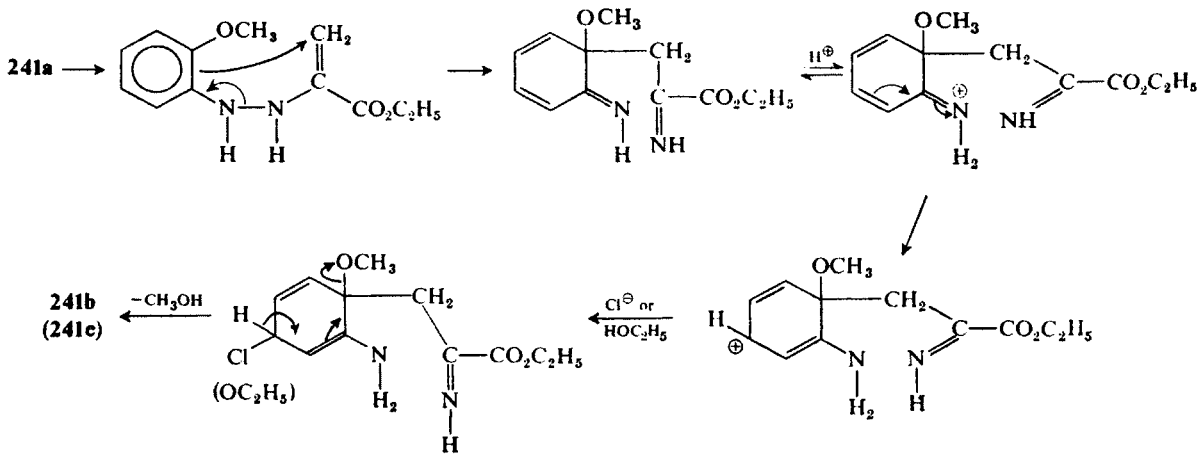


241d 241e

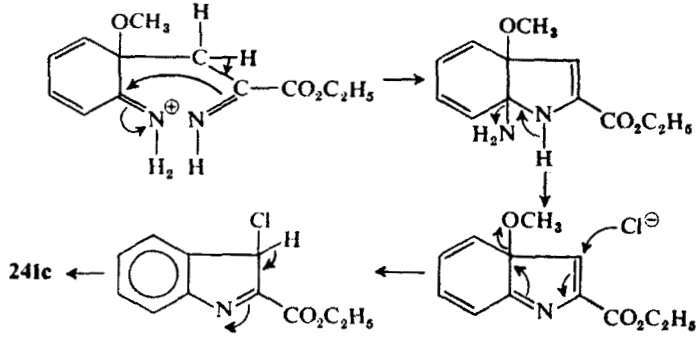
dimers, as well as a substance considered on the basis of mass spectral evidence to be ethyl 6-ethoxyindole-2-carboxylate (**241e**), were also found to be present in the reaction mixture. A similar reaction of **241a** in 3 *N* ethanolic hydrogen chloride provided **241b**, **241d**, and **241e** in yields of 18.4, 15.8, and 3.8%, respectively.[238b] If alcoholic sulfuric acid was used as the cyclizing medium,[238b] then only **241d** (12.8%) and **241e** (2.0%) along with a trace of ethyl indole-2-carboxylate were obtained.

The formation of **241b** and **241e** was considered to occur[238a, 238b] by a sequence of reactions shown in Scheme 16a while **241c** was thought to be formed by a route such as that in Scheme 16b.

The indolization of 2,6-dichlorophenylhydrazones with zinc chloride at

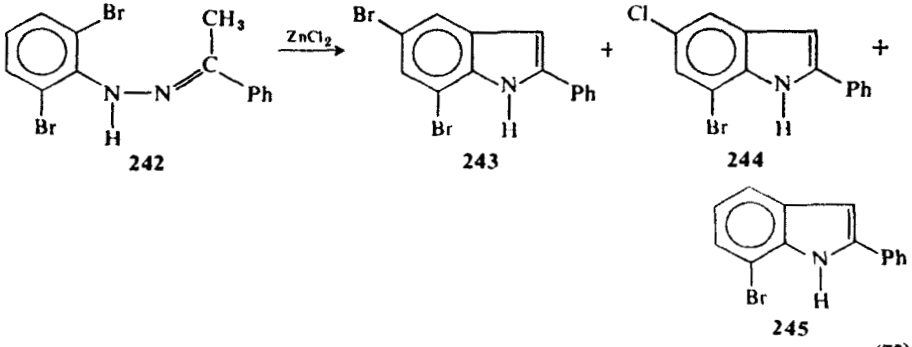

241a
OCH3
CH2
CO2C2H5
H
H
241b
(241c)
−CH3OH
Cl
(OC2H5)
Cl⊖ or
HOC2H5
NH2
NH

Scheme 16a

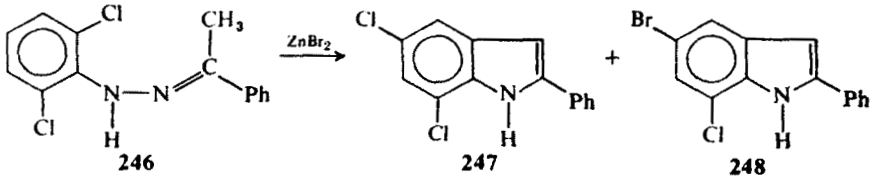


Scheme 16b

240–260° with or without a solvent was found to provide 5,7-dichloroindoles in very small yield.[171] This 1,3-migration of the halogen atom was found to be an intramolecular transfer and to occur at some stage *during* indole formation.[171] When it was found[239] that zinc chloride indolization of acetophenone 2,6-dibromophenylhydrazone (**242**) gave both 5,7-dibromo-2-phenylindole (**243**) and 7-bromo-5-chloro-2-phenylindole (**244**) (along with a very small amount of 7-bromo-2-phenyl indole **245**) (Eq. 73) and that zinc bromide



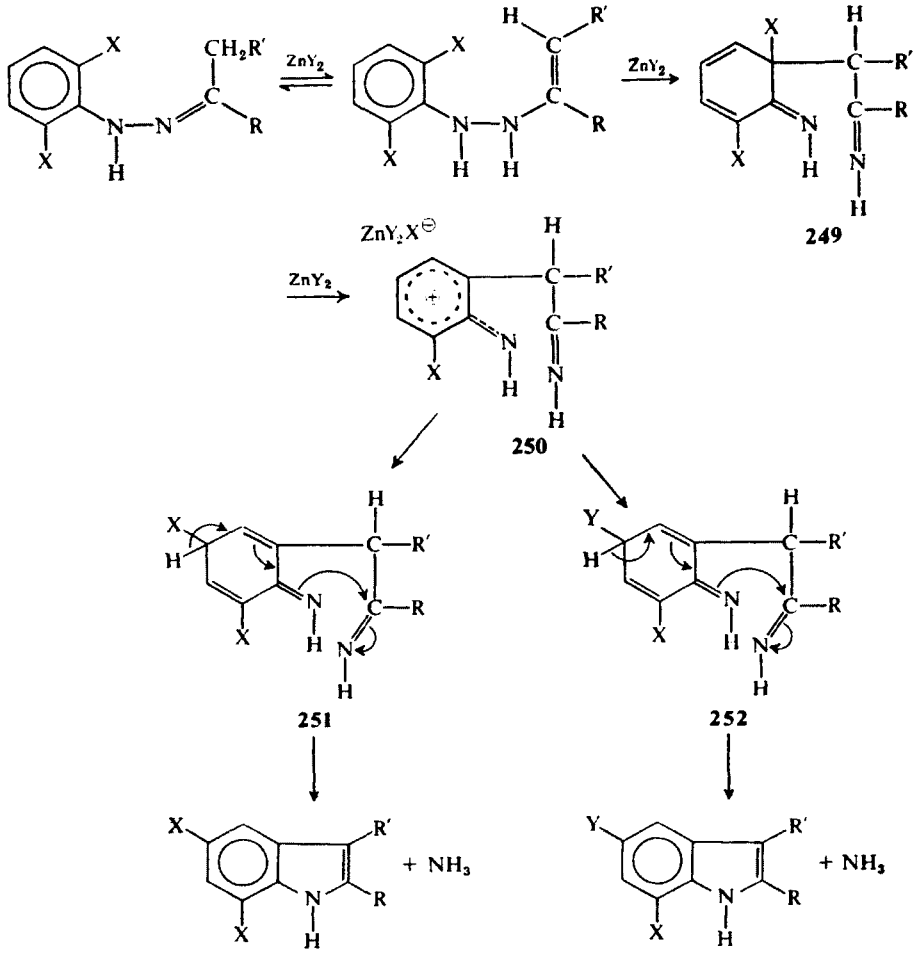
(73)



(74)

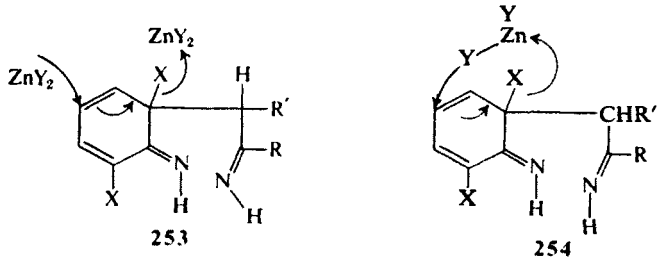
indolization of acetophenone 2,6-dichlorophenylhydrazone (**246**) provided both 5,7-dichloro-2-phenylindole (**247**) and 5-bromo-7-chloro-2-phenylindole (**248**) (Eq. 74), it was clear that the view that 1,3-halogen migration occurred by means of a "positive" halogen[229] was not compatible with the relative oxidation potentials of bromide and chloride ions.[239] The mechanism

advanced[239] to account for the above observations agrees fully with the Robinson mechanism and involves the concept of an intermediate dienone-imine **249** in which the allylic halogen, X, is removed as a negative species by the catalyst ZnY_2 to produce a transient cation **250** (Scheme 17). This cation



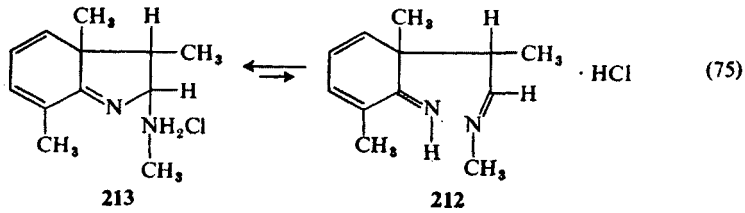
Scheme 17

250 is then subject to nucleophilic attack by the complex $(ZnY_2X)^{\ominus}$ to provide **251** and/or **252** which subsequently cyclize and aromatize to the indoles. The details of the conversion **249** → **250** → **251** (**252**) are not yet clear since the halogen transfer or migration may occur alternatively by (*1*) an S_Ni transformation in which the anionic species is separated to a greater extent from the cation in the transition state, (*2*) an S_N2' attack, **253**, or (*3*) a cyclic transition state **254**. Such detail may well vary depending upon the

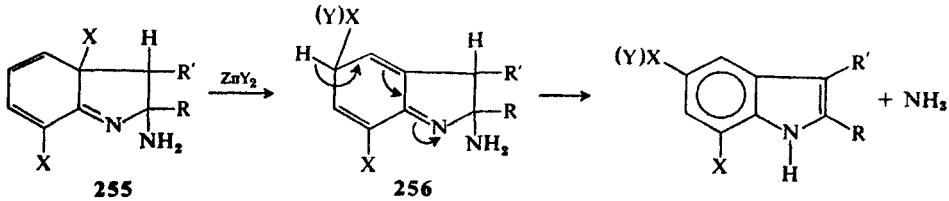


253 254

circumstances. Since the dienone-imine **213** has been isolated, and in order to account for the products observed, **213** is believed to have the ability to isomerize to **212**[233] (Eq. 75), it may well be that an intermediate of the type **255** should be considered since **255** could undergo similar halogen transfer to **256** which then forms the products observed (Eq. 76).



213 212 (75)



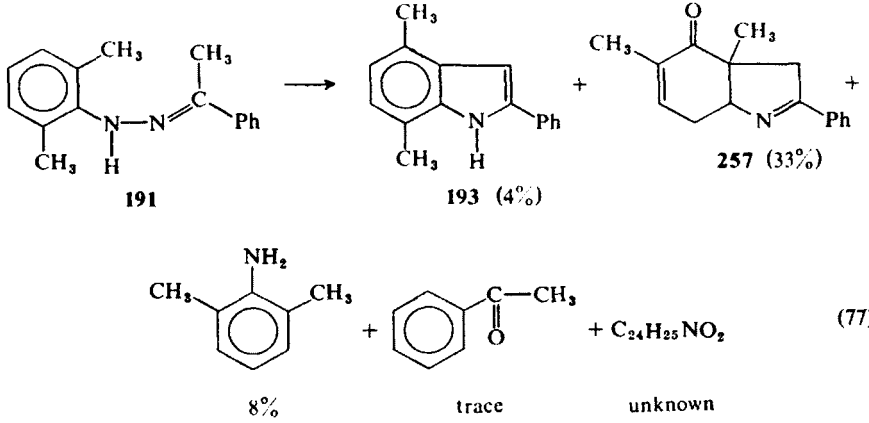
255 256 (76)

As was pointed out,[239] the mechanism developed by Carlin and Larson[239] accommodates the formation of 6-hydroxy-1,2,3,4-tetrahydrocarbazole (**81**) during the indolization of cyclohexanone *o*-chlorophenylhydrazone (**78**)[106] since any anionic species including solvent could attack, competitively, the cationic species **250**.

The formation of the small amount of 7-bromo-2-phenylindole (**245**) from the indolization of acetophenone 2,6-dibromophenylhydrazone (**242**)[239] still requires explanation, though it could arise from reduction by a readily oxidizable species present in the reaction mixture as was postulated for the formation of 8-chloro-1,2,3,4-tetrahydrocarbazole (**79**) from the reaction of *N'*-methyl-2,6-dichlorophenylhydrazine with cyclohexanone[227] via reductive elimination of an "allylic" halogen. However, this explanation seems to be unlikely to account for the isolation, in 4% yield, of 2-phenylindole from the

zinc chloride indolization of 4-chloroacetophenone 2,6-dichlorophenylhydrazone.[240]

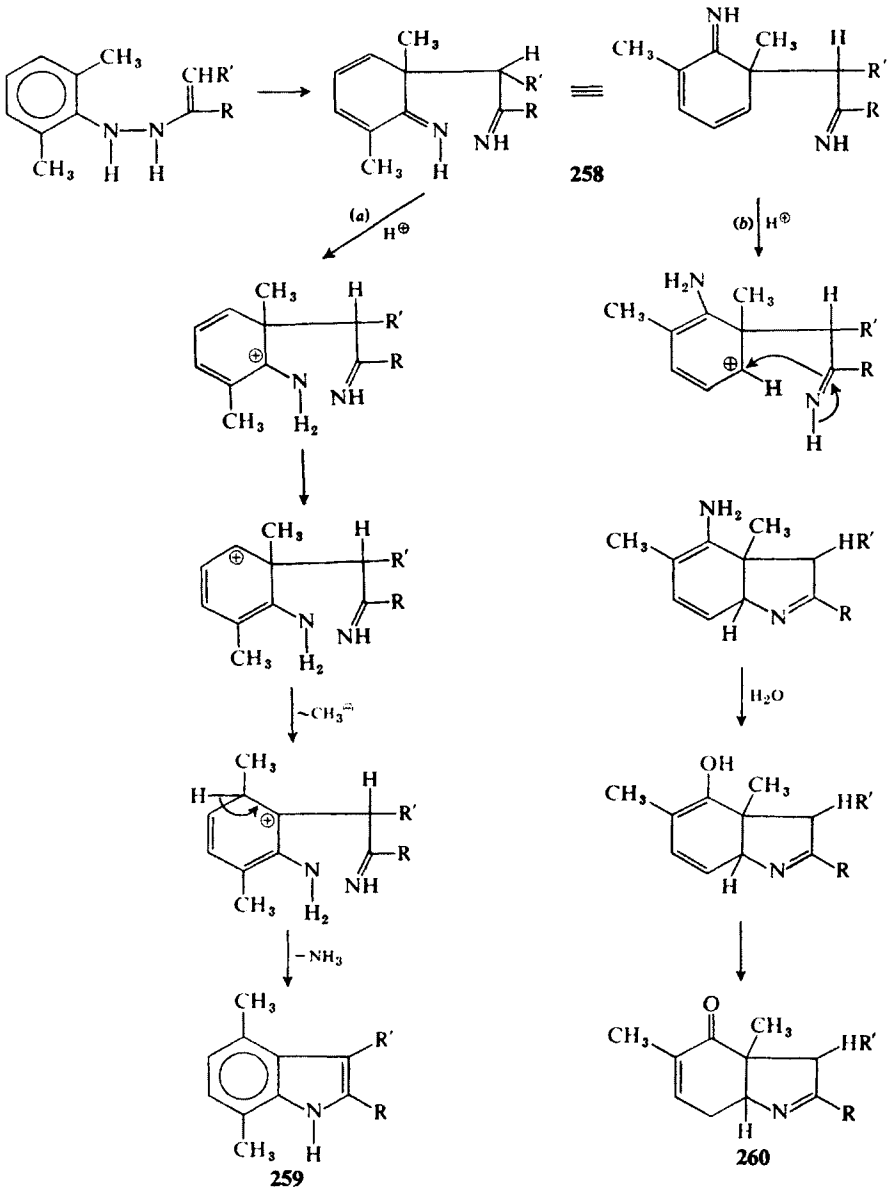
b. Rearrangements of Alkyl Groups. That indolization of ethyl pyruvate 2,6-dimethylphenylhydrazone (**191**) when heated with zinc chloride gave a very small yield of ethyl 4,7-dimethylindole-2-carboxylate (**193**),[97] a product that could only have arisen from migration of a methyl group, was corroborated by the results obtained when acetophenone 2,6-dimethylphenylhydrazone was heated with zinc chloride in nitrobenzene[34, 241] (Eq. 77). Four of the 5 products, isolated in the yields indicated, were identified. The formation of **193** and 3*a*,4,7,7*a*-tetrahydro-2-phenyl-3*a*,5-dimethyl(3*H*)pseudoindolone-4 (**257**), the major product, was explained on the basis of the same



(77)

general mechanism developed to explain the migration or substitution of halogen atoms.[239] The dienone-imine intermediate **258** can react either by Route *a* involving a 1,2-shift of the methyl group to produce **259** or by Route *b* to produce **260** (Scheme 18). That formation of **257** involves retention of the β-nitrogen atom of the 2,6-dimethylphenylhydrazine has been demonstrated[242] by the fact that acetophenone β-^{15}N-2,6-dimethylphenylhydrazone (**191**) (β-^{15}N) when indolized gave **260** (R′ = H, R = Ph) containing full ^{15}N activity while only a trace of ^{15}N activity was found in **259** (R′ = H, R = Ph).

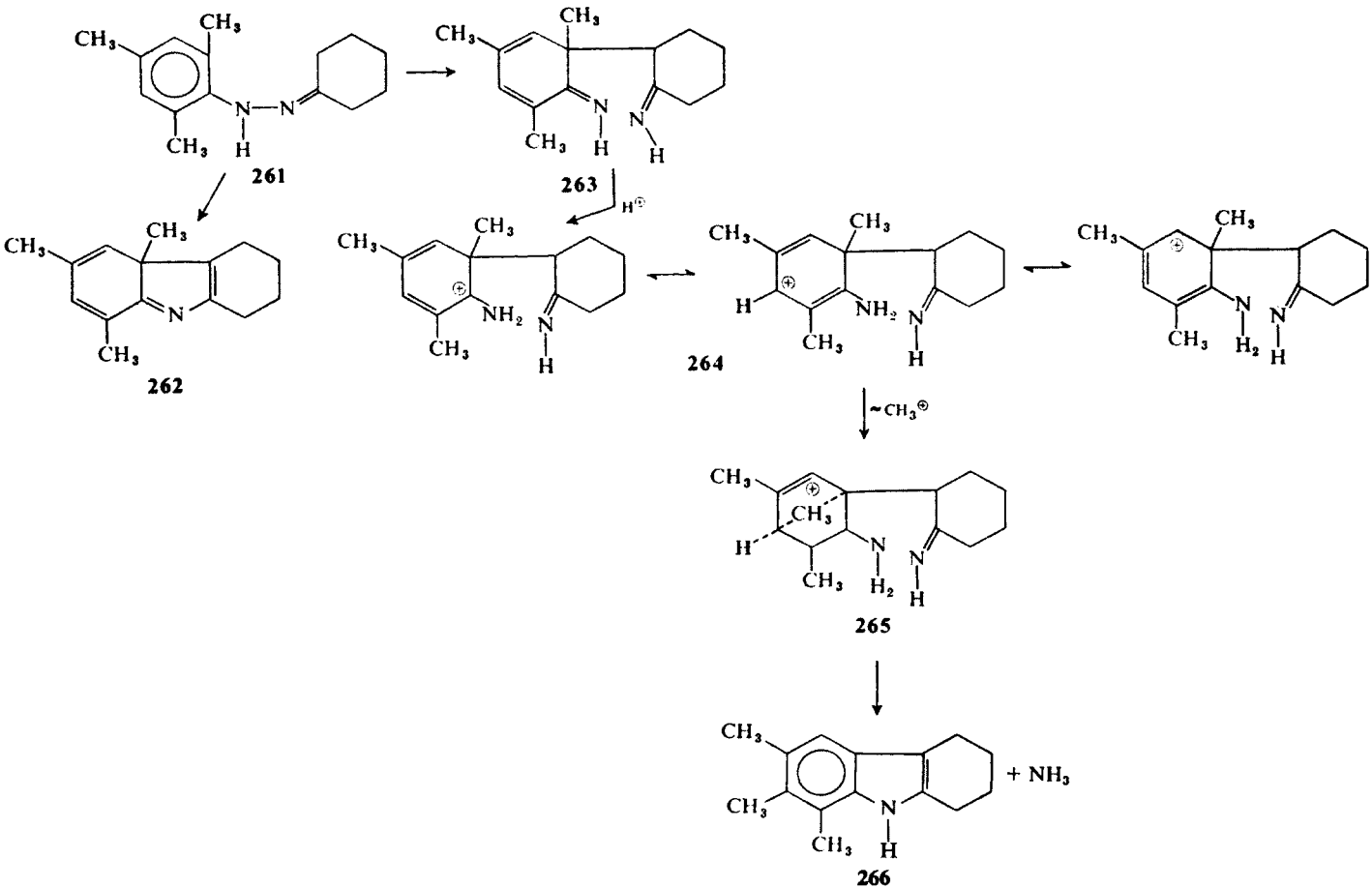
Contrary to the conclusion that indolization of cyclohexanone mesitylhydrazone (**261**) in boiling acetic acid provides 6,8,12-trimethyl-1,2,3,4-tetrahydroisocarbazole (**262**),[238] it has now been found[35, 243] that the product is in fact 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole (**266**). The formation of **266** can be explained by the assumption of the dienone-imine intermediate **263**, which under the influence of an acid catalyst can form the resonance



Scheme 18

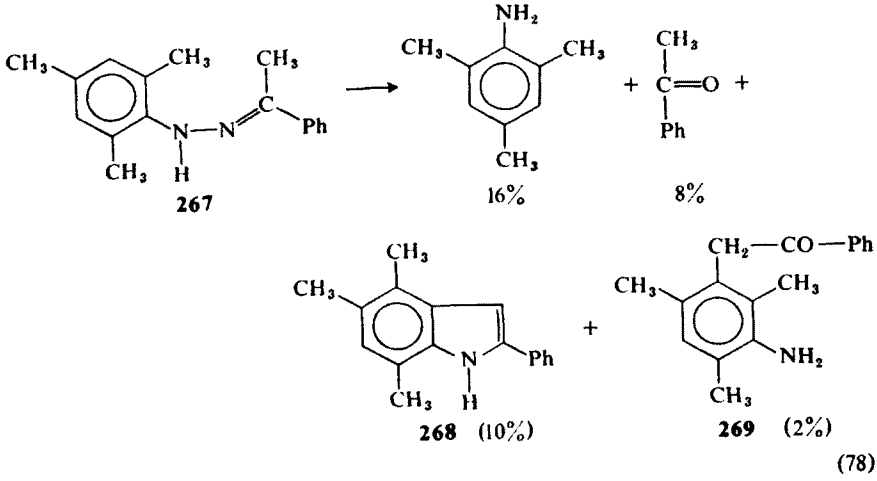
stabilized carbonium ion species **264** and thus undergo a series of three 1,2-methyl shifts or, preferably, one 1,4-methyl migration, **265** to form **266** (Scheme 19).

Carlin and Harrison[244] have provided evidence that groups other than methyl will also undergo 1,2- or possibly 1,4-migration. Acetophenone

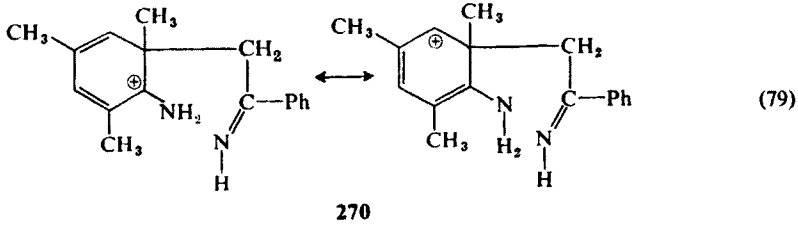


Scheme 19

mesitylhydrazone (**267**) heated in nitrobenzene with zinc chloride gave four products: mesidine, acetophenone, 4,5,7-trimethyl-2-phenylindole (**268**), and 3-phenacylmesidine (**269**) (Eq. 78). Again the two products **268** and **269**

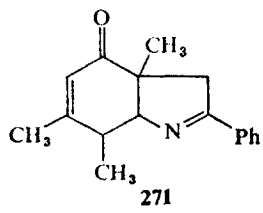


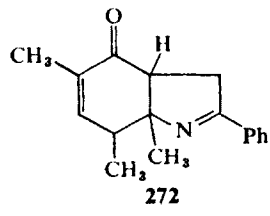
(78)

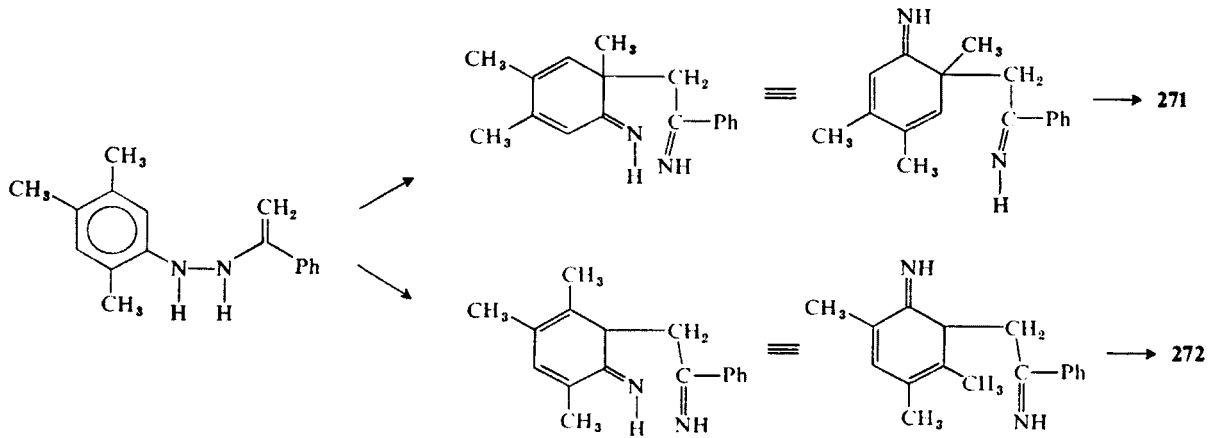


(79)

can be considered to occur as the result of a 1,2-methyl shift and a 1,2- (or probably 1,4-) shift of a phenacylimino group in the cationic diene structure **270** (Eq. 79). In the preparation of authentic **268** from the indolization of acetophenone 2,4,5-trimethylphenylhydrazone, there was obtained a by-product whose structure is considered to be either **271** or **272**[244] because of the similarity of the ir and uv spectra with those of **257**.[34, 241] These compounds could arise via the two possible dienone-imine intermediates as shown in Scheme 20.

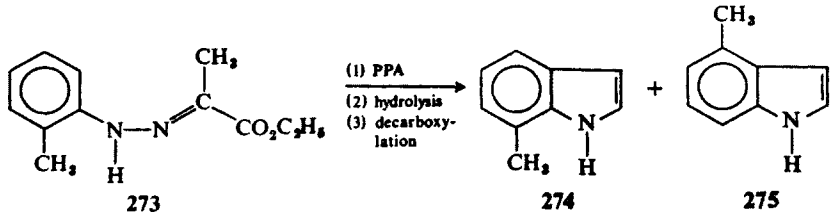






Scheme 20

The reactions described above indicate that the migration of an alkyl group is likely to occur during indolization of arylhydrazones containing alkyl substituents in both the 2 and 6 positions of the aromatic ring. However, evidence now available[48] shows that a 1,2-methyl shift is possible if only one *ortho* position is so substituted. The cyclization of ethyl pyruvate *o*-methylphenylhydrazone (**273**) with polyphosphoric acid provides some 4-methylindole (**275**) along with the main product 7-methylindole (**274**) (Eq. 80).

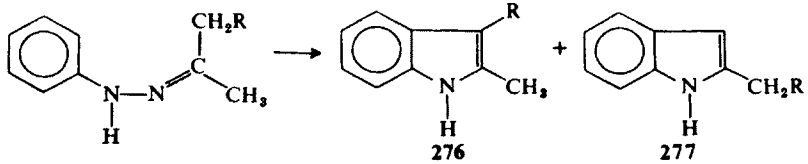


(80)

6. *The Direction of Indolization*

a. Arylhydrazones of Unsymmetrical Ketones. (1). *Dialkyl Ketones.*

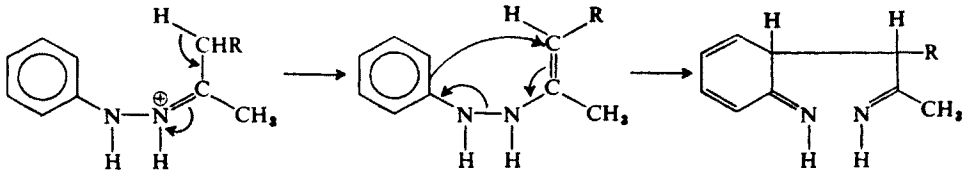
The indolization of alkyl methyl ketone arylhydrazones can give two indoles, **276** and **277** (Eq. 81). Two reports have appeared[23, 245] in which ethyl methyl ketone phenylhydrazone has produced 2-ethylindole (**277**, R = CH_3)



(81)

along with the major product **276** (R = CH_3). However, in nearly every other case of an unsymmetrical alkylmethyl or arylmethyl methyl ketone arylhydrazone the only product obtained was the 2-methylindole **276**. The latter observation has applied to the arylhydrazones of such ketones as ethyl methyl ketone,[89, 115, 123, 192, 246] methyl *n*-propyl ketone,[98, 247] benzyl methyl ketone,[246] methyl β-phenylethyl ketone,[26, 93] methyl alkylthiomethyl ketones,[105] and methyl neopentyl ketone.[96] The methylene group of the longer alkyl chain reacts exclusively in preference to the methyl group.[9, 89, 118, 120, 248, 249] The rationale for this behavior appears to involve the ability of the substituent R to favor loss of the proton from the adjacent methylene group to form the enehydrazine and/or to stabilize the incipient carbonium ion formation at the R-substituted carbon of the olefinic bond in **278** leading to the formation of

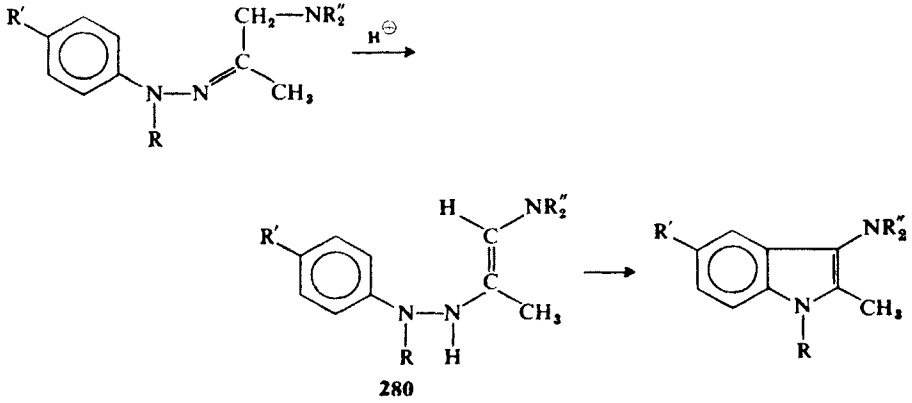
the new C—C bond of the dienoneimine **279** (Stage 2 of the Robinson mechanism)[9] (Eq. 82). The indolization of the *N*-benzyl- and 4-chlorobenzyl-



278 **279**

(82)

phenylhydrazones of methyl dialkylaminomethyl ketones produces only the 2-methyl ketones[250] in agreement with the general finding stated above and also with the view that the preferred enehydrazine **280** is that in which the incipient carbonium ion formation can be best stabilized, in this case by conjugation with the electron pair of the adjacent amino nitrogen[10] (Eq. 83).



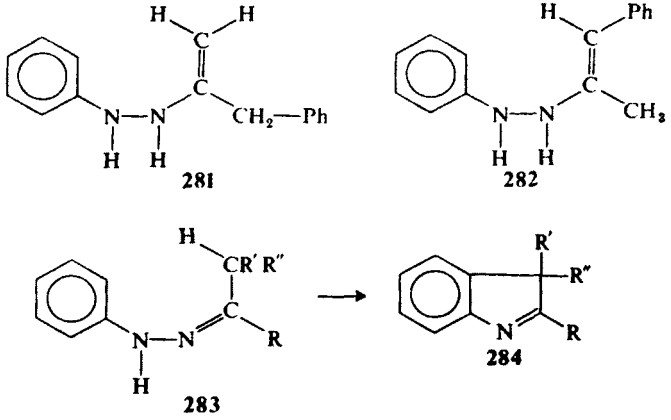
280

(83)

It is interesting that acetone phenylhydrazone could not be indolized by Amberlite IR-120[147] and acetophenone phenylhydrazone failed to cyclize with PPE.[155, 157] Both arylhydrazones can be cyclized by more vigorous catalysts. Gray and Archer[251] have noted the markedly greater stability of the phenylhydrazones of methyl as compared with methylene ketones and suggest that this could be ascribed to the relative stabilities of the respective carbonium ions.

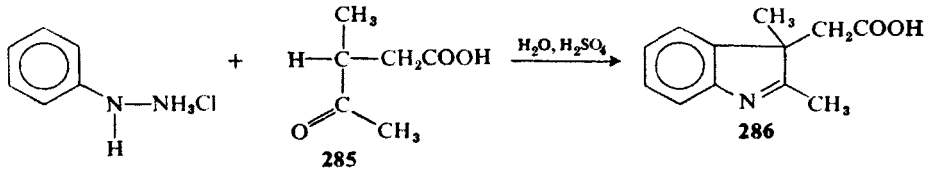
Recent work by Buu-Hoi et al.[91] has shown that the indolization of benzyl methyl ketone phenylhydrazone (**104**) with PPA catalyst provides 2-benzylindole (**106**) as the chief product, along with some of the isomeric 2-methyl-3 phenylindole (**105**), whereas only **105** (86% yield) is obtained if hydrogen chloride, zinc chloride, or boron trifluoride is used as catalyst. This is

unexpected on the basis of the relative stabilities of the two possible enehydrazine intermediates **281** and **282**. Whether PPA generally favors C—C bond formation involving the methyl rather than the methylene group of unsymmetrical alkyl methyl ketones or whether this is so only in the case of benzyl methyl ketone was not determined.[91]



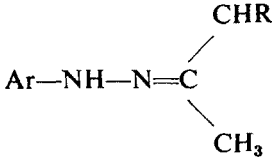
(84)

Arylhydrazones of methyl *sec*-alkyl ketones such as methyl isopropyl ketone (**283**; R, R′, R″ = CH_3) cyclize to give exclusively the 2-methylindolenines (**284**; R, R′, R″ = CH_3) (Eq. 84). This directive effect has been used to prepare 2,3-dimethyl-3*H*-indoleacetic acid (**286**) from 3-methyllevulinic acid (**285**)[252] (Eq. 85).



(85)

Arylhydrazones of dialkylketones in which neither of the alkyl groups are methyl can cyclize in both directions. Some general rules governing the direction of indolization of dialkyl ketones were stated as early as 1902 by Plancher and Bonavia.[253] (1) Methyl ketone arylhydrazones of the type

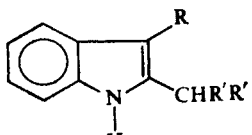


(R, R′ ≠ H) give only the corresponding 2-methylindolenine (**284**, R, R′, R″ = CH_3).[254–256] (2) Methyl ketone

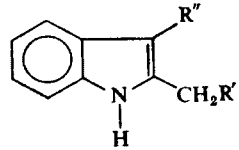
arylhydrazones of the type Ar—NH—N=C(CH$_2$R)(CH$_3$) give only the 2-methyl-3R-substituted indoles. A few exceptions to this general rule have been noted above. (3) Dialkyl ketone arylhydrazones of the type

C_6H_5—NH—N=C(CHR′R″)(CH$_2$R)

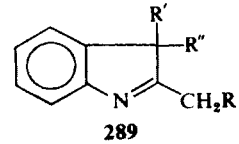
give both the indoles **287** and **288** (if R′ = H) or **289** instead of **288** if R′, R″ ≠ H.



287

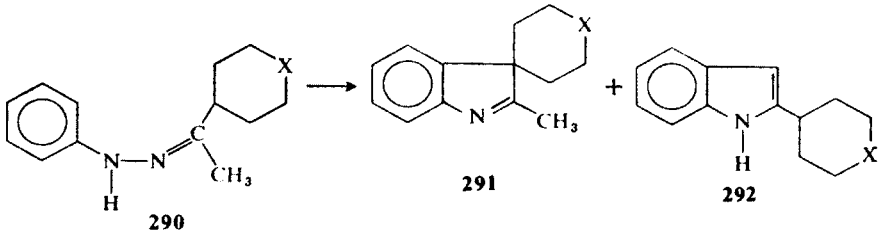


288



289

Exceptions to Rule (*1*) have appeared. Whereas indolization of cyclohexyl methyl ketone phenylhydrazone (**290**, X = CH$_2$) with glacial acetic acid[257] gave only the indolenine, 1-cyclohexane-3-(2-methylindolenine)spiran (**291**; X = CH$_2$), Lyle and Skarlos[158] obtained the indolenine **291** (X = N—CH$_3$

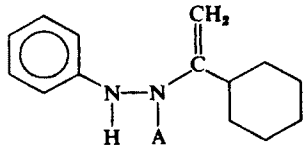


290 **291** **292**

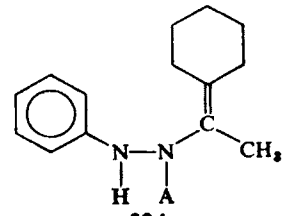
(86)

or CH$_2$) from the hydrazone **290** (X = N—CH$_3$ or CH$_2$) with zinc chloride or acetic acid, *but with PPA* obtained predominantly the 2-substituted indoles **292** (X = N—CH$_3$ or CH$_2$) along with a small amount of the isomer **291** (X = N—CH$_3$ or CH$_2$) (Eq. 86). This is in agreement with Buu-Hoi's finding[91] that PPA indolizes benzyl methyl ketone phenylhydrazone **104** to form mainly the 2-benzylindole **106**. Lyle and Skarlos explained their results on the basis of a steric interaction between the cyclohexyl ring and the "size" of the Acid A catalyst attached to the β-nitrogen of the enehydrazine intermediate. The small "size" of the (proton from) PPA provides little

interference with the cyclohexyl ring in the transition state and thus permits the enehydrazine **293** to be in a preferred position for reaction, whereas if Acid A is large, as in the case of zinc chloride or acetic acid (here the whole molecule of acetic acid is considered to be involved), the enehydrazine **293** would be sterically less favored and the alternate enehydrazine **294** which is also formed would be in a more favorable position to react.

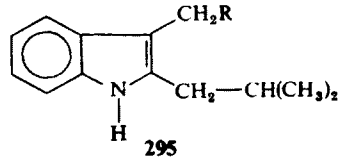


293



294

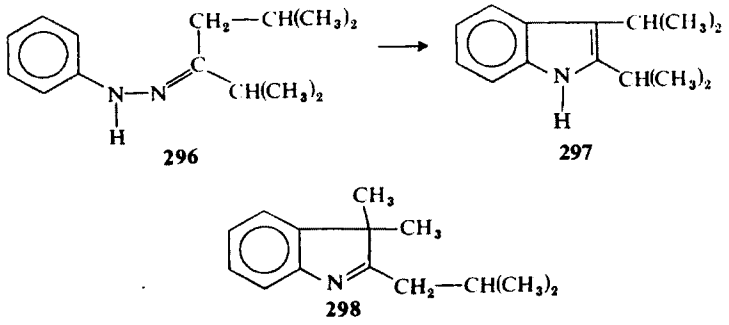
Some general studies have been made concerning the direction of cyclization of arylhydrazones of the type indicated in Rule (*3*).[26, 248, 258] Although indolization of ethyl *n*-propyl ketone phenylhydrazone should give the two products 2,3-diethylindole and 3-methyl-2-*n*-propylindole, only *one* product was apparently obtained when a catalytic amount of cuprous chloride was employed.[258] The structure of this product was not clarified. Cuprous chloride (0.1 g) converted the phenylhydrazone and *p*-tolylhydrazone of benzyl ethyl ketone exclusively to 2-benzyl-3-methylindole and 2-benzyl-3,5-dimethylindole, respectively.[26] Fischer cyclization with zinc chloride gave both possible products from the phenylhydrazones of ethyl *n*-propyl ketone and ethyl *n*-hexyl ketone,[248] whereas the same cyclizing conditions were considered to provide only one product **295** (R = H) and **295** (R = CH_3), respectively,



295

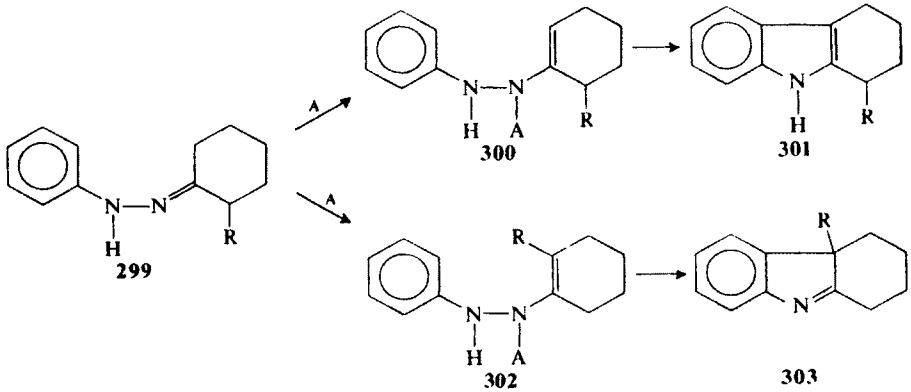
from the phenylhydrazones of isobutyl ethyl ketone and isobutyl *n*-propyl ketone.[248] The zinc chloride-catalyzed indolization of isobutyl isopropyl ketone phenylhydrazone (**296**) is reported to produce only 2,3-diisopropylindole (**297**) and none of the 2-isobutyl-3,3-dimethyl-3*H*-indole (**298**) (Eq. 87). It is clear that this general area requires additional and careful study with the aid of modern experimental techniques to separate products and establish structures.

(2). *Alicyclic Ketones.* The arylhydrazones of unsymmetrical alicyclic ketones can also indolize in two directions.[9, 10] Usually both isomers are



(87)

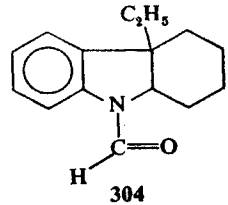
found, but in some cases only one has been obtained. Here also, the direction of pyrrole ring formation is influenced by the type of catalyst used. It has already been pointed out that aqueous acetic acid will convert **299** (R = CH_3, cf. **101**) to a mixture of **301** (R = CH_3, cf. **102**) and **303** (R = CH_3, cf. **103**) in which the carbazolenine **303** largely predominates, whereas aqueous or alcoholic sulfuric acid produces a greater proportion of the carbazole **301** (R = CH_3)[107, 201] (Eq. 88). In contradiction, it is reported[259] that sulfuric



(A = Acidic catalyst)

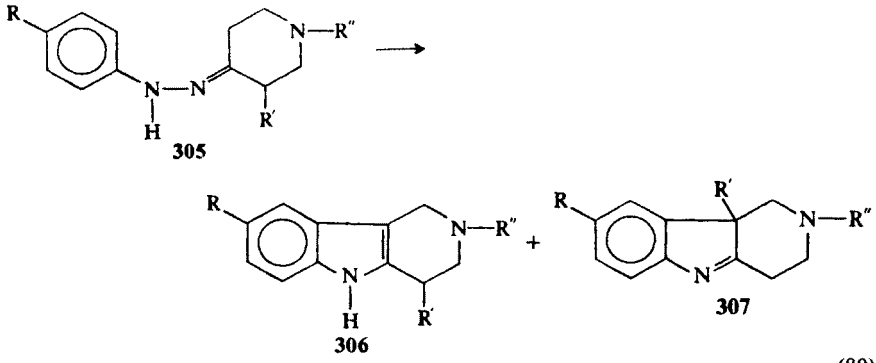
(88)

acid converts the hydrazone **299** (R = CH_3) to a 3:1 mixture of **303** (R = CH_3) and **301** (R = CH_3). It has also been shown[157] that polyphosphate ester (PPE) converts **299** (R = C_2H_5) to a 2:1 mixture of **303** (R = C_2H_5) and **301** (R = C_2H_5). Ban et al.[260] have shown that 98–100% formic acid cyclizes 2-ethylcyclohexanone phenylhydrazone (**299**, R = C_2H_5) completely to the carbazolenine **303** (R = C_2H_5) with only a trace of the tetrahydrocarbazole **301** evident. Under the conditions of the reaction some of the carbazolenine was converted by the formic acid to 11-ethyl-9-formyl-1,2,3,4,10,11-hexahydrocarbazole (**304**). Buu-Hoi[261] has found that glacial



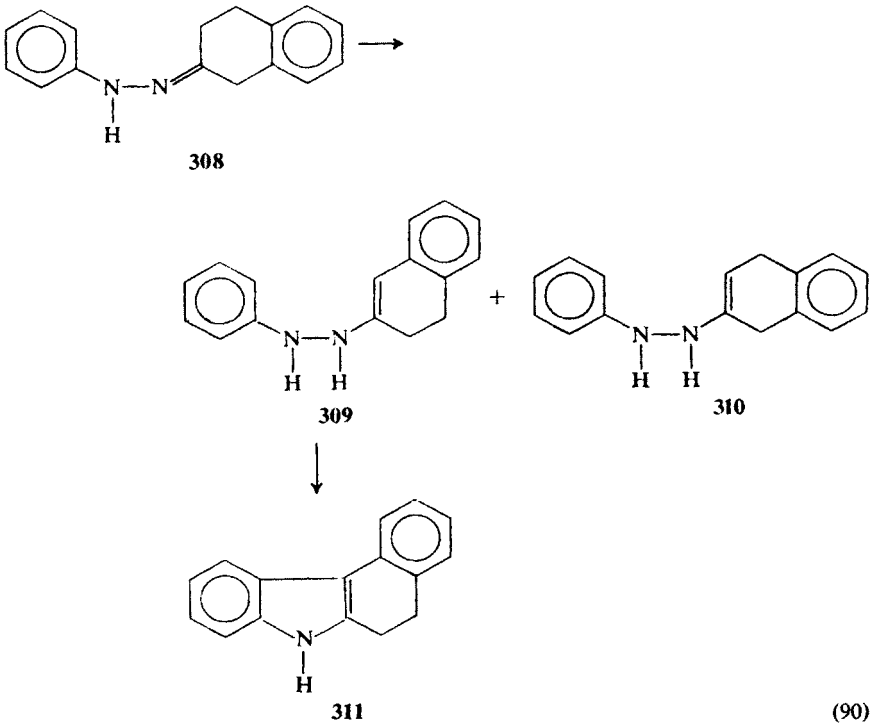
304

acetic saturated with dry hydrogen chloride cyclized 2-*t*-butylcyclohexanone phenylhydrazone **299** (R = *t*-butyl) to a 5:4 mixture of the carbazolenine **303** (R = *t*-butyl) and the tetrahydrocarbazole **301** (R = *t*-butyl). But if zinc chloride or PPA was used as catalyst, then the ratio of **301** to **303** (R = *t*-butyl) was greater than unity. If R is *β*-cyanoethyl, then **299** is converted by zinc chloride or by 20% sulfuric acid to a mixture of **301** and **303** (R = CH_2CH_2CN) in which the tetrahydrocarbazole **301** predominates.[262] The tetrahydrocarbazole **301** also predominates when **299** [R = $CH_2N(CH_3)_2$] is cyclized with ethanol saturated with dry hydrogen chloride.[259] Except for the contradictory findings of Grandberg et al.[259] concerning the effect of dilute sulfuric acid on 2-methylcyclohexanone phenylhydrazone and Buu-Hoi's observation[261] that PPA favors formation of 1-*t*-butyl-1,2,3,4-tetrahydrocarbazole from the phenylhydrazone of 2-*t*-butylcyclohexanone, the above observations could fit into the framework of Lyle and Scarlos' postulation[158] that the "size" of the acidic species has a pronounced influence in determining the direction of ring formation. Glacial acetic acid, acetic acid containing hydrogen chloride or water or alcohol, formic acid, and PPE would then necessarily be "large" acids, favoring Structure **302** while PPA, aqueous or alcoholic sulfuric acid, and hydrogen chloride in ethanol would be "small" acids permitting the physical arrangement in Structure **300**. It is reasonable to assume that the transition state leading to the formation of the new C—C bond (Stage 2) would be more readily attained if the physical bulk of the substituents such as R in **302** are small or absent. This steric effect of the substituent R may well outweigh by a considerable margin the advantage such an alkyl substituent might provide in stabilizing the incipient carbonium ion. That the bulk of the substituent R is significant in determining the direction of cyclization has already been shown in the thermal indolization of a series of 2-substituted-cyclohexanone phenylhydrazones.[163] The cyclization of the phenylhydrazone of 1,3-dimethyl-4-piperidone (**305**, R = H or C_2H_5O, R′ = R″ = CH_3) with hydrogen chloride in ethanol is reported[263] to give the corresponding *γ*-carboline **306** which agrees with the postulation of the "size" of the acid (Eq. 89). However, Ebnöther et al.[264] found that alcoholic hydrogen chloride favored the formation of **307** from **305** (R′, R″ = alkyl or benzyl). It is obvious that a knowledge of the structure of the acidic species under the conditions of the reaction is necessary, and a careful comparative study of the indolization by different acidic catalysts is required.



(89)

The observation[265] that 2-tetralone phenylhydrazone (**308**) gives only the angular product **311** when indolized with dilute sulfuric acid is in agreement

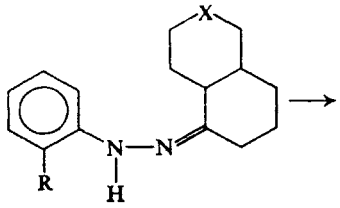


(90)

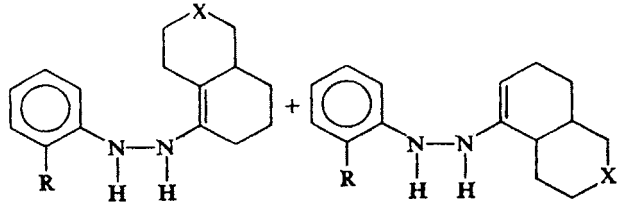
with the view that the formation of the enehydrazine **309** and its reaction to form the new C—C bond (Stage 2) should be preferred to the route involving the alternate enehydrazine **310**[9] (Eq. 90). However, the exclusive formation of 2-benzyl-3-methylindole from the cuprous chloride-catalyzed cyclization of benzyl ethyl ketone phenyl hydrazone is not in agreement with this view.

Both enehydrazines **309** and **310** appear to involve no serious steric opposition either with the acid catalyst at the β-nitrogen atom or in the transition state leading to the new C—C bond formation.

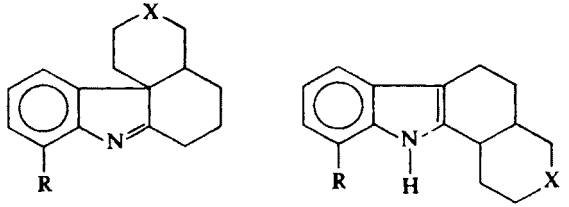
It is useful to consider the relationship of the steric effect of the acid catalyst[158] to the tendency of arylhydrazones of bicyclic and polycyclic ketones to form enehydrazines preferably "toward a ring junction"[10, 266] and thus favor the formation of 3*H*-indoles. Georgian[266] has found that the phenylhydrazones of *trans*-α-decalone (**312a**) and *N*-acetyl-5-ketodecahydroisoquinoline (**312b**) in boiling acetic acid give good yields of a product considered to be the 3*H*-indole **315a** or **b** (Scheme 21). None of the isomer



312a; R = H, OCH_3; X = CH_2
312b; R = H; X = $NCOCH_3$



313a; R = H, OCH_3; X = CH_2 **314a**; R = H, OCH_3; X = CH_2
313b; R = H; X = $NCOCH_3$ **314b**; R = H; X = $NCOCH_3$

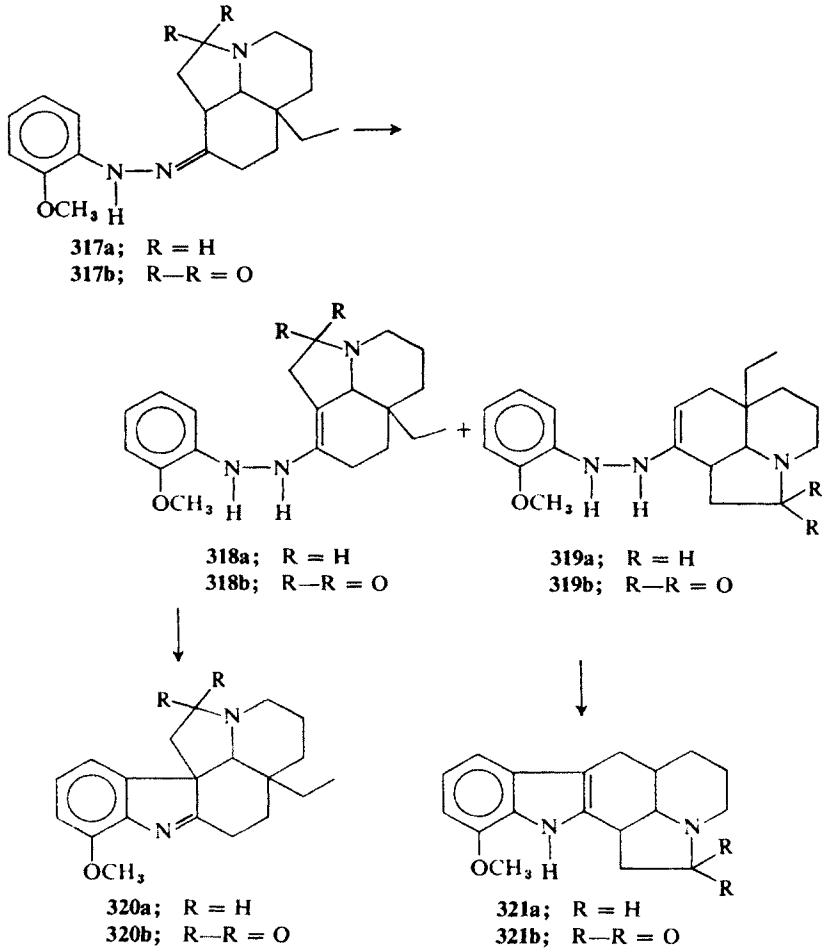


315a; R = H, OCH_3; X = CH_2 **316a**; R = H, OCH_3; X = CH_2
315b; R = H; X = $NCOCH_3$ **316b**; R = H; X = $NCOCH_3$

Scheme 21

316a or **b** was reported. The preferred reaction of the enehydrazine **313a** or **b** rather than **314a** or **b** agrees with the theory of "size" of the acid catalyst. Stork and Dolfini[267] found that the arylhydrazone **317a** in hot acetic acid gave

the 3*H*-indole **320a**, a result also in agreement with the view that the bulk of the acid catalyst causes a preference for **318a** rather than **319b** (Scheme 22). Later it was found[268] that **317a** in acetic acid gave both **320a** and **321a** but no mention was made concerning relative amounts of yields of these two isomers. With the ketone **317b**, it was found that only the 1*H*-indole **321b** was obtained.[267] This is contrary to what would be expected on the basis of the "size" postulation. However, as was pointed out,[267] the formation of **321b** rather than **320b** could be due to the larger number of "trigonal atoms in the transition state" leading to the formation of **320b** via **318b** and the consequent increase in strain that such a route requires. If R = H, the number of such trigonal atoms is reduced (Scheme 22).



317a; R = H
317b; R—R = O

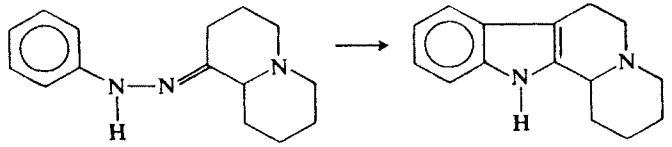
318a; R = H
318b; R—R = O

319a; R = H
319b; R—R = O

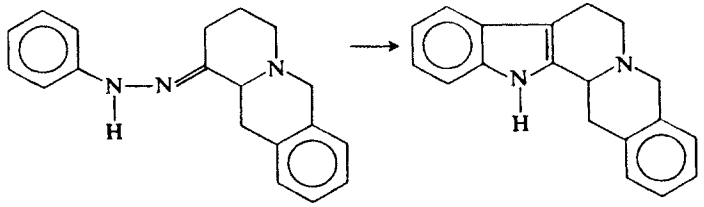
320a; R = H
320b; R—R = O

321a; R = H
321b; R—R = O

Scheme 22

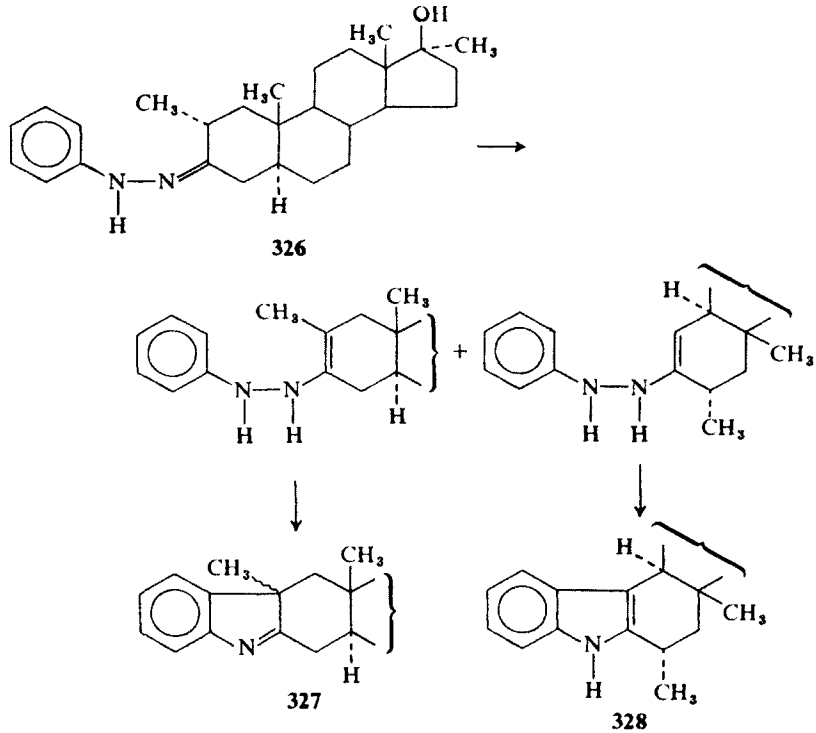


322 324 (91)



323 325 (92)

Recent work[269] reveals that absolute ethanol saturated with dry hydrogen chloride converted the phenylhydrazones of hexahydro-2*H*-quinolizin-1(6*H*)-one (**322**) and 3,4,11,11*a*-tetrahydro-2*H*-benzo[b]quinolizin-1(6*H*)-one (**323**) to the 1*H*-indole structures **324** and **325**, respectively (Eqs. 91 and 92). Apparently none of the 3*H*-indoles were obtained. This also is in agreement

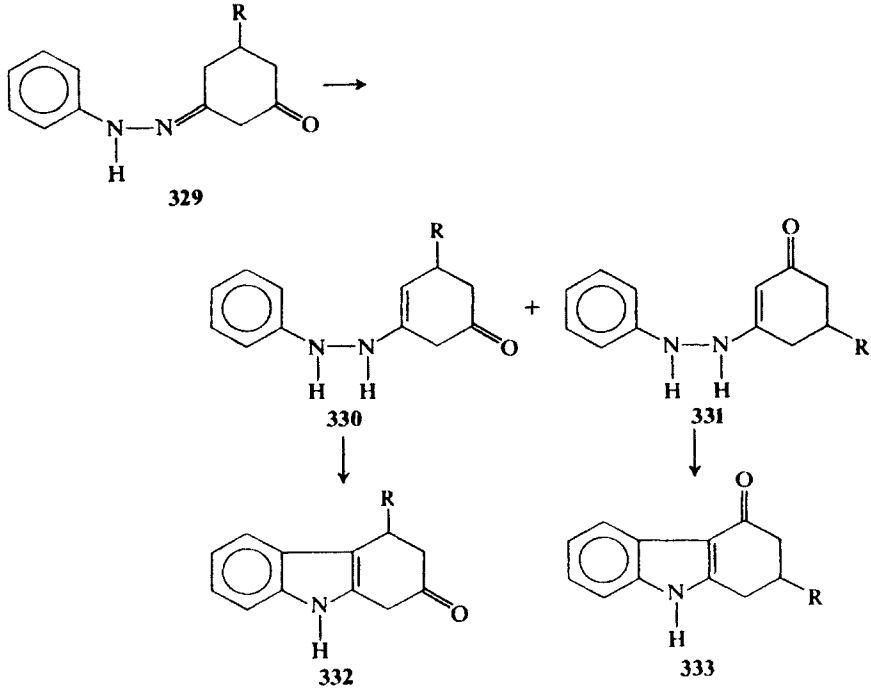


Scheme 23

with the theory of the "size" of the acid. It would be instructive to indolize **312** and **317** with alcoholic hydrogen chloride and **322** and **323** with acetic acid to ascertain the preferred course of reaction under these new conditions.

The cyclization of 2α,17α-dimethylandrostan-17β-ol-3-one phenylhydrazone (**326**) is claimed to produce the 3*H*-indole **327** rather than the 1*H*-indole **328**[270] (Scheme 23). If this is indeed so, then this provides another example of the cyclization of unsymmetrical ketone hydrazones in agreement with the view of Lyle and Skarlos.[158] For other interesting examples of indolization of steroid ketones the excellent review of B. Robinson[10] should be consulted.

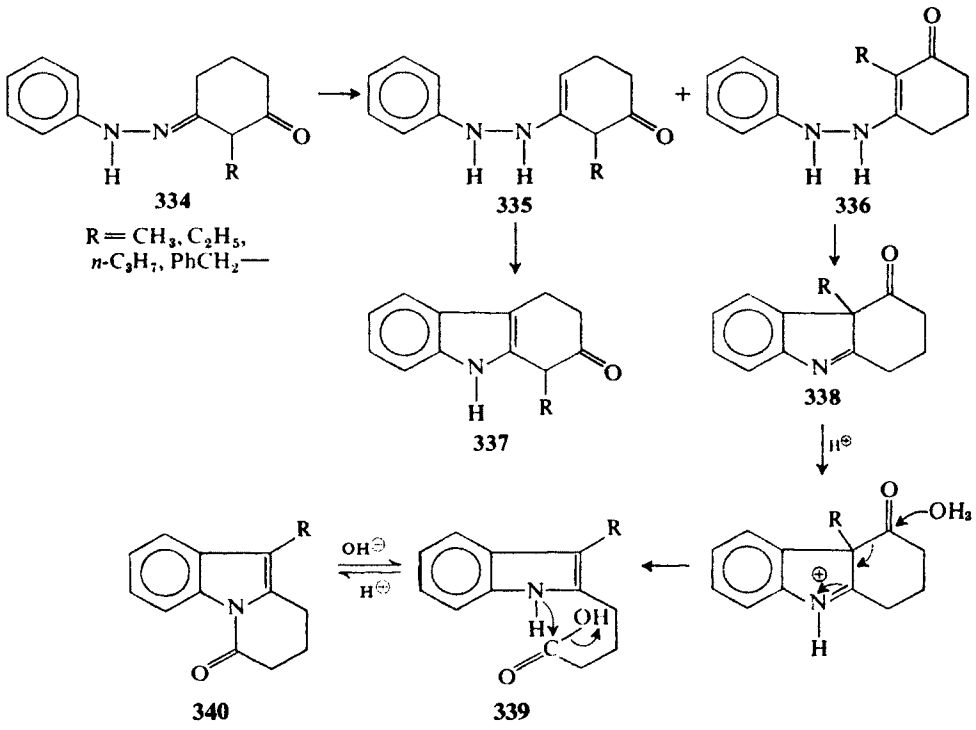
b. Arylhydrazones of 1,3-Diketones. Although the monoarylhydrazones of cyclohexane-1,3-dione **329** should provide two products **332** and **333**, only one, **333** (R = H or CH_3), has been obtained[271] (Scheme 24). Similarly,



Scheme 24

only one of the two possible products has been obtained from the indolization of the phenylhydrazones of several 2-substituted-cyclohexane-1,3-diones.[272] The reaction of the hydrazones **334** gave an excellent yield of the lactams **340** of the respective 1*H*-indoles **339**. These 1*H*-indoles **339** are believed to be

formed from the 3*H*-indoles **338** which arranged to **339** under the influence of the aqueous sulfuric acid used for the indolization (Scheme 25). Since

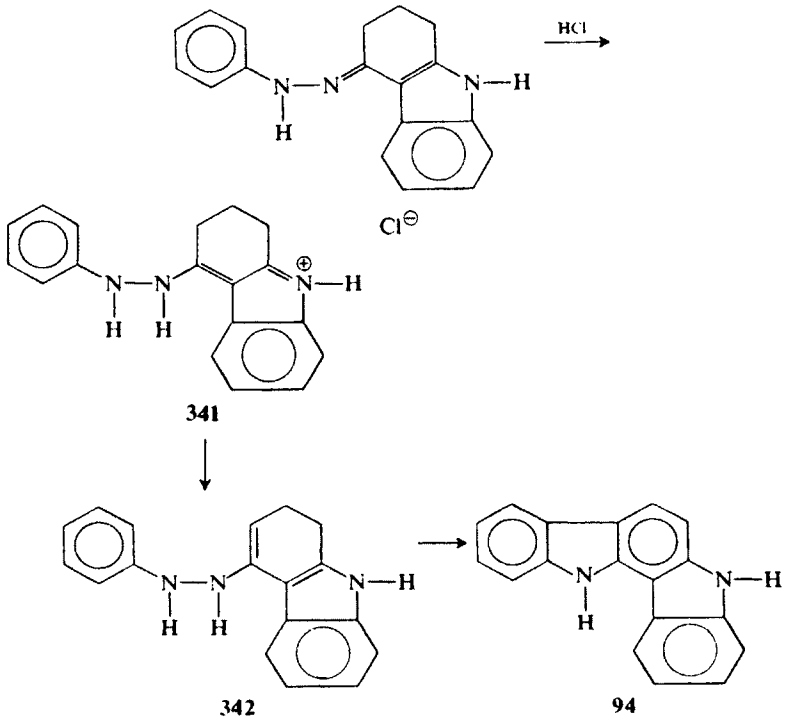


Scheme 25

dilute sulfuric acid can be classed as a "small" acid, the formation and reaction of the enehydrazine **335** to the 1*H*-indole **337** should have been preferred on the basis of the discussion in the previous section. But it is possible that the enehydrazines **331** and **336** are favored because of the extended conjugated system present in both of them and not found in the alternate enehydrazines **330** and **335**. This could account for the observed course of the reaction.

It is possible to form the phenylhydrazone of 4-oxo-1,2,3,4-tetrahydrocarbazole (**333**; R = H), the indolization product of the monophenylhydrazone of cyclohexane-1,3-dione, by the reaction of phenylhydrazine with **333** (R = H) in ethanol with a trace of acetic acid followed by ethanolic hydrogen chloride.[273] The compound obtained was the hydrochloric acid salt and considered to have the enehydrazine structure **341** on the basis of its analogy to the structure of the enehydrazine obtained from the reaction of

phenylhydrazine with 1-oxo-1,2,3,4-tetrahydrocarbazole.[273] This enehydrazine **341** is difficult to indolize, as might be expected on both steric and electronic grounds, and was unaffected by boiling acetic acid.[274] In fact, when the phenylhydrazone of 4-oxo-9-methyl-1,2,3,4-tetrahydrocarbazole was treated with concentrated hydrochloric acid or with boron trifluoride, only hydrolysis to the original 4-oxotetrahydrocarbazole occurred.[274] However, when **341** was heated under vacuum at 360°, it indolized and simultaneously dehydrogenated to form not the 3*H*-indole expected from structure **341**, but the 1*H*-indole **94**, thus showing that **341** rearranged to the tautomeric enehydrazine **342** which then indolized in preference to **341** (Scheme 26).

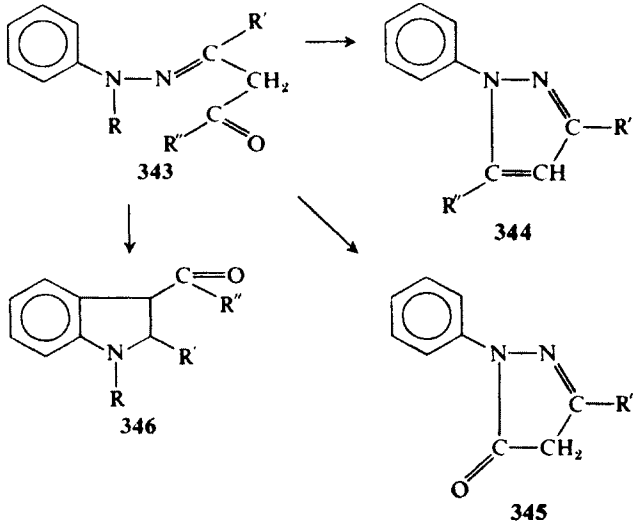


Scheme 26

Product **94** was identical to that obtained[141] from the diindolization and subsequent dehydrogenation of biscyclohexanone *m*-phenylenedihydrazone (**92**) which thus supports the finding[141] that this *m*-phenylenedihydrazone produces the angular compound indolo-[3′,2′-1,2]carbazole (**94**) rather than the linear isomer indolo-[2′,3′-2,3]carbazole (**95**).

Upon attempted indolization, the monoarylhydrazones of acyclic 1,3-diketones **343** (R = H, R′ and R″ = alkyl) do not provide indoles but instead

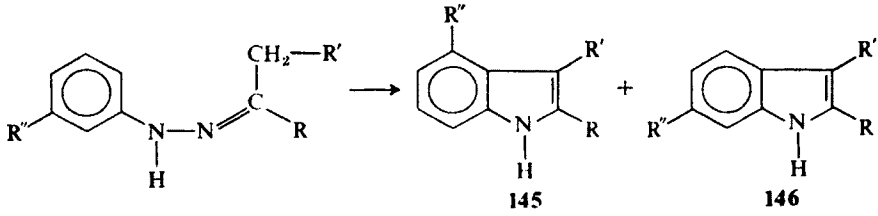
form pyrazoles **344**.[10, 42] Only one pyrazole is possible if the 1,3-diketone is symmetrical, but two isomers are obtained if it is unsymmetrical ($R' \neq R''$)[275] (Scheme 27). This is analogous to the conversion of the monoarylhydrazones of



Scheme 27

3-keto acids or 3-keto esters **343** (R = H, R″ = OH or alkoxy) to pyrazol-3-ones **345**.[9, 10, 42] However, if an alkyl group replaces the hydrogen atom on the α-nitrogen of the hydrazone **343** (R = alkyl), then pyrazole or pyrazol-3-one formation is prevented[10, 276] and the indole is thus permitted to form.

c. *meta*-SUBSTITUTED PHENYLHYDRAZONES. The indolization of phenylhydrazones substituted in the *meta*-positions of the phenyl ring can provide the two isomeric 4- and 6-substituted indoles **145** and **146** (Eq. 93). Many



(93)

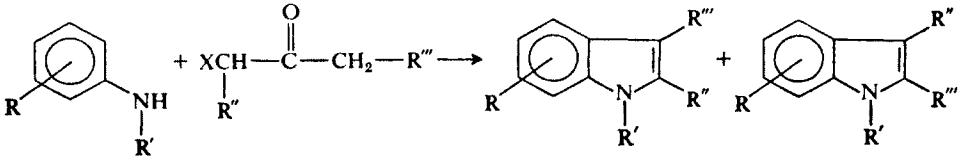
reports have appeared providing information concerning the relative proportions of these two isomers obtained. Much of this is at best only qualitative since yields were frequently quite low and the isolation and separation of the two isomers in many instances has been difficult and incomplete.

Ockenden and Schofield[192] examined the proportion of the isomers **145** and **146** obtained upon indolization of a number of *meta*-substituted phenylhydrazones of ethyl methyl ketone and deoxybenzoin, and concluded that strongly *ortho-para* directing groups (electron donors) generally gave more of the 6-isomer **146** than the 4-isomer **145**. In some cases the 6-isomer was obtained exclusively (*m*-CH_3O).[105, 134, 277, 278] In contrast, *ortho-meta* directing substituents (electron-withdrawing groups) gave a larger proportion of the 4-substituted isomer **145**. Halogens in the *meta* position provide either **145** or **146**[94, 192] or mixtures of both isomers.[63, 279] The majority of the reports support this general postulation and include such substituents as NO_2,[115, 117, 128, 192] CF_3,[101] CH_3,[202, 280] F,[63] and Cl.[105] However, a substantial number of cases give results which are contrary to this view: CF_3,[281] COOH,[202] NO_2.[115, 282] The direction of indolization can be changed considerably by changes in the catalytic conditions[192] and even reversed by use of different acid catalysts.[115, 192] This general problem has been discussed by B. Robinson.[9, 10] It is clear that additional work must be done, and the role of the acid catalyst clarified.

For further information concerning aspects of the Fischer indole synthesis, such as extension of the Fischer reaction, indolizations of pyridines, and the peculiar effect of cuprous chloride on certain arylhydrazones, the reader should consult the two excellent reviews by B. Robinson.[9, 10]

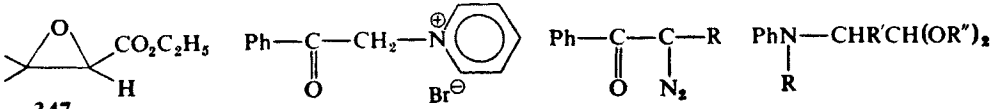
B. The Bischler Indole Synthesis

The reaction of arylamines with α-halogenated ketones, α-hydroxyketones and α-anilino ketones, providing a route to a variety of indoles, is known as the Bischler indole synthesis (Eq. 94). The closely related preparation of indoles by the reaction of arylamines with glycidic acid esters **347**,[283, 284]



R′ = alkyl or H; R″, R‴ = alkyl, aryl, or H; X = halogen, OH, NHAr (94)

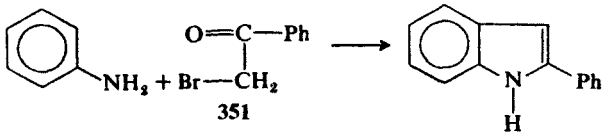
1-phenacylpyridinium bromide (**348**),[285, 287] diazoacetophenones **349**,[287] and α-alkyl-α-arylaminoacetaldehyde dialkylacetals **350**[286] can be considered



347 **348** **349** **350**

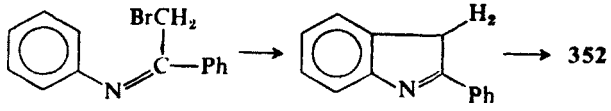
as extensions of the Bischler reaction. The Bischler reaction has been the subject of two reviews[4, 5] and has received comprehensive examination and discussion in several articles.[288–293] This reaction has permitted the preparation of a variety of tetrahydrocarbazoles by a convenient "one step" process from easily accessible substituted anilines and 2-chlorocyclohexanones[294, 295] in over-all yields of 30–60%, as good or better in many cases than those obtained by the Fischer cyclization. It has also been used as a convenient route to *N*-substituted indole-3-acetic acids[296, 297] and to 3-indolylacetamides useful for the preparation of tryptamines.[298, 299]

The reaction was first discovered by Möhlau[300] who obtained a "diphenyl diisoindole" from a heated mixture of phenacyl bromide (**351**) and aniline. Möhlau's compound was at first considered[301] to be 3-phenylindole but later shown[67] to be 2-phenylindole (**352**) (Eq. 95). Fischer and Schmidt[67] stated that **352** could have been formed as the result of a rearrangement of the 3-phenylindole,[301] which was formed first as inspection would predict, to the 2-phenylindole (**352**), since they had shown that 3-phenylindole, obtained



351 **352** (95)

from the cyclization of α-phenylacetaldehyde phenylhydrazone, was converted by hot zinc chloride to 2-phenylindole. However, the realization that Möhlau's reaction mixture involved no zinc chloride and that the aniline and aniline hydrobromide mixture used by Möhlau did not rearrange 3-phenylindole to **352** (even at 230° [288]) caused Fischer and Schmidt[67] to believe that a "direct" cyclization had occurred by a route involving the reaction of aniline with **351** to form the anil **353** which cyclized to 2-phenylindolenine (**354**) and then rearranged to the more stable indole **352** (Eq. 96). However, Fischer and

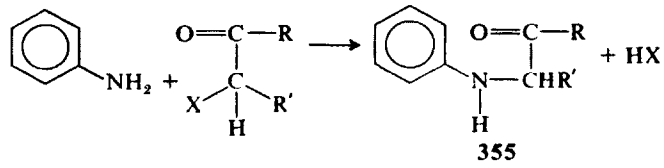


353 **354** (96)

Schmidt's hypothesis became untenable when it was clearly shown that phenacylaniline, the product of the reaction of aniline with phenacyl bromide (**351**), gave Möhlau's indole **352** when boiled with aniline.

A study of the problem of the formation of 2-phenylindole from the reaction of phenacyl bromide with excess aniline led Bischler[302, 303] to propose a mechanism involving three steps. These have been stated clearly by Julian et al.[290]

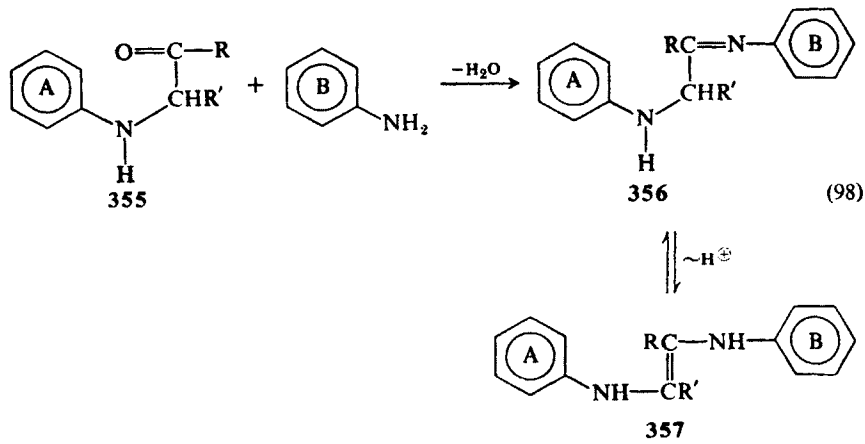
(*1*). Formation of an α-arylaminoketone **355** by the reaction of an α-halo- (or α-hydroxy-) ketone with an arylamine (Eq. 97).



(97)

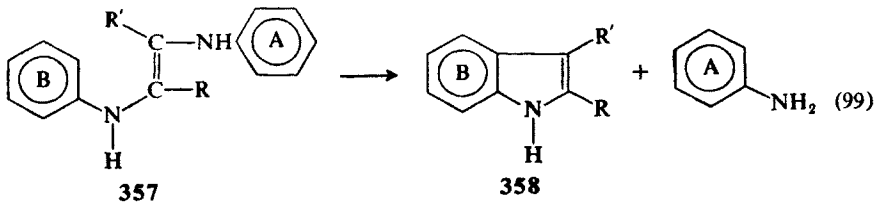
X = halogen, OH

(*2*). Reaction of a second molecule of arylamine with the α-arylamino-ketone **355** to form an "anilino-anil" **356** which by a 1,3-proton shift could form the enediamine **357** (the origin of the term "enediamine theory"[289]) (Eq. 98).



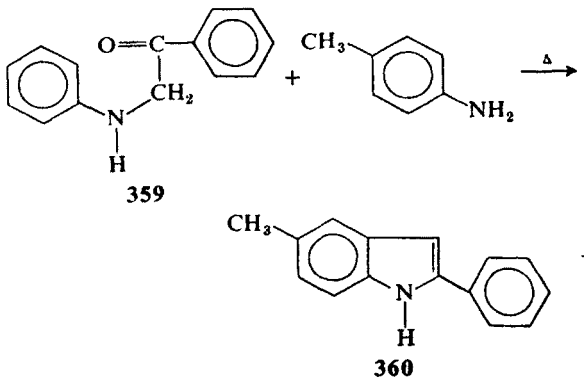
(98)

(*3*). Cyclization of **356** or the enediamine **357**, with expulsion of the arylamino group (A) *first* found in the structure **355**. The new arylamino moiety (B) then forms the indole structure **358** (Eq. 99).



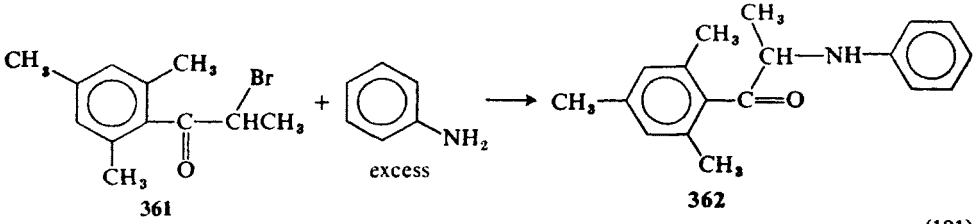
(99)

Support for this hypothesis was obtained by Bischler from the discovery that 5-methyl-2-phenylindole (**360**) was the only indolic product obtained from the reaction of phenacyl anilide (**359**) heated in a 10-fold excess of *p*-toluidine (Eq. 100). That a *second* molecule of amine is essential for the



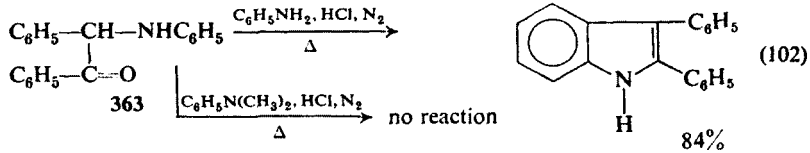
359 360 (100)

reaction has found additional support. The reaction of α-bromopropiomesitylene (**361**) gave α-phenylaminopropiomesitylene (**362**) which could not be converted to an indole,[290] no doubt because a second molecule of aniline was unable to react with the carbonyl group due to steric hindrance (Eq. 101).



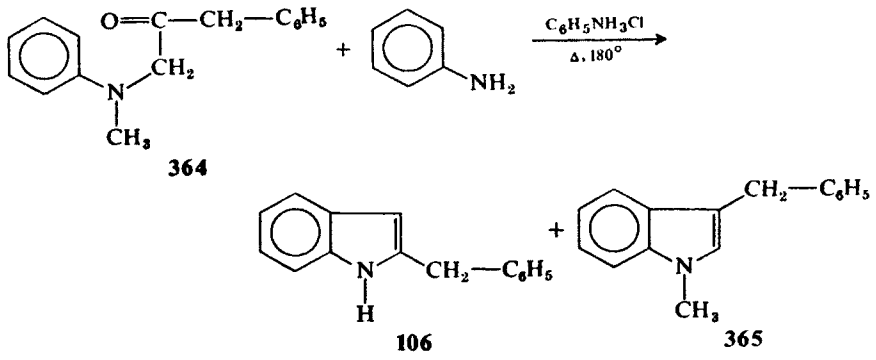
361 362 (101)

Furthermore, although an equimolar proportion of desylaniline (**363**) and aniline heated under nitrogen in the presence of a few drops of 10% hydrochloric acid gave an excellent yield of 2,3-diphenylindole, a similar mixture of desylaniline (**363**) and *N*,*N*-dimethylaniline, under the same conditions, failed to react and gave a 98% recovery of desylaniline (Eq. 102).[290] Julian



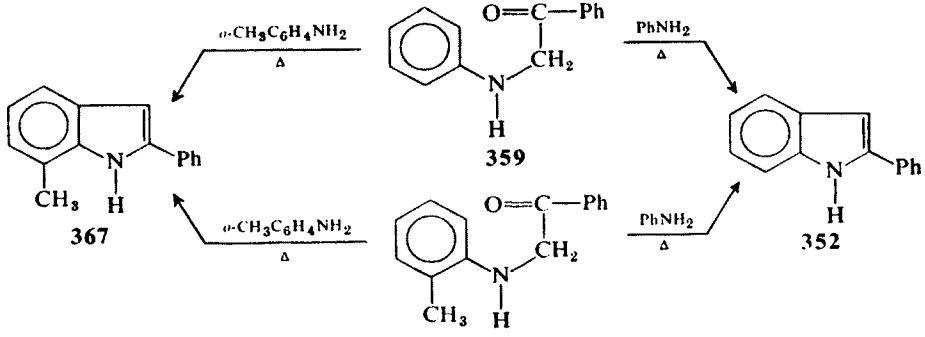
363 84% (102)

and Pikl[304] found that 1-phenylmethylamino-3-phenyl-2-propanone, (**364**) reacted with excess aniline to produce mainly 2-benzylindole (**106**), the product predicted from the Bischler mechanism, and involving the second arylamine (aniline), although a very small amount (0.2 g) of 3-benzyl-1-methylindole (**365**) was also found (Eq. 103). The reaction of **364** with excess *N*-methylaniline in the presence of some hydrogen chloride gave only 2-benzyl-1-methylindole, also in agreement with the Bischler hypothesis.



(103)

Additional support for the Bischler hypothesis was found (*1*) by the isolation of only 2-phenylindole (**352**) when either phenacyl anilide (**359**) or phenacyl *o*-toluidide (**366**) were heated with excess aniline, and the isolation of only 7-methyl-2-phenylindole (**367**) when either **359** or **366** were heated with excess *o*-toluidine (Eq. 104)[289, 302]; (*2*) by the isolation of only 2-*p*-

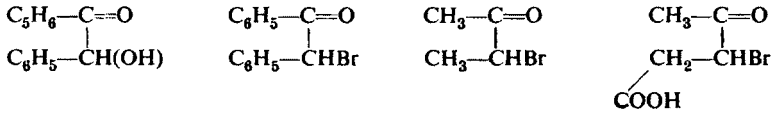


(104)

tolylindole from the heated mixture of *p*-methylphenacyl anilide and excess aniline (Ref. 291, p. 847); (*3*) by the isolation of only 1,2-dimethyl-3-phenylindole from the reaction of 1-phenyl-1-phenylamino-2-propanone with excess *N*-methylaniline (Ref. 288, p. 763); and (*4*) by the apparent formation of only 1,2-dimethylindole when *N*-ethyl-*N*-phenylaminoacetone is heated in excess *N*-methylaniline in the presence of some hydrochloric acid.[305]

Julian et al.[290] have pointed out that although an enediamine of the type **356** or **357** ($R = R' = C_6H_5$) has been made[306] and converted into 2,3-diphenylindole (**358**; $R = R' = C_6H_5$) when heated in the presence of hydrogen chloride, the weakness of the diamine theory is that in Structure **357** one cannot determine *a priori* which arylamino group is the *first* one. If the structure of the final indolic product is considered, no ambiguity occurs at

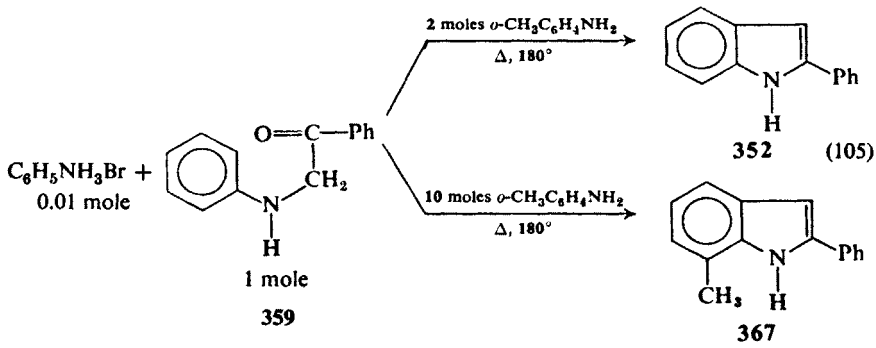
all in this respect when the two arylamino groups are identical. If R and R′ are equal, no problem occurs regarding the location of R(R′) in the α or β position. These two points are illustrated in the reaction of benzoin (**368**)[290] or desyl bromide (**369**)[302] with excess aniline, both of which can and do



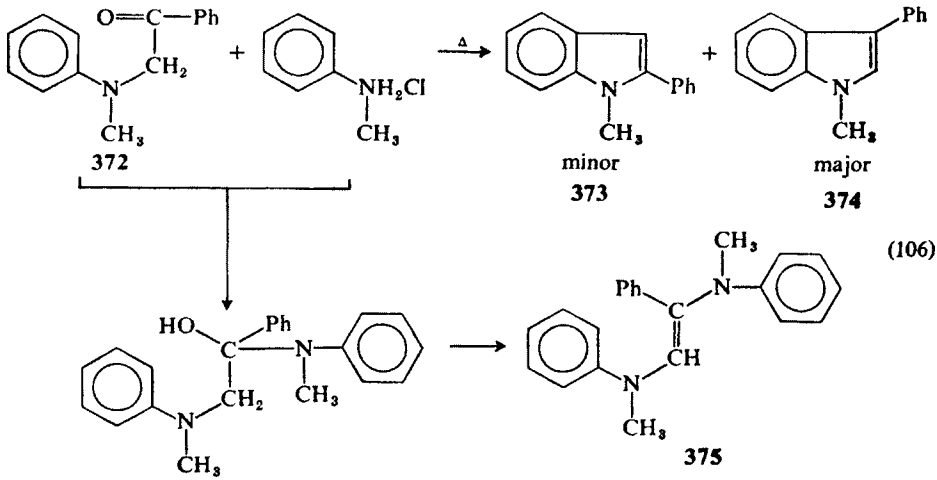
368 **369** **370** **371**

provide only 2,3-diphenylindole (**119**), and in the reaction of 3-bromo-2-butanone (**370**) with excess aniline to produce 2,3-dimethylindole.[307] Even β-bromolevulinic acid (**371**) reacts with excess aniline to produce, after loss of carbon dioxide, the compound 2,3-dimethylindole.[301, 308] If the arylamino groups in **357** are not the same, then one should expect *two* indole products, one of which has retained the arylamino group (A) and the second possesses the other arylamino moiety (B). Indeed, there are several reports that indicate that both of these possible products have been formed.

One of these reports[289] shows that when a 1:2 molar mixture of phenacyl anilide (**359**) and *o*-toluidine containing 0.01 mol of aniline hydrobromide is heated to 180° for a few minutes, only 2-phenylindole (**352**) is obtained, whereas in a repetition of the experiment using a 9-molar excess of *o*-toluidine, only 7-methyl-2-phenylindole (**367**) is obtained (Eq. 105). The product

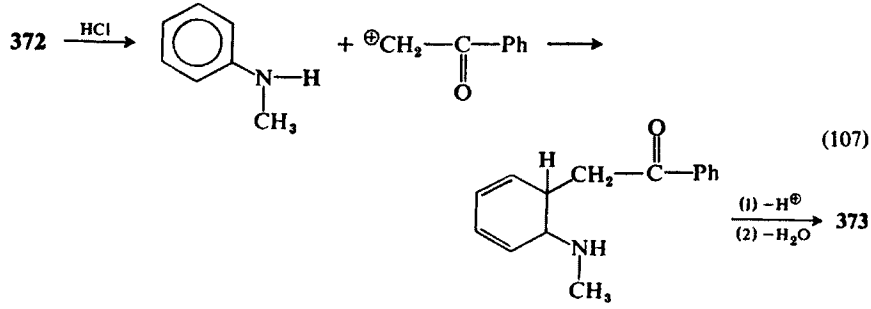


isolated thus depends upon the relative amount of *o*-toluidine present and this clearly indicates that both compounds **352** and **367** are produced simultaneously, and the problem is really one of isolation. Another report (Ref. 288, p. 763) describes the reaction of equimolar quantities of phenacyl *N*-methylanilide (**372**) and *N*-methylaniline hydrochloride to produce the major product 1-methyl-3-phenylindole (**374**) along with a small amount of 1-methyl-2-phenylindole (**373**) (Eq. 106). The results could be interpreted as arising from the Bischler diamine **375** which then cyclizes preferentially to



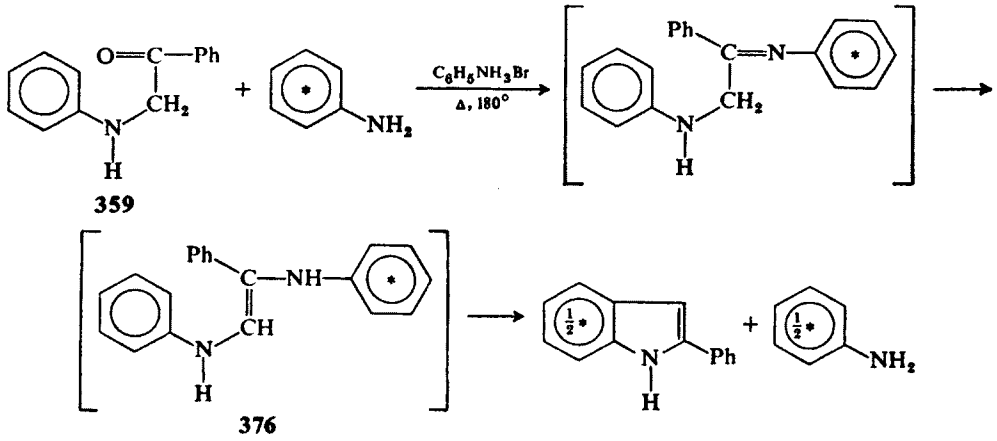
(106)

374. Verkade and Janetzky,[288] however, stated that this reaction **372** → **373** + **374** was clear evidence that a "direct cyclization" of **372** to **374** was the preferred path of reaction and that the product **373** arose due to acid-catalyzed cleavage of **372** to *N*-methylaniline and the phenacyl cation which then attacked the arylamine in the *ortho* position, and subsequently cyclized to **373** (Eq. 107).



(107)

In another report,[292] Weygand and Richter showed that an equimolar mixture of phenacyl anilide (**359**) and aniline-^{14}C, containing a catalytic amount of aniline hydrobromide, heated to 180° for several minutes gave the two products 2-phenylindole and aniline in which the activity was equally divided (Scheme 28). No 3-phenylindole was observed. The same results were obtained when α-(*m*-bromoanilino)acetophenone was heated with an equimolar quantity of *m*-^{82}Br-$C_6H_4NH_2$ in the presence of a catalytic amount of *m*-bromoaniline hydrobromide. These results can also be interpreted by the Bischler diamine theory. However, it is clear by comparison of the results of the previous reaction of **372** with *N*-methylaniline hydrochloride[288] with



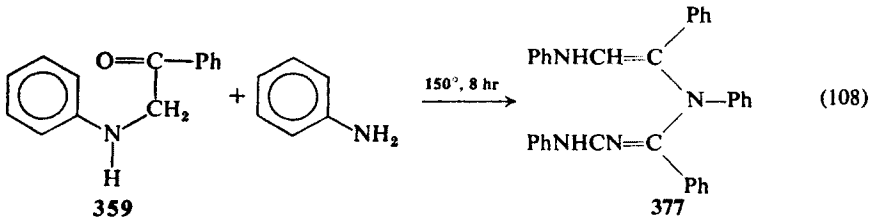
Scheme 28

those from the reaction described by Weygand and Richter,[292] that if a diamine such as **375** and **376** were indeed an intermediate, then both the diamines should have given the same proportion and types of products. Since no 3-phenylindole was obtained from the ^{14}C-labeled experiment, it is clear that the main reaction of **372** must follow a different mechanistic route than does the reaction of phenacyl anilide with aniline-^{14}C. It is also obvious that the presence of the phenyl (Ph) group in **376** would make it unlikely that the labeled and unlabeled anilino moieties should be eliminated with equal ease, as Weygand and Richter's results demand.

Consideration of the mechanism of the Bischler reaction has required the examination of the following points: (*1*) the requirement of an acid to effect the reaction; (*2*) the formation of the arylamino ketone and its ability to isomerize; and (*3*) the comparative behavior of primary and secondary aryl-amines in their reaction with α-halo- or α-hydroxyketones, and the subsequent cyclization of the resulting arylaminoketones to indoles.

(*1*). Although Bischler's work[302, 303] indicated that a heated mixture of an α-arylaminoketone and an arylamine reacts to form an indole, it has since become quite apparent that an acid is required for effective reaction. Japp and Murray[309, 310] found that desyl anilide **363** would react with boiling aniline to produce 2,3-diphenylindole only if at least a trace of aniline hydrochloride was present. Accordingly they suggested that the desyl anilide employed by Bischler and Fireman[303] was not completely free of aniline hydrobromide. Traces of acid were found to be essential for the preparation of several 2-phenylindoles from the appropriate α-arylaminoketones.[311] It has also been found that pure phenacyl anilide, boiled with pure aniline[288] according to Bischler's directions,[302, 303] gave only unchanged phenacyl anilide. Furthermore, under neutral or alkaline conditions no rearrangement

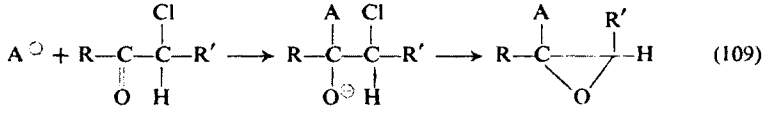
or cyclization has been found to occur.[291, 312] Pure phenacyl anilide **359** can be distilled under vacuum and will react with aniline in the absence of acids to form a triamine **377** which cannot be converted to an indole[289] (Eq. 108).



359 **377** (108)

A number of acidic species have been tested for their ability to affect the Bischler synthesis.[289] Those which are effective are the halogen acid salts of arylamines and quaternary ammonium salts, while zinc chloride and aluminum chloride cause only decomposition.[289] Of significance was the finding that the hydrogen bromide salt of phenacyl anilide[289] and of α-*p*-tolylphenacyl anilide[291] could be heated to ~200° for 10 min, resulting only in decomposition but with no detectable formation of indole. The addition of only a small amount of an arylamine (aniline) to this salt changed the result completely and caused cyclization to the indole. This clearly shows that not only is an acid necessary but some free arylamine is also required.

(*2*). It has been pointed out[4, 290] that the reaction of α-haloketones and α-hydroxyketones with arylamines may not be simply one of direct displacement of the halogen or hydroxy group by the arylamino moiety. There is the possibility that the arylamine first reacts with the carbonyl group followed by elimination of hydrogen halide. This view has been presented by Kohler and Brown[313] who suggested that few if any reactions of α-haloketones proceed by direct replacement of the halogen. The suggestion is made that anionic attack occurs at the carbonyl group with subsequent formation of an epoxide (Eq. 109).



(109)

Nevertheless, the bulk of the reactions of α-halo- and α-hydroxyketones with arylamines appear to involve the direct displacement of the halogen or hydroxy group by the arylamino moiety as the first step. The reaction of both ethyl bromomethyl ketone (**378**) and α-bromoethyl methyl ketone (**380**) with aniline at room temperature provides the corresponding anilinomethyl ethyl ketone (**379**) and methyl α-anilinoethyl ketone (**381**)[307] (Eqs. 110 and 111). The α-arylaminoketones employed by Janetzky and Verkade[314] were

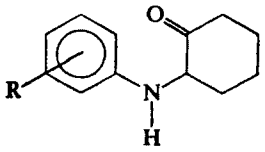
$$CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_2Br + C_6H_5NH_2 \xrightarrow[20\ hr]{ether} CH_3-CH_2-\overset{\overset{O}{\|}}{C}-CH_2NHC_6H_5 \quad (110)$$

378 **379**

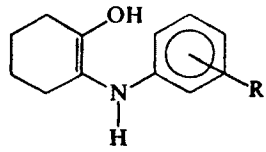
$$CH_3-CHBr-\overset{\overset{O}{\|}}{C}-CH_3 + C_6H_5NH_2 \xrightarrow[20\ hr]{} CH_3-CH(NHC_6H_5)-\overset{\overset{O}{\|}}{C}-CH_3 \quad (111)$$

380 **381**

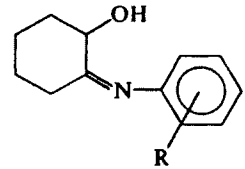
prepared from the corresponding α-bromoketones in aqueous ethanol containing excess sodium bicarbonate. Campaigne and Lake,[295] in a study of the stepwise reaction of 2-chlorocyclohexanone with arylamines, found that these two reactants would condense readily in a high boiling solvent such as cellosolve in the presence of sodium carbonate and a small amount of quinoline or pyridine to yield the corresponding α-anilino cyclohexanone **382**. The ir spectrum clearly showed the structure to be **382**, thus excluding the isomers **383** or **384**. The reaction of *N*-methylaniline with ethyl γ-bromoacetoacetate



382

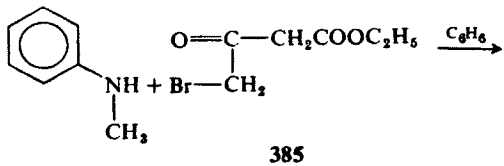


383

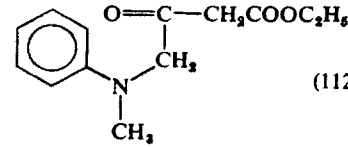


384

(**385**) is reported to occur readily in benzene at room temperature to provide an excellent yield of the γ-*N*-methylanilino derivative **386** (Eq. 112). The



385

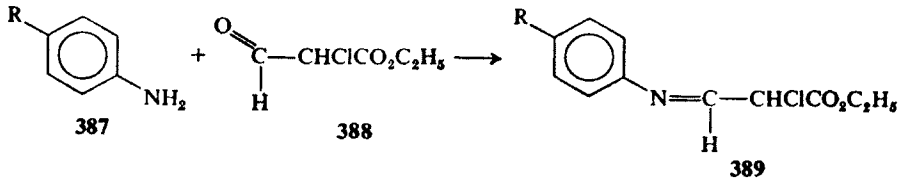


386

(112)

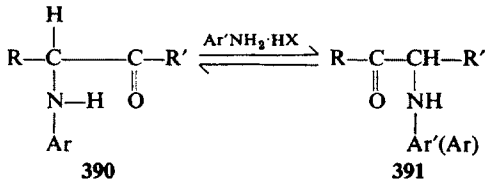
reaction with aniline gives similar results.[296] The formation of indoles from the reaction of 2-hydroxycyclohexanone with arylamines is best accomplished by the stepwise procedure of condensing these two reactants with a few drops of halogen acid at moderate temperatures to form the α-arylaminocyclohexanone.[315, 316] It is interesting that, in contrast to the results stated above, ethyl formylchloroacetate (**388**) reacts with *para*-substituted anilines **387** (R = CH_3, CH_3O, NO_2) to form the anil **389** which has retained the halogen[84, 317] (Eq. 113).

A number of investigations (Refs. 290; 291, p. 858; 293; 312; 318; 319) have shown that α-arylaminoketones of the type **390** can be isomerized, often



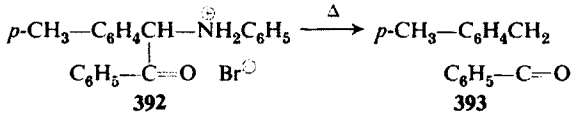
(113)

reversibly, to the type **391** (Eq. 114). This can be done by the application of



(114)

moderate temperature conditions and is catalyzed by small quantities of a strong acid such as the halogen acids.[290, 291, 293, 312] Higher temperatures and the presence of the acid catalyst may cause indolization. The rearrangement also apparently requires the presence of free arylamine or the arylamine hydrohalide, since the pure halogen acid salt **392** when heated alone failed to rearrange or to indolize but instead decomposed with loss of the arylamino group to provide **393**[291] (Eq. 115). Tertiary arylamine hydrohalides also



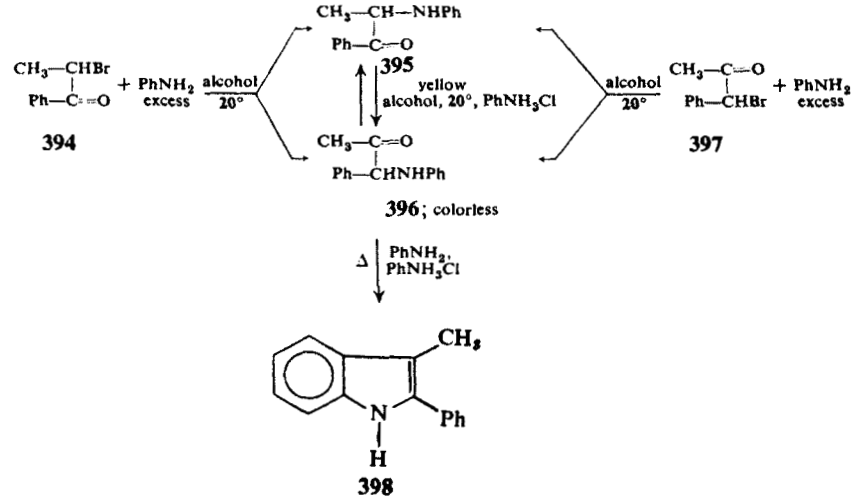
(115)

catalyze the isomerization but considerably less effectively than do the primary arylamine hydrohalides.[293, 318, 319] The pure α-arylamino ketones **390** or **391** are also quite stable since both **390** and **391** (Ar = R = C_6H_5, R′ = *p*-CH_3—C_6H_4) are unchanged when heated to 200° for 30 min.

If the arylamino moiety in **390** or **391** has an alkyl group attached to the nitrogen in place of the hydrogen atom, then no detectable isomerization has been found even in the presence of halogen acids and excess *N*-alkylarylamine. Only direct indolization occurs.[291]

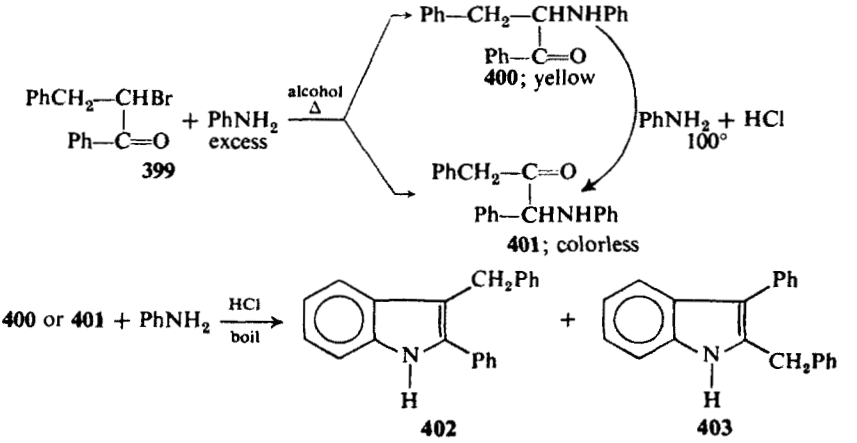
It has been shown[290] that both α-bromopropiophenone (**394**) and α-bromobenzyl methyl ketone (**397**) gave mixtures of the two α-arylaminoketones **395** (yellow) and **396** (colorless) when left with excess aniline in ethyl alcohol at room temperature. The isomeric α-arylaminoketones **395** and **396** could be obtained pure by formation from the corresponding bromides **394** and **397** and aniline in the presence of sodium bicarbonate, and each was shown to form a *mixture* of the two isomers when heated in alcohol containing aniline hydrochloride or hydrobromide. Significantly, both

395 and **396** when heated together or separately in boiling aniline containing aniline hydrochloride apparently gave *only* 3-methyl-2-phenylindole (**398**) (Scheme 29).

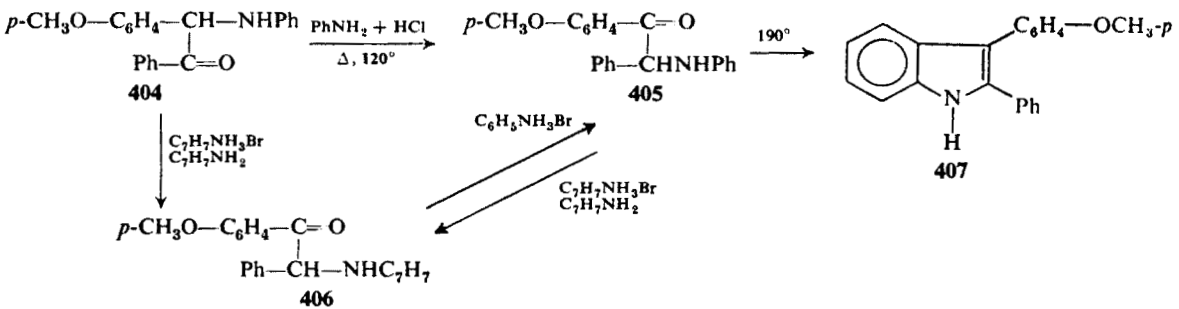


Scheme 29

The reaction of α-bromo-β-phenylpropiophenone (**399**) with excess aniline in boiling ethyl alcohol gave a mixture of the α-phenylaminoketones **400** (yellow) and **401** (colorless). The yellow isomer **400** has been converted to **401**, in part, when heated at 100° in aniline containing a drop of concentrated hydrochloric acid. Either isomer **400** or **401**, when heated with boiling aniline containing aniline hydrochloride, gave a *mixture* of the *two* indoles 3-benzyl-2-phenylindole (**402**) and 2-benzyl-3-phenylindole (**403**)[290, 312] (Scheme 30).



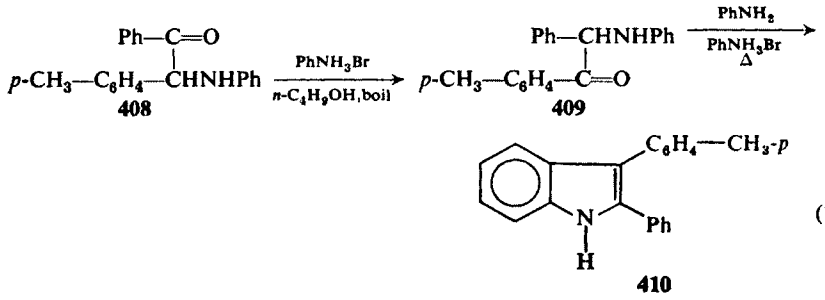
Scheme 30


p-CH3O—C6H4—CH—NHPh
Ph—C=O
404
PhNH2 + HCl
Δ, 120°
p-CH3O—C6H4—C=O
Ph—CHNHPh
405
190°
C6H4—OCH3-p
N
H
Ph
407
C7H7NH3Br
C7H7NH2
C6H5NH3Br
C7H7NH3Br
C7H7NH2
p-CH3O—C6H4—C=O
Ph—CH—NHC7H7
406

Scheme 31

When α-phenylamino-*p*-methoxybenzyl phenyl ketone (**404**) was heated to 120° in the presence of aniline and aniline hydrobromide, it was converted to **405**.[319] If the temperature was raised to 190°, *only* 3-*p*-anisyl-2-phenylindole (**407**) was obtained. If **404** was heated with excess *p*-toluidine containing some of the hydrogen bromide salt, the original phenylamino group was replaced by the *p*-toluidine residue and the *rearranged* product **406** was formed. Furthermore, both **405** and **406** could be interconverted by moderate heating with the appropriate arylamine but no rearrangement was apparent[319] (Scheme 31).

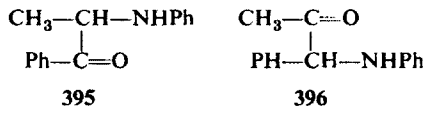
Brown and Mann (Ref. 291, p. 858) have shown that α-phenylamino-α-*p*-tolylacetophenone (**408**) heated in boiling *n*-butyl alcohol in the presence of an equimolar proportion of aniline hydrobromide is converted to the more stable isomer α-phenyl-*p*-methylphenacyl anilide (**409**) which apparently does not rearrange back to **408**. Both **408** and **409**, when heated in boiling



(116)

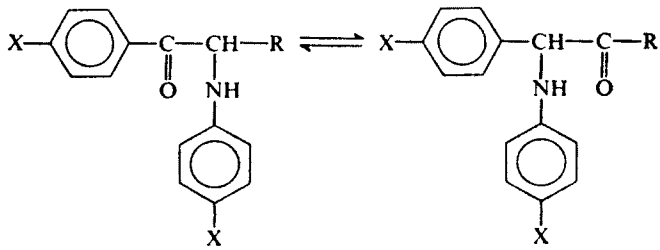
aniline containing aniline hydrobromide, are converted only to 2-phenyl-3-*p*-tolylindole (**410**). A minute catalytic amount (0.006 mol) of aniline hydrobromide is sufficient to cause **409** to cyclize readily to the indole **410** and no rearrangement of the substituents (Ph, CH_3—C_6H_4) appears to occur in this case. It is thus apparent that **408**, when subjected to indolizing conditions, first isomerizes to the more stable isomer **409**, and it is the latter isomer that then cyclizes to the indole[291] (Eq. 116).

The work described in the preceding paragraphs demonstrates that isomerization of α-arylaminoketones can occur under catalysis by arylamine hydrohalides and involves a displacement of the original amine either by the added amine or probably by the original amine liberated during such displacement. The oxygen and arylamino moiety have in effect exchanged positions on the relevant carbon atoms. Nelson et al.[293] have studied the mechanism of this rearrangement, and found no incorporation of ^{18}O when α-phenylaminopropiophenone (**395**) was isomerized to α-phenylaminobenzyl methyl ketone (**396**) in refluxing 95% ethanol containing 5% water enriched in ^{18}O and catalyzed by either aniline hydrobromide or pyridine hydrobromide. Both catalysts did effect isomerization but the aniline hydrobromide was much superior to the tertiary amine salt. The results clearly



395 **396**

showed that oxygen migration was *intra*molecular. Their subsequent work[318] involved a study of the isomerization of halogen-labeled α-arylaminoketones **411** and **412** (X = Cl or Br, R = CH_3 or *p*-CH_3O—C_6H_4), using pyridine hydrobromide or γ-picoline hydrobromide as a catalyst. With X = Cl or Br and R = CH_3, no detectable rearrangement was discerned either with **411**

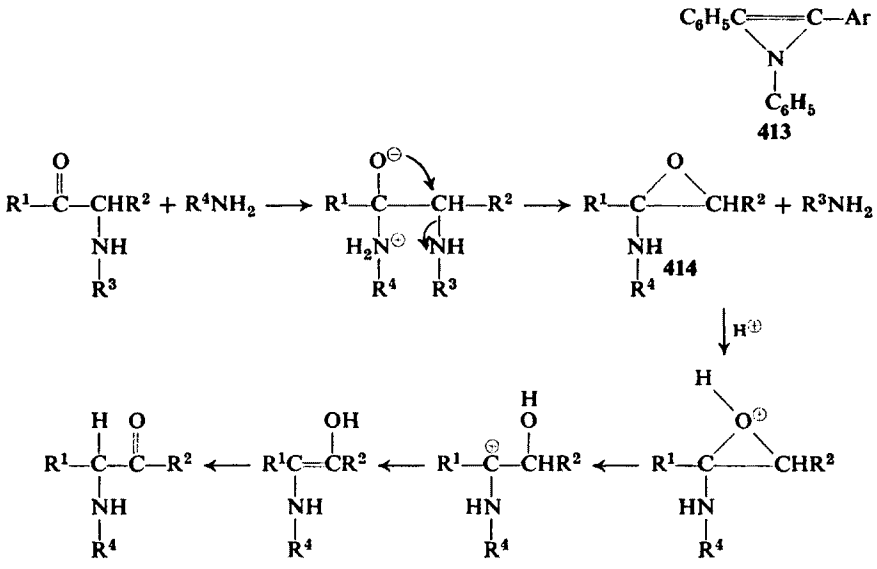


411 **412**

or **412** using either of the tertiary amine salts as catalyst. However, with X = Cl or Br and R = *p*-CH_3O—C_6H_4, these two catalysts in ethylene glycol did convert **411** to the more stable isomer **412**. This agrees with the findings of Cowper and Stevens[319] and Brown and Mann[291] cited above regarding the effects of the *p*-CH_3O or *p*-CH_3 substituent on the relative stability of the isomers. When a *mixture* of **411** (X = Cl, R = *p*-CH_3O—C_6H_4) and **411** (X = Br, R = *p*-CH_3O—C_6H_4) was isomerized to **412**, mass spectrometry showed the presence of fragments containing *both* chlorine and bromine in the same fragment. This clearly showed that migration of the arylamino moiety was *inter*molecular. Nelson's results[293, 318] support the view that tertiary amine salts catalyze the isomerization of the α-arylaminoketones.[319]

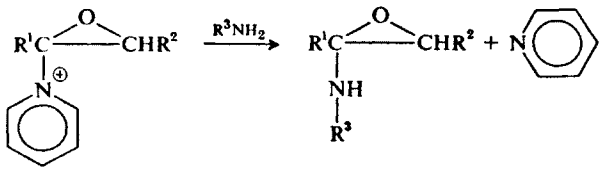
The mechanism of Cowper and Stevens,[319] proposed to support their view that migration of the arylamino group was *intra*molecular involving no amine exchange, and thus might occur by an intermediate such as **413**, was rejected by Brown and Mann[291] because it was sterically unlikely. Nelson's results led to the proposal of the Scheme 32 mechanism[293, 318] which involves the formation of an amino epoxide **414**.

Catalysis by tertiary amine salts was considered to occur by a similar sequence involving a displacement of the tertiary amine which has added to the carbonyl group, by the amino group R^3NH_2 originally in the α-arylaminoketone. This could occur either at the aminoepoxide stage **415** or the enol

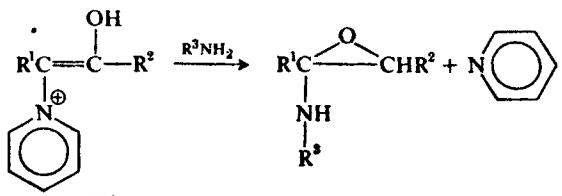


Scheme 32

stage **416** (Eqs. 117 and 118). These details have not been clarified. However, since arylamines are known to react with glycidic esters[283, 284] such as ethyl

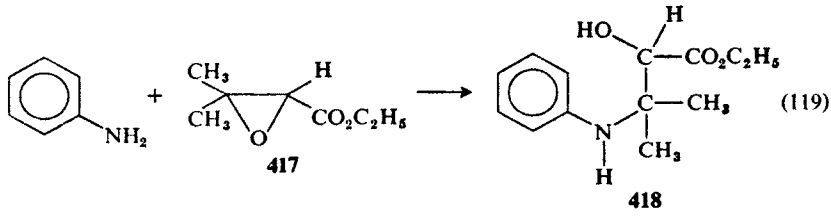


(117)



(118)

3,3-dimethylglycidate **417** to form the α-hydroxy-β-anilino species **418** (Eq. 119), it is more likely that the amine R^3NH_2 liberated by the reaction of the tertiary amine with the original α-arylaminoketone would either attack **415** at the carbon remote from the tertiary amine and regenerate the α-arylaminoketone, or attack the original arylaminoketone and thus bring about the isomerization. That the liberated amine would react with more of



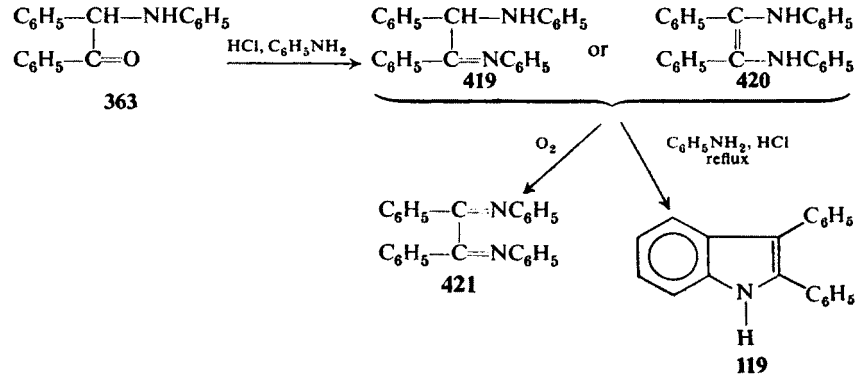
(119)

the original arylaminoketone in this manner has been suggested by Weygand and Richter.[292] It was also considered by Cowper and Stevens[319] but dismissed as a possibility when they postulated that the amine migration was *intra*molecular and not *inter*molecular.

From the preceding discussion it is evident that an arylamine first reacts with an α-halo- or α-hydroxyketone by direct displacement of the halogen or hydroxy substituent to form the corresponding α-arylaminoketone. This may isomerize to provide an equilibrium mixture of two α-arylaminoketones (**390** and **391**). In some cases the equilibrium is well to one side and its position is dependent upon the nature of the group R and R′ in **390** or **391**. If both R and R′ are phenyl groups then the substituent in the phenyl ring plays a role in determining the position of equilibrium of the two isomers **390** and **391**. Such rearrangements occur *prior* to indole formation and with retention of the oxygen atom. It also appears that the isomer which is more stable produces the indole by formation of a bond between the carbon of the carbonyl group and the *ortho* position of the arylamino moiety. This carbonyl carbon then becomes C-3 in the indole structure (cf. **405** → **407** and **409** → **410**). This final conversion of the arylamino ketone **409** to the indole **410** could not be accomplished by heating to 180° with zinc chloride (Ref. 291, p. 858), although higher temperatures no doubt would effect this cyclization. However, the conversion is easily achieved at this temperature by the catalytic action of aniline hydrochloride in aniline,[291] and it is thus clear that the latter catalyst plays a particular role in the cyclization procedure.

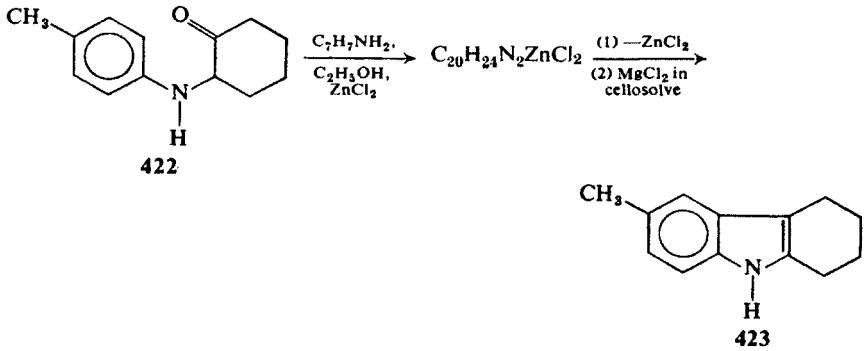
If indeed the anil **356** or the enediamine **357** does play a part in the mechanistic sequence of the Bischler reaction, then it must do so at some stage *after* any acid-catalyzed isomerization of the original α-arylaminoketone has occurred, and at a temperature above that at which only isomerization of the α-arylaminoketones occurs. This may be so, since indole formation does require a higher temperature. That an anil **356** or enediamine **357** might actually be involved has been supported by the work of Julian et al.[290] From their finding that the ring closure to the indole is slower than aniline anil formation, both catalyzed by hydrochloric acid, they were able to adjust conditions of the reaction of desylaniline **363** with aniline in the presence of hydrochloric acid so that a compound $C_{26}H_{22}N_2$ could be isolated in a reasonably pure state which analyzed correctly for either the aniline anil **419**

or the enediamine **420**. One half of this substance was converted with oxygen to the dianil **421** in excellent yield, while the other half, when boiled with aniline containing 4 drops of concentrated hydrochloric acid, was converted to 2,3-diphenylindole (**119**). Both **421** and **119** were obtained in excellent yield. Although it was not known at the time whether the compound $C_{26}H_{22}N_2$ was **419** or **420**, this could now be determined very easily by its nmr spectrum (Scheme 33).



Scheme 33

Campaigne and Lake[295] also obtained evidence for an aniline anil **356** or the enediamine **357** when they refluxed an ethanol solution of 2-*p*-toluidinocyclohexanone (**422**) and *p*-toluidine in the presence of anhydrous zinc chloride and obtained a substance $C_{20}H_{24}N_2ZnCl_2$ which they believed to be the zinc chloride complex of the anil of **422**. This complex could be hydrolyzed to **422** or, after removal of the zinc chloride, could be cyclized to 6-methyl-1,2,3,4-tetrahydrocarbazole (**423**) (Eq. 120).

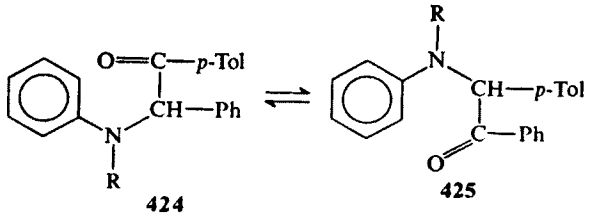


(120)

(*3*). Both primary and secondary arylamines react readily with α-haloketones to form the corresponding α-arylaminoketones. Usually an excess

of the arylamine is used to neutralize the halogen acid produced.[288, 289, 291, 297] Excess sodium bicarbonate,[295, 314] calcium carbonate,[289] or potassium carbonate[291] has been used to destroy the halogen acid, and this is particularly advantageous for the preparation of those α-arylaminoketones that are subject to acid-catalyzed isomerization.[291] Generally alcohol is the solvent employed for this preparation[288, 289, 291] and has been found best for the reaction of α-chlorocyclohexanone with arylamines.[295] In the latter case, higher boiling alcohols were found to increase the rate of reaction but did not improve yields.[295] Aqueous alcohol has been employed when excess sodium bicarbonate was used.[314] In dry benzene as solvent, a mixture of 1 mol of ethyl γ-bromoacetoacetate and 2 mols of *N*-alkyl-*p* (*o*, or *m*) -anisidine when left at room temperature gave a precipitate of arylamine hydrobromide along with a good yield of the γ-arylaminoacetoacetate.[296, 297] The reaction of phenacyl halides with primary arylamines is reported to be more vigorous than that with secondary arylamines.[289] Hence the former reaction required cooling while the latter was carried out at room temperature or under refluxing conditions.

Brown and Mann (Ref. 291, p. 858) made a comparative study of the isomerization and indolization of α-primaryarylaminoketones. **424** and **425** R = H, and of α-secondaryarylaminoketones, **424** and **425**, R = CH_3 or

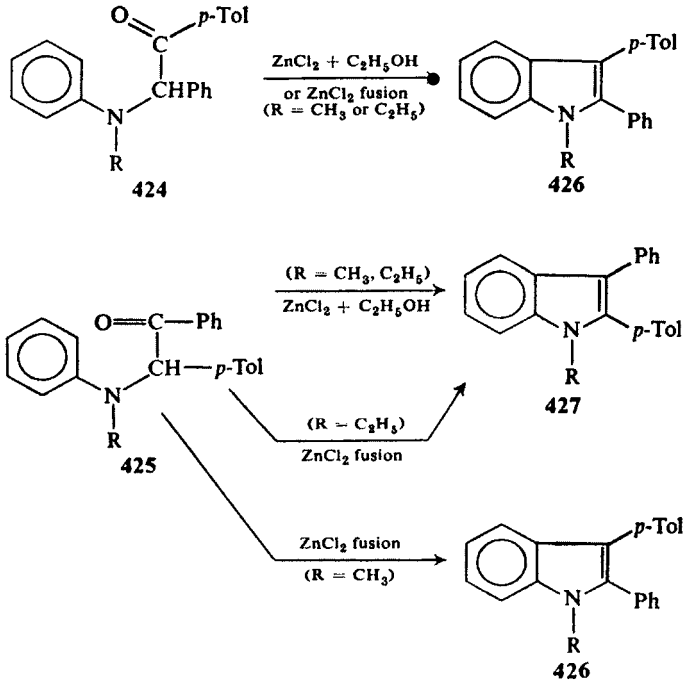


424 **425**

C_2H_5. The arylaminoketones were chosen with the two groups, Ph (phenyl) and *p*-Tol (*p*-CH_3—C_6H_4), as closely alike as possible, yet sufficiently different to permit distinction, to avoid the marked difference in migration tendency which could arise if one of these were an alkyl group. They found that the pure α-primaryarylamino ketones were stable at 200°, but in the presence of even small amounts of acid and moderate heat they isomerized, while at higher temperatures and still in the presence of acid, indolization occurred. For these compounds they found that isomer **425** (R = H) changed to the more stable isomer **424** (R = H) under the moderate conditions, whereas the reverse did not occur. Increase of temperature caused **424** (R = H) to indolize to 2-phenyl-3-*p*-tolylindole (**410**). Thus the sequence of changes was found to be **425** (R = H) $\xrightarrow{H^{\oplus},\Delta}$ **424** (R = H) $\xrightarrow{H^{\oplus},\Delta}$ **410**.

In sharp contrast, the α-secondaryarylaminoketone **424** and **425** (R = CH_3 or C_2H_5) showed no tendency to isomerize when heated with or without

acids (Ref. 291, p. 858). Compound **425** (R = CH_3 or C_2H_5), which because of its structural similarity to the less stable isomer **425** (R = H) might be expected to isomerize, was quite unchanged when heated in boiling *n*-butyl alcohol containing either hydrogen bromide or the hydrobromide of aniline or of the *N*-alkylanilines. The isomers **424** and **425** (R = CH_3 or C_2H_5), when heated with zinc chloride in refluxing ethyl alcohol, and isomer **424** (R = CH_3 or C_2H_5) as well as isomer **425** (R = C_2H_5), when fused with zinc chloride, all gave the indoles **426** and **427**, respectively (R = CH_3 or C_2H_5), the products expected from direct ring closure (Scheme 34). But

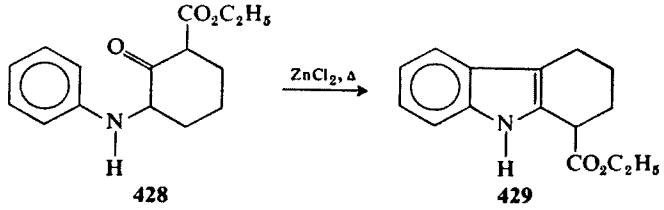


Scheme 34

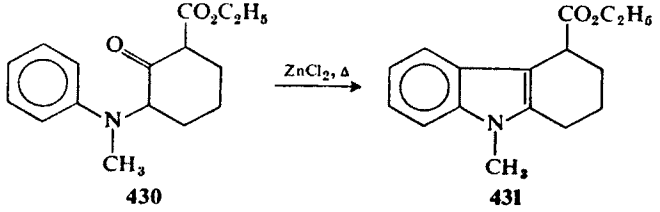
isomer **425** (R = CH_3) when fused with zinc chloride provided a crude reaction product from which only compound **426** (R = CH_3) was obtained and this only in small amount. This substance, **426** (R = CH_3), is apparently the result of a rearrangement of **425** to **424** (R = CH_3) which has occurred under the indolization conditions. It is suggested (Ref. 291, p. 858) that the product **427** (R = CH_3), which was expected from direct ring closure of **425** (R = CH_3) under the conditions of fusion with zinc chloride, might still be in the reaction mixture and even in larger amount. The conclusion is also drawn (Ref. 291, p. 858) that the *N*-ethyl compounds are more stable than the

N-methyl homologues and thus isomerize less readily. However, the isolation of a small amount of the rearranged product **426** (R = CH_3) from **425** (R = CH_3) clearly points to the possibility that the α-secondaryarylamino-ketones **424** and particularly **425** (R = CH_3 or C_2H_5) might isomerize to some extent under the indolizing conditions to give the alternate indole product. But because this alternate product is in minor amount or because of its particular structure, it might be more difficult to isolate.

That α-primaryarylaminoketones, upon indolization with zinc chloride, are more readily susceptible to a rearrangement during some phase of the reaction than are the α-secondaryarylaminoketones, is supported by the report[320] that zinc chloride converted 2-phenylamino-6-carbethoxycyclo-hexanone (**428**) to 1-carbethoxy-1,2,3,4-tetrahydrocarbazole (**429**) whereas *N*-methyl-2-phenylamino-6-carbethoxycyclohexanone (**430**), under similar



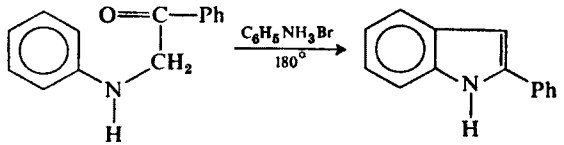
428 **429** (121)



430 **431** (122)

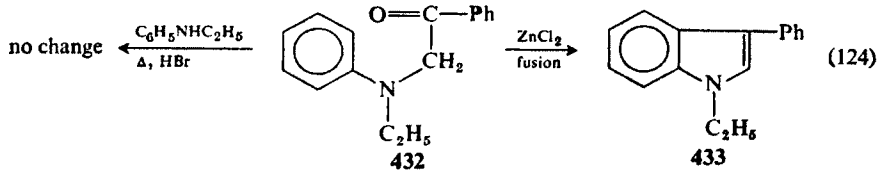
conditions, gave 4-carbethoxy-9-methyl-1,2,3,4-tetrahydrocarbazole (**431**), a product apparently resulting from direct cyclization (Eqs. 121 and 122).

It has also been found that the primaryarylaminoketone, phenacyl anilide (**359**), reacts rapidly at 180° in the presence of a minute quantity of



359 **352** (123)

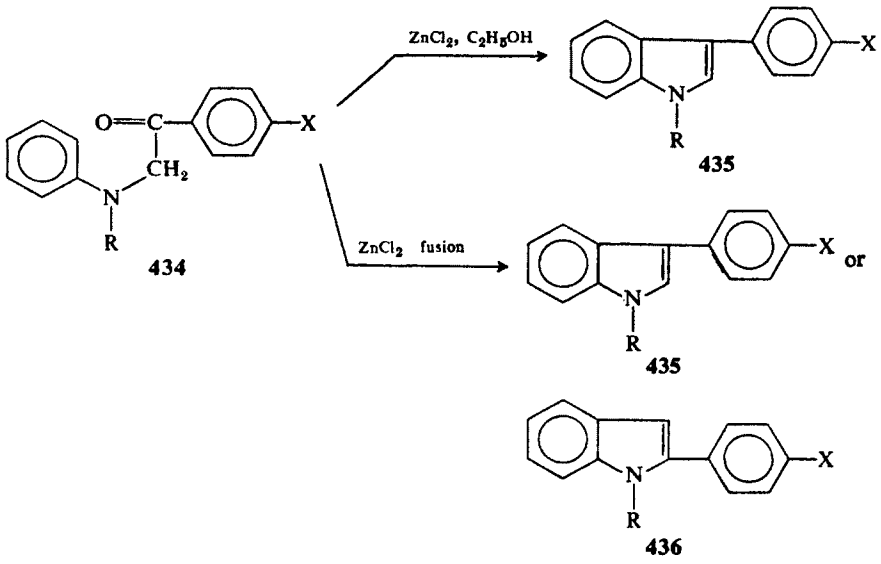
aniline hydrobromide or hydroiodide to form 2-phenylindole (**352**)[289] (Eq. 123). This was not considered to arise from isomerization of a precursor



432 **433** (124)

3-phenylindole to 2-phenylindole because it had been found that 3-phenylindole does not rearrange when heated with an arylamine hydrohalide[288] although hot zinc chloride does effect this isomerization.[67] In contrast to the facile indolization of the primaryarylaminoketones, the secondaryarylaminoketone phenacyl *N*-ethylanilide (**432**) was unchanged when heated with a small amount of *N*-ethylaniline hydrobromide. Thus α-primaryarylaminoketones are considered to be more susceptible to acid-catalyzed cyclization than are their *N*-alkyl homologs.[289] Compound **432**, when fused with zinc chloride, gave 1-ethyl-3-phenylindole (**433**), the product of direct cyclization (Eq. 124). It is interesting that phenacyl *N-methyl*anilide when heated with alcoholic zinc chloride also gave 1-methyl-3-phenylindole, the direct cyclization product, but when fused with zinc chloride, produced the rearranged substance 1-methyl-2-phenylindole,[289] a behavior similar to that found in the zinc chloride fusion of **425** ($R = CH_3$) above.

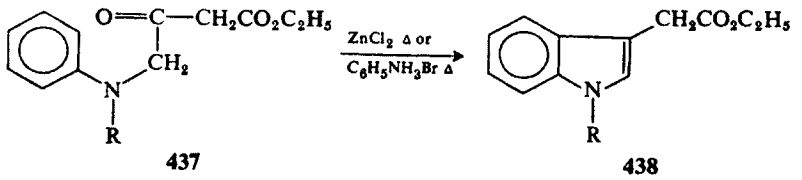
A more extensive examination of the reactions of phenacyl-*N*-alkylanilines of the type **434**, in which R is CH_3 or C_2H_5 and X is CH_3, Cl, or C_6H_5 (Ref. 291, p. 847), showed that in all cases boiling ethanolic zinc chloride gave only the 1-alkyl-3-arylindoles **435**, the products of direct cyclization. When **434** was fused with zinc chloride the product or products obtained depended upon the structure of **434**. In some cases (for $R = CH_3$ and $X = C_6H_5$, or for $R = C_2H_5$ and $X = Cl$ or C_6H_5) the only product obtained was 1-alkyl-3-arylindole **435**, while in other cases [for $R = CH_3$ and $X = CH_3$, Cl, or C_6H_5 (at higher temperatures) or for $R = C_2H_5$ and $X = CH_3$ or C_6H_5 (at higher temperatures)] the rearranged product **436** was obtained (Scheme 35). For the compounds in which $R = CH_3$ and $X = CH_3$ or C_6H_5, the formation of the rearranged product **436** could have occurred by rearrangement from the isomer **435** since in separate experiments using the authentic 3-aryl isomers, this was found to occur. But for compounds in which $R = CH_3$ and $X = Cl$, and in which $R = C_2H_5$ and $X = CH_3$, Cl, or C_6H_5, such isomerization of **435** to **436** was considered to be unlikely since zinc chloride at 250° failed to convert the authentic 1-alkyl-3-arylindoles **435** to the isomeric 1-alkyl-2-arylindoles (Ref. 291, p. 847). Accordingly, to explain these results Brown and Mann (Ref. 291, p. 847) suggested that fusion of the secondaryarylaminoketones **434** with zinc chloride gave two different reactions, one in which a direct ring closure occurred and the other involving an isomerization, probably by a mechanism similar to that for the normal Bischler reaction.



Scheme 35

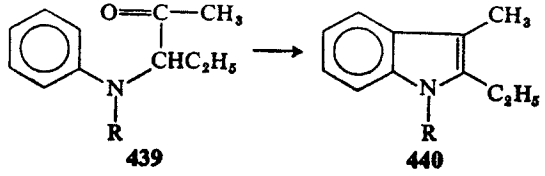
The same authors found that when **434** was heated in boiling excess *N*-alkylaniline containing the hydrobromide or hydrochloride of the *N*-alkylaniline, *two* indoles were usually formed, one of which was invariably a 2-arylindole (having lost the alkyl group from the nitrogen) and the other either 1-alkyl-2-arylindole (**436**) or 1-alkyl-3-arylindole (**435**). The loss of the alkyl group to form the 2-arylindole was considered to occur prior to indole formation since authentic 1-alkyl-2-arylindoles, subjected to the same reaction conditions, did not lose the 1-alkyl group.

Another reported difference between α-primaryarylaminoketones and α-secondaryarylaminoketones is their behavior in the presence of hot excess zinc chloride (Ref. 291, p. 858). The secondaryarylaminoketones readily cyclize directly to the corresponding indole while the primaryarylaminoketones frequently either show no reaction or suffer decomposition. Thus, α-phenyl-*p*-methylphenacyl *N*-methylanilide (**424**, R = CH_3) heated with excess zinc chloride gave only 1-methyl-2-phenyl-3-*p*-tolylindole (**426**, R = CH_3), whereas the primaryarylaminoketone **424** (R = H) when heated with a 10 molar excess of zinc chloride at 180° for 15 min was unchanged, but at 220° decomposed extensively. But this same primary amine **424** (R = H) when heated with excess aniline containing aniline hydrobromide produced 2-phenyl-3-*p*-tolylindole (**410**) with no complication at all (Ref. 291, p. 858). Hot zinc chloride or aniline hydrobromide converted ethyl *N*-alkyl-γ-phenylaminoacetoacetate (**437**, R = CH_3, C_2H_5, or $PhCH_2$) to the corresponding ethyl 1-alkyl-3-indolylacetate **438** in yields of 25–56%[296] whereas



437 438 (125)

γ-phenylaminoacetoacetic acid when heated with zinc chloride failed to cyclize (Eq. 125). Further support is found in the report[314] that 3-phenylmethylamino-2-pentanone (**439**; R = CH_3), when heated at 180° with 2.5 times its weight of zinc chloride, gave the indole **440** (R = CH_3) in quantitative yield, while 3-phenylamino-2-pentanone (**439**, R = H) under similar conditions gave no reaction (Eq. 126). However, if **439** (R = H) was heated to

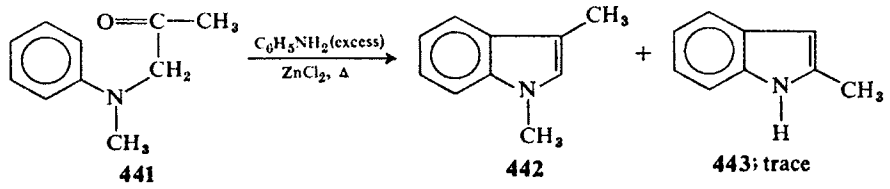


439 440 (126)

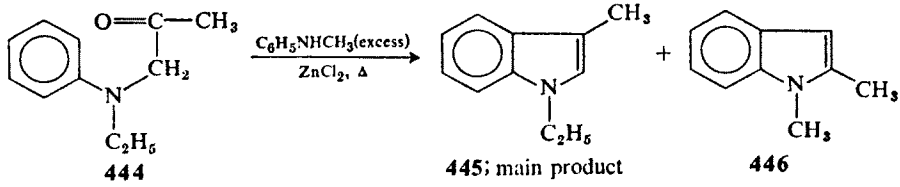
180° with only an equal weight of zinc chloride, then a 36% yield of the indole **440** (R = H) was obtained. On the other hand, if **439** (R = H) was heated for 30 min at 140° with an equimolar quantity of aniline hydrochloride, the indole **440** (R = H) was obtained in 92% yield.

It is thus clear that zinc chloride in moderate amounts does permit indolization of α-primaryarylaminoketones, though in lower yields, a feature which may be due to decomposition under the more stringent conditions of hot zinc chloride. In fact, several cases have been reported in which α-primaryarylaminoketones have been converted satisfactorily to indoles by fusion with zinc chloride. A good yield of 2-phenylindole is obtained by heating phenacyl anilide with an equal weight of zinc chloride at 180°.[288] A 56% yield of 2,3-dimethylindole is achieved when 3-phenylamino-2-butanone is heated with zinc chloride[321] though this yield is increased to 67% if the arylaminoketone is heated with twice its weight of aniline hydrochloride.[321]

The work described above shows that α-secondaryarylaminoketones, when fused with zinc chloride or heated with zinc chloride in alcohol, provide indolic products by an apparent direct cyclization (Ref. 291, p. 858). However, some examples have been reported wherein direct cyclization has occurred preferentially when α-secondaryarylaminoketones are heated with zinc chloride in an excess of *an arylamine*. When *N*-methyl-1-phenylamino-2-propanone (**441**) is heated with zinc chloride in a large excess of aniline, 1,3-dimethylindole (**442**) is produced, accompanied by a very small amount of



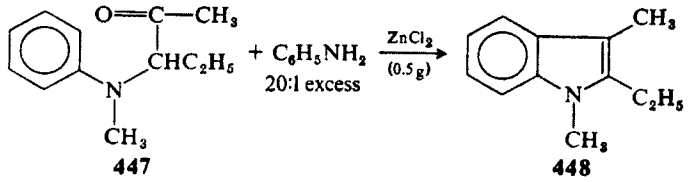
(127)



(128)

2-methylindole (**443**)[305] (Eq. 127). The *N*-ethyl homolog **444**, heated with zinc chloride in excess *N*-methylaniline, gave 1-ethyl-3-methylindole (**445**) as the main product along with some 1,2-dimethylindole (**446**) (Eq. 128). The minor products in both cases must have been formed as the result of a displacement of the secondaryarylamine moiety in **441** and **443** by the arylamine solvent under the influence of the zinc chloride, and this is accompanied by a rearrangement during the process to provide **443** and **446**. It is interesting that **444**, heated with excess *N*-methylaniline in the presence of a catalytic amount of *N*-methylaniline hydrochloride, gave only **446**, the product arising from a displacement-rearrangement process. Thus, at least with the two secondaryarylaminoketones **441** and **444**, zinc chloride favors the direct cyclization in contrast to the displacement-rearrangement which is the sole process when the halogen acid in excess arylamine is the catalyst. But it is clear that even with zinc chloride as catalyst some displacement-rearrangement product is obtained.

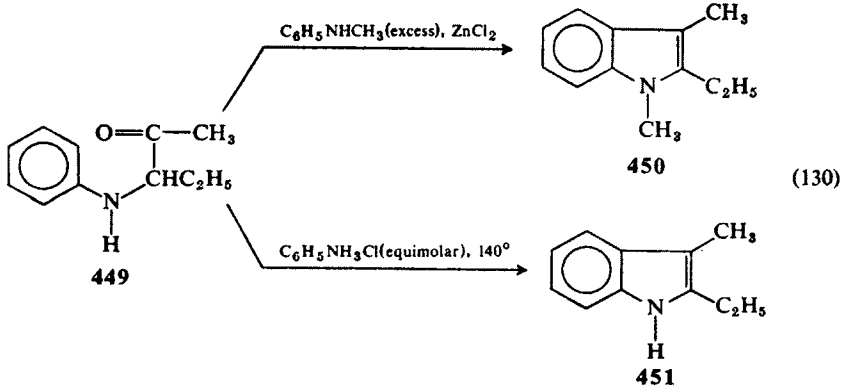
The observation[314] that *N*-methyl-3-phenylamino-2-pentanone (**447**) heated in a large excess (20:1) of aniline with a catalytic amount of zinc chloride gave only 2-ethyl-1,3-dimethylindole (**448**), the product of apparent



(129)

direct ring closure, also supports the view[291] that α-secondaryarylaminoketones in the presence of the zinc chloride prefer to cyclize by direct ring

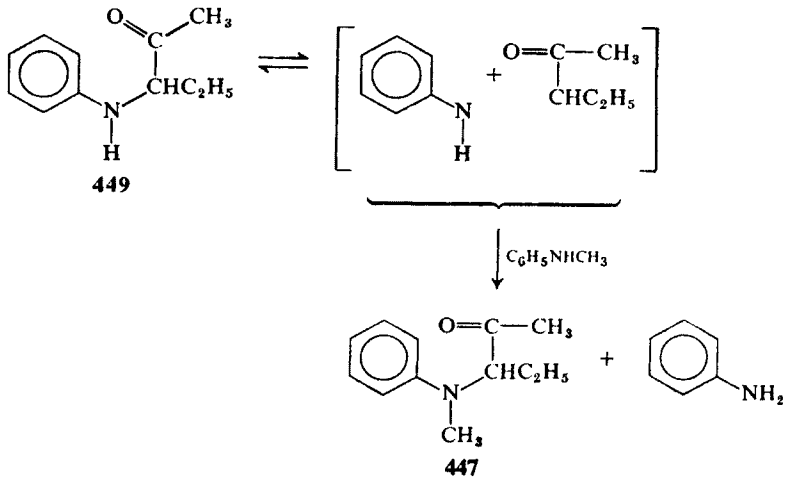
closure (Eq. 129). In contrast, the homologous primaryarylaminoketone **449** heated in a 15:1 excess of *N*-methylaniline with either a catalytic amount (0.5 g) of zinc chloride or an amount of zinc chloride equal to 2.5 times the weight of **449** gave an excellent yield of 2-ethyl-1,3-dimethylindole (**450**), the product of a reaction in which a displacement of the original arylaminoketone has occurred, but in which no apparent rearrangement has taken place[314] (Eq. 130). This has been stated as an example of "apparent direct ring closure" whereas the conversion of **447** to **448** is considered as an example of "true direct ring closure."[314] The reaction of **449** with an equimolar amount of aniline hydrochloride at 140° gave 2-ethyl-3-methylindole (**451**), apparently also a direct cyclization product (Eq. 130).



(130)

In the conversion of **449** to **450** it is clear that the catalyst zinc chloride favors displacement of the phenylamino group by the secondary arylamine, used as solvent, *before* cyclization to the indole takes place. Such a replacement occurs only to a small extent, if at all, when the α-secondaryarylaminoketone is the starting material (cf. **441**, **444**, and **447**). It thus appears that the α-primaryarylaminoketones are more readily subject to displacement of their arylamino groups, before cyclization occurs, than are the α-secondaryarylaminoketones—a feature implied in the work of Brown and Mann.[291] On this basis it is likely that a similar displacement occurs in the conversion of **449** to **451** but cannot be identified in this reaction because both arylamino groups involved are the same.

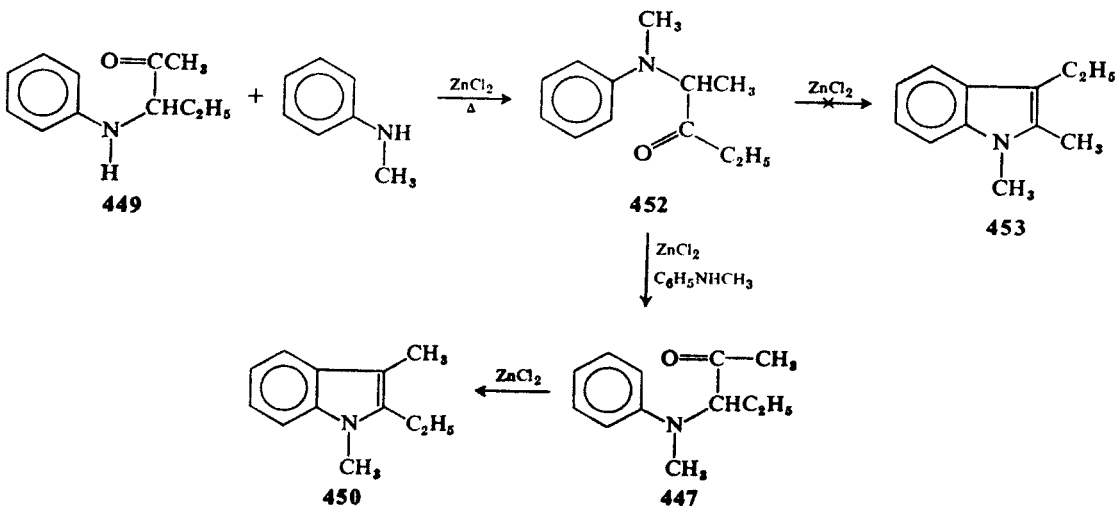
In previous cases cited, wherein such a displacement was observed (cf. **441** and **444**), a rearrangement accompanied the reaction. No rearrangement is apparent in the conversion of **449** to **450** even though displacement has occurred completely. Such a displacement might occur by the cleavage of the C—N bond as in Scheme 36, analogous to the mechanism suggested[288, 289]



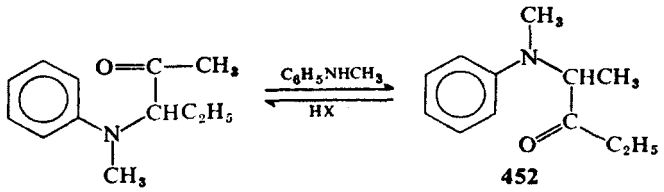
Scheme 36

for the Bischler reaction. In the presence of excess *N*-methylaniline the ketone **449** is thus converted practically entirely to *N*-methyl-3-phenylamino-2-pentanone (**447**) which then cyclizes directly to **450**. On the other hand, the displacement may occur by attack of the arylamine solvent on the carbonyl group as suggested for the initial stages of the Bischler mechanism[302, 303] to form first the rearranged α-arylaminoketone **452**. If this occurs, and since compound **453**, the product expected from direct cyclization of **452**, apparently was not found,[314] then it follows that **452** must rearrange to **447** under the reaction conditions faster than it can cyclize directly to **453** (Scheme 37). This implies that of the two isomeric α-secondaryarylaminoketones **447** and **452**, the former is the more stable. This would also mean that these particular α-secondaryarylaminoketones *do* rearrange before cyclization occurs. It is thus imperative that the rearrangement tendencies of the pair of isomers **447** and **452** and of the pair **449** and **454** be examined. The products obtained from the reaction of **447** and **449** in an excess of the corresponding arylamines containing some halogen acid indicates that not only is **447** more stable than **452** but that **449** is more stable than **454**. Or, from another point of view, both **447** and **449** cyclize directly to the corresponding indole more readily than do the respective isomers **452** and **454** (Eqs. 131 and 132).

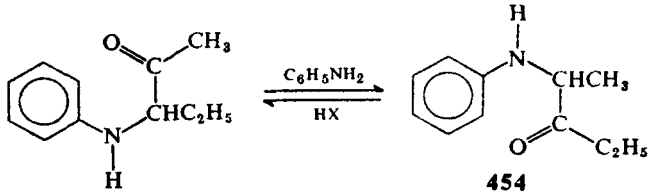
Some cases are recorded in which α-secondaryarylaminoketones undergo direct cyclization in the presence of excess arylamine containing only the arylamine hydrohalide as catalyst. For example, *N*-methyl-1-phenylamino-2-propanone (**441**) when heated in excess aniline containing aniline hydrochloride provides mainly 1,3-dimethylindole (**442**), the result of direct


O=CCH3
CHC2H5
N
H
449
+
NH
CH3
ZnCl2
Δ
CH3
N
CHCH3
C
O
C2H5
452
ZnCl2
ZnCl2
C2H5
N
CH3
CH3
453
ZnCl2
C6H5NHCH3
CH3
N
C2H5
CH3
450
ZnCl2
O=C—CH3
CHC2H5
N
CH3
447

Scheme 37

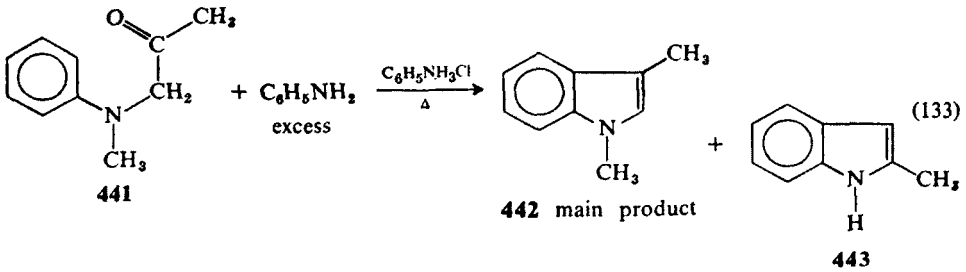


447 452 (131)



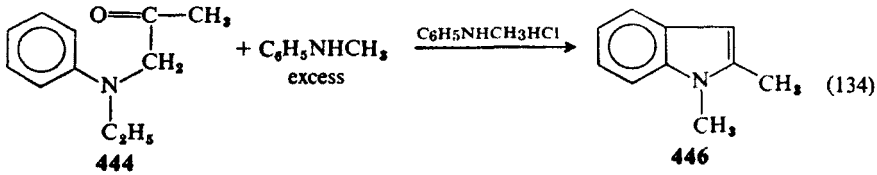
449 454 (132)

cyclization, but accompanied by 2-methylindole (**443**) to the extent of 15% of the total product (Eq. 133). Compound **443** is the substance expected from



441 **442** main product **443** (133)

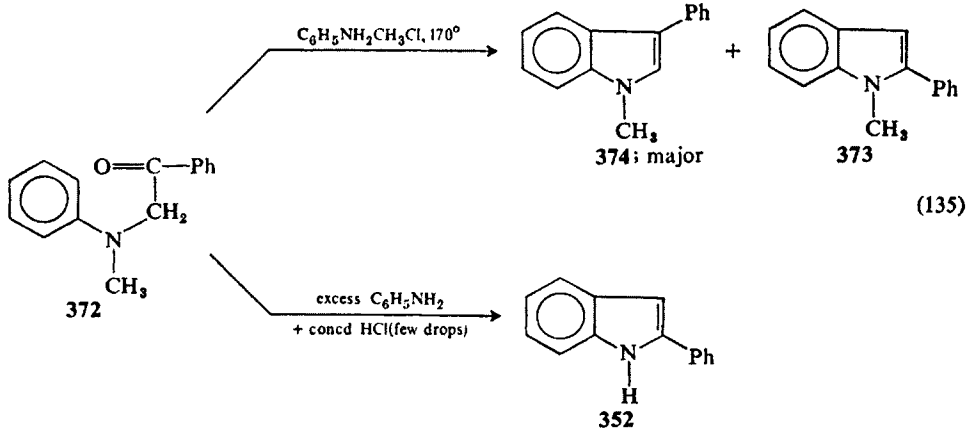
a displacement-rearrangement process.[305] The *N*-ethyl homolog **444**, similarly treated but in excess *N*-methylaniline, gave only the product **446** expected from displacement and rearrangement[305] (Eq. 134). Whether this difference



444 **446** (134)

in behavior is due to the difference in the alkyl groups on the nitrogen atom or due to the difference in the arylamine solvent is not clear. It would be instructive to determine the result of heating **444** in excess aniline as had been done for **441**.

The compound phenacyl *N*-methylanilide (**372**), heated to 170° with an equal weight of *N*-methylaniline hydrochloride, gave 1-methyl-3-phenylindole (**374**) as the major product along with a very small amount of 1-methyl-2-phenylindole (**373**) (Eq. 135). Product **374** appears to be the result of direct

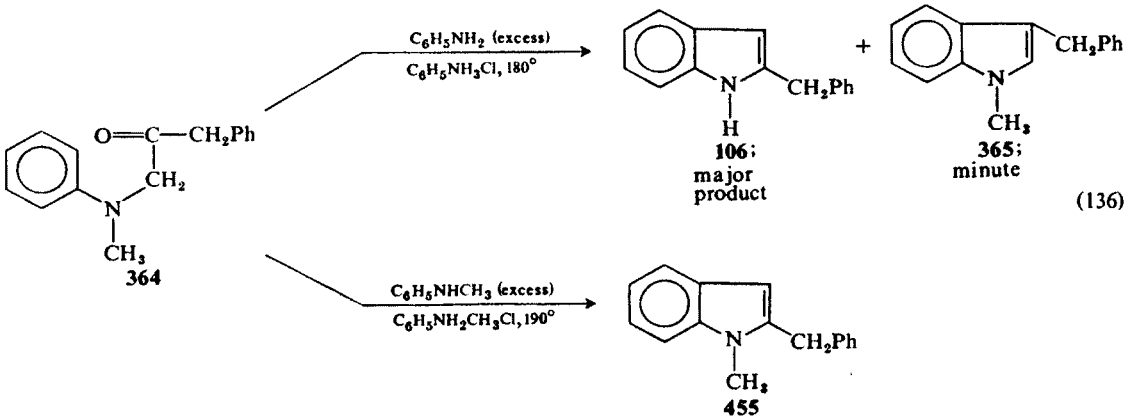


(135)

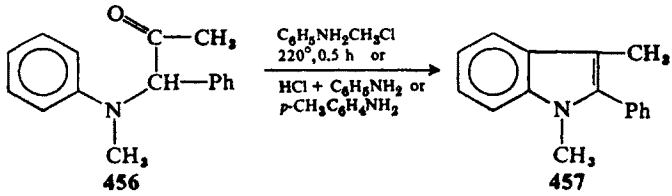
cyclization of **372**, while **373** could be the result of displacement with rearrangement as envisaged by Bischler. But if **372** is heated with excess aniline in the presence of a few drops of concentrated hydrochloric acid, only the displacement-rearrangement product 2-phenylindole (**352**) is formed[288a] (Eq. 135). It would be useful also in this case to determine whether heating **372** in *excess N*-methylaniline in the presence of some halogen acid would favor formation of the displacement-rearrangement product as found in the conversion of **444** to **446**.

Julian and Pikl[304] have reported that when 8 g of *N*-methyl-1-phenylamino-3-phenyl-2-propanone (**364**) was heated at 180° in excess aniline containing some aniline hydrochloride, it provided in good yield the displacement-rearrangement product **106** accompanied by a very small amount (0.2 g) of the direct cyclization product **365** (Eq. 136). However, if the temperature of the reaction was 128° rather than 180°, then the proportion of the direct reaction product **365** increased to 30%. The same authors found that if **364** was heated at 190–200° in excess *N*-methylaniline containing a small amount of *N*-methylaniline hydrochloride, only the rearranged product 2-benzyl-1-methylindole (**455**) was obtained. This might actually be the displacement-rearrangement product analogous to the conversion of **364** to **106**.

A final example of an α-secondaryarylaminoketone which appears to cyclize by the direct route in the presence of an equal weight of *N*-methylaniline hydrochloride is *N*-methyl-α-phenylaminobenzyl methyl ketone (**456**). The only product obtained in excellent yield is 1,3-dimethyl-2-phenylindole

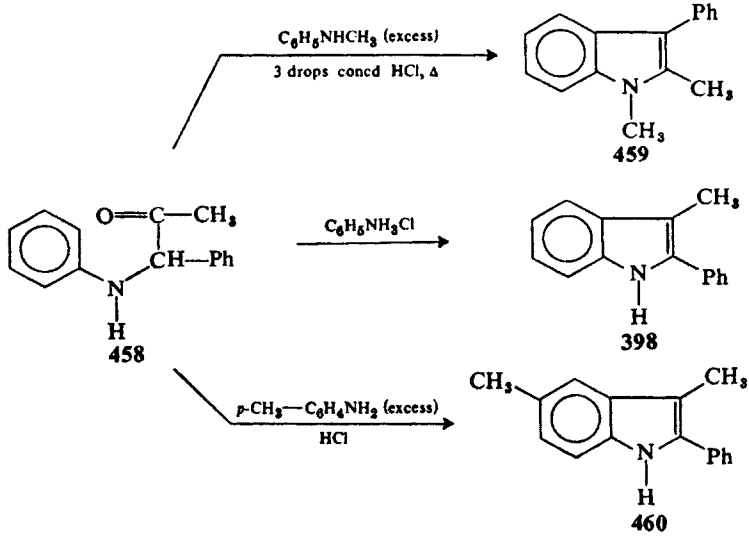

C6H5NH2 (excess)
C6H5NH3Cl, 180°
O=C—CH2Ph
CH2
N
CH3
364
CH2Ph
N
H
106;
major
product
+
CH2Ph
N
CH3
365;
minute
C6H5NHCH3 (excess)
C6H5NH2CH3Cl, 190°
CH2Ph
N
CH3
455

(136)



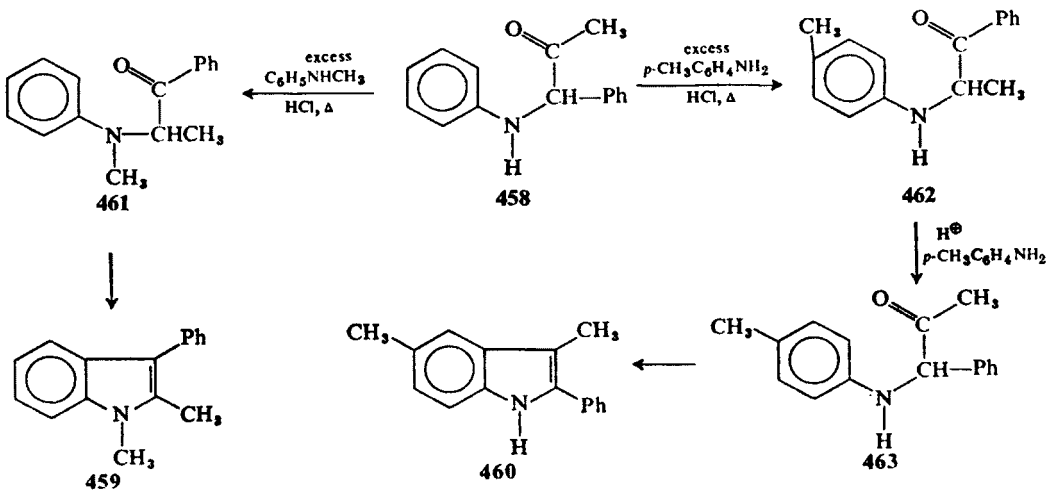
(137)

(**457**)[288a] (Eq. 137). The same product **457** is obtained, also in excellent yield, when **456** is heated with either excess aniline or excess *p*-toluidine in the presence of a catalytic amount of hydrochloric acid.[288a] Thus, **456** appears to cyclize directly before any displacement of its secondary arylamino group occurs or before any isomerization of **456** takes place. It is interesting that α-phenylaminobenzyl methyl ketone (**458**) heated with excess *N*-methylaniline in the presence of a few drops of concentrated hydrochloric acid gives only 1,2-dimethyl-3-phenylindole (**459**), the displacement-rearrangement product, whereas when **458** is heated with excess *p*-toluidine containing a catalytic amount of concentrated hydrochloric acid the only product obtained is 3,5-dimethyl-2-phenylindole (**460**), the result of a displacement but no rearrangement. Also, when **458** is heated with an equal weight of aniline hydrochloride, only 3-methyl-2-phenylindole (**398**) is produced (Scheme 38). The results suggest that the primaryarylaminoketone **458** does



Scheme 38

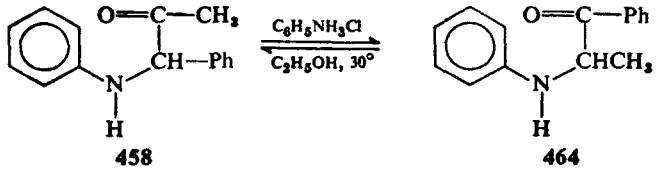
suffer displacement of its phenylamino group by the secondary arylamine, giving rise to the secondaryarylaminoketone **461** which cyclizes before it rearranges (Scheme 39) in agreement with Brown and Mann's findings.[291]


excess
$C_6H_5NHCH_3$
HCl, Δ
excess
p-$CH_3C_6H_4NH_2$
HCl, Δ
$H^{\oplus}$
p-$CH_3C_6H_4NH_2$
461
458
462
459
460
463

Scheme 39

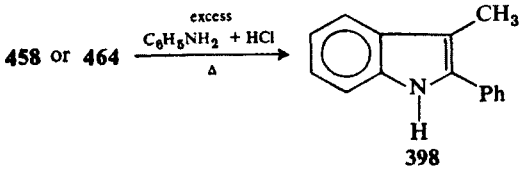
On the other hand, the phenylamino group in **458** is displaced by the *p*-toluidine moiety, probably to form **462** which rearranges rapidly to the isomer **463** before any cyclization occurs (Scheme 39).

Support for the isomerization of **462** to **463** and the preferential cyclization of **463** is obtained from the finding[290] that the isomers **458** and **464** can be equilibrated when warmed with aniline hydrochloride in ethyl alcohol (Eq. 138) but when either isomer is heated vigorously in aniline containing aniline



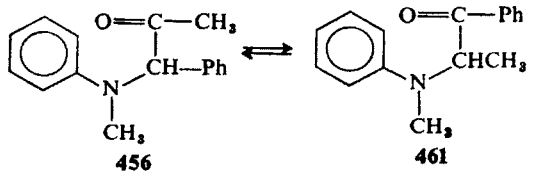
458 **464** (138)

hydrochloride, only 3-methyl-2-phenylindole (**398**) is formed (Eq. 139). It



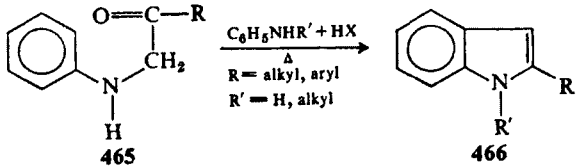
398 (139)

is clear that the tendency to isomerize and the relative stability of the *N*-alkyl isomers **456** and **461** should also be examined (Eq. 140).



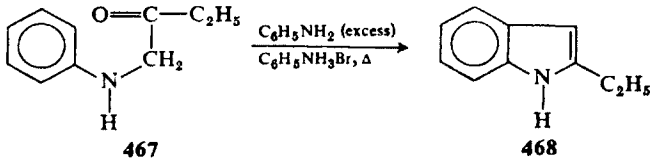
456 **461** (140)

The α-primaryarylaminoketones **465** in which R is alkyl or aryl, when heated in the presence of excess arylamines containing a halogen acid, generally provide the displacement-rearrangement product **466** (Eq. 141).



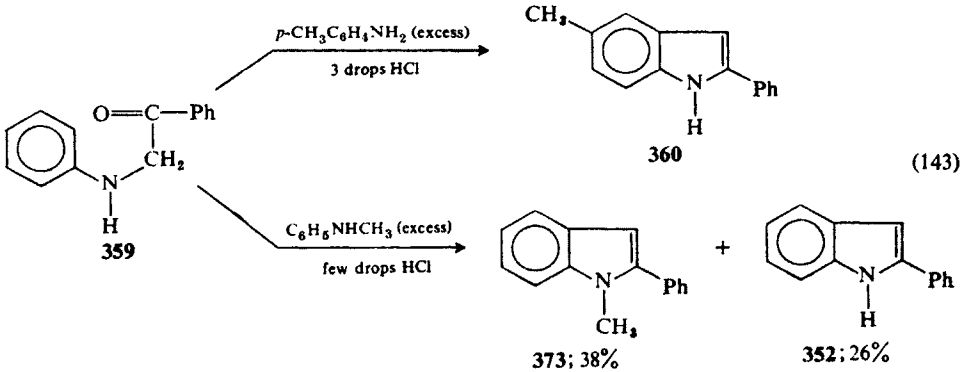
465 **466** (141)

This can be illustrated by several examples. Although the formation of 1-phenylamino-2-propanone (**465**, R = CH_3) by the reaction of α-haloacetone with aniline has been unsuccessful,[322] the preparation of 1-phenylamino-2-butanone (**467**) by the same procedure has been achieved.[307] Treatment of **467** with excess boiling aniline containing aniline hydrobromide gave only



467 468 (142)

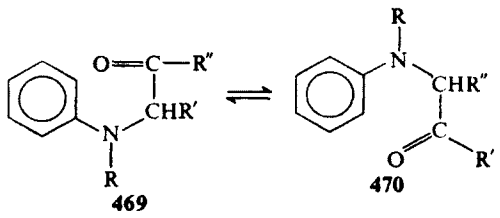
the rearrangement (and displacement?) product **468** (Eq. 142). Similar treatment of the homologous 1-phenylamino-2-pentanone, presumably obtained from the reaction of aniline with 1-bromo-2-pentanone,[323] failed to provide an indole; therefore, it is not known whether a rearranged product, 2-*n*-propylindole, would be formed. Only displacement-rearrangement products **360** and **373** were obtained from the reaction of phenacyl anilide (**359**) with boiling excess *p*-toluidine or boiling excess *N*-methylaniline in the presence of a few drops of concentrated hydrochloric acid[288a] (Eq. 143). The 2-phenyl-



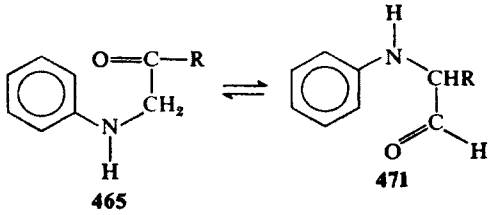
(143)

indole (**352**) obtained as a second product of the latter reaction might also be the result of a displacement-rearrangement process in which the aniline, displaced by *N*-methylaniline, becomes part of the solvent and reacts apparently more readily with the remaining phenacyl anilide (**359**) than does the solvent.

It is quite obvious from the preceding general discussion that more information must be obtained concerning the relative ease of isomerization and of direct cyclization of various isomeric pairs of α-arylaminoketones **469** and **470**. Certainly both the steric and electronic properties of the substituents

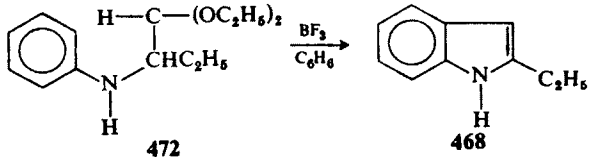


R, R′, and R″ could influence these reactions. It would be revealing to discover whether the phenacyl anilide **465** (R = Ph) or 1-phenylamino-2-propanone (**465**, R = CH_3) would isomerize to the corresponding isomers α-phenyl-α-phenylaminoacetaldehyde (**471**; R = Ph) and α-phenylamino-



465 **471**

propionaldehyde (**471**, R = CH_3) or *vice versa*, and which of the two isomeric pairs would cyclize more readily. It has been found[286] that α-phenylaminobutyraldehyde diethylacetal (**472**) in the presence of boron trifluoride in



472 **468** (144)

benzene produces 2-ethylindole (**468**) (Eq. 144), but that the homolog, α-phenylaminopropionaldehyde diethylacetal, when heated in the presence of *aniline hydrobromide*, failed to indolize. On steric grounds, one should expect **471** to cyclize more readily than would its isomer **465**.

In much of the experimental work described above, comparisons were made between α-arylaminoketones of different structures and subjected to different reaction conditions. Certainly, careful studies should be made in which compounds which are to be compared are given identical treatment. More attention should also be devoted to the examination of all products to be obtained or measured in as quantitative a manner as possible.

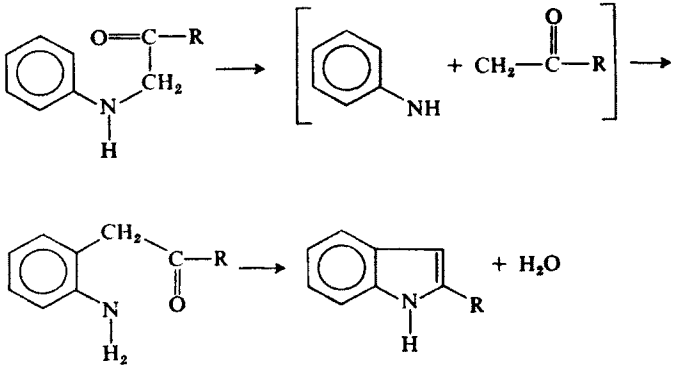
1. *Mechanisms Advanced for the Bischler Reaction*

Three mechanisms have been proposed to explain the course of the Bischler reaction. These can be considered as (*a*) the Bischler or enediamine mechanism, (*b*) the "ortho shift" hypothesis, and (*c*) α-aminoketone isomerization and direct cyclization mechanism.

a. THE BISCHLER OR ENEDIAMINE MECHANISM.[4, 5, 290, 302, 303] This mechanism, which has been described earlier in this exposition, requires the quantitative reaction of a second arylamine with the α-arylaminoketone to form

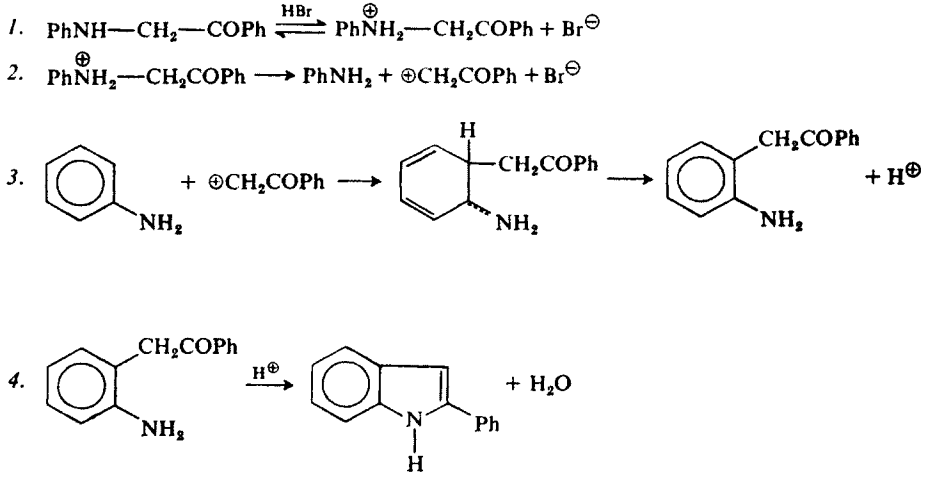
an "anilino-anil" **356** or "enediamine" **357** which then decomposes by expulsion of the original arylamino residue to form the indole. If the diamine is present only in a small amount and decomposes rapidly under the reaction conditions to form the indole, then the liberated original arylamine can become the "second arylamine" and thus can react with the arylaminoketone to form an indole containing the nitrogen of the original amine. This must occur in cases where the Bischler reaction takes place when no arylamine is added[292, 318] and is supported by the finding that an alpha C—N bond is easily cleaved under strong acidic conditions.[324] Several reports do show that an indole containing the original amine nitrogen is also obtained as one of the products.[288, 289] No doubt Bischler[302, 303] was unable to obtain such an indole because of the large excess of added amine. The ^{14}C-labeled experiments of Weygand and Richter[292] certainly cannot be accommodated by the three steps (see p. 319) proposed for the Bischler reaction.

b. THE "ORTHO SHIFT" HYPOTHESIS. This hypothesis was advanced by Janetzky and Verkade[288] and by Crowther, Mann, and Purdie.[289] The extensive studies of Verkade et al.[26, 288, 305, 314, 321, 324a, 325] led to the postulation that α-arylaminoketones could cleave to form a ketone and an arylamine residue which then by an *intra*molecular migration formed an *ortho*-substituted arylamine that cyclized to the indole (Scheme 40). An inter-



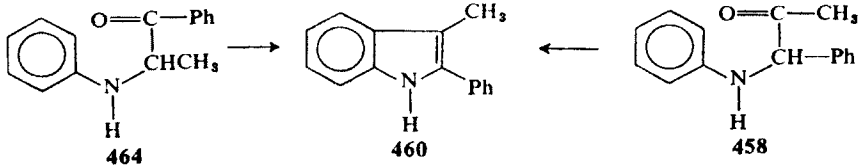
Scheme 40

molecular reaction with added amine would also provide the same results. Independently of Verkade et al., Crowther, Mann, and Purdie[289] proposed a similar scheme but in more modern terms. According to their view, the reaction took place by the sequence of steps given in Scheme 41. The reaction of the carbonium ion with the *para* position of the original amine or the added amine is also quite possible and no doubt would provide side products and thus result in a decrease in yield of the desired indole.



Scheme 41

The objection[290] to this scheme was that it does not explain why an "ortho shift" occurs with α-methylphenacyl anilide (**464**) to form 3-methyl-2-phenylindole (**460**) but does not occur when α-phenylaminobenzyl methyl ketone (**458**) is converted to the same product **460** (Eq. 145).

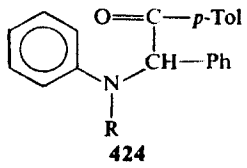


(145)

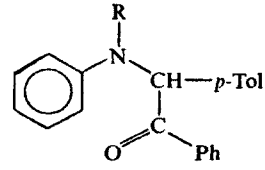
c. The α-Arylaminoketone Isomerization and Direct Cyclization hypothesis. As a result of the discovery[312] that the reaction of aniline with α-bromo-β-phenylpropiophenone (**399**) at 60° gave a mixture of the two α-arylaminoketones, α-benzylphenacyl anilide (**400**) and α-phenylaminodibenzylketone (**401**), and that such isomeric pairs of α-arylaminoketones are interconvertible under the influence of acid catalysts,[290, 291, 307, 319, 323] Brown and Mann[291] proposed a mechanism to explain the course of the Bischler reaction of phenacyl anilides in the presence of arylamines and arylamine hydrohalides, and which took into account the following features they had discovered.[291]

(*1*). The pure compounds **424** and **425** are stable to 200°.

(*2*). In the presence of acid and moderate heat, **425** (R = H) isomerizes



424



425

to **424** (R = H) but the reverse does not occur. The *N*-alkylated derivatives do not isomerize. Hydrogen bromide in the presence of an arylamine is a better catalyst than is hydrogen bromide alone.

(*3*). The pure, dry hydrobromic acid salt of **425** does not isomerize when heated, but decomposes instead.

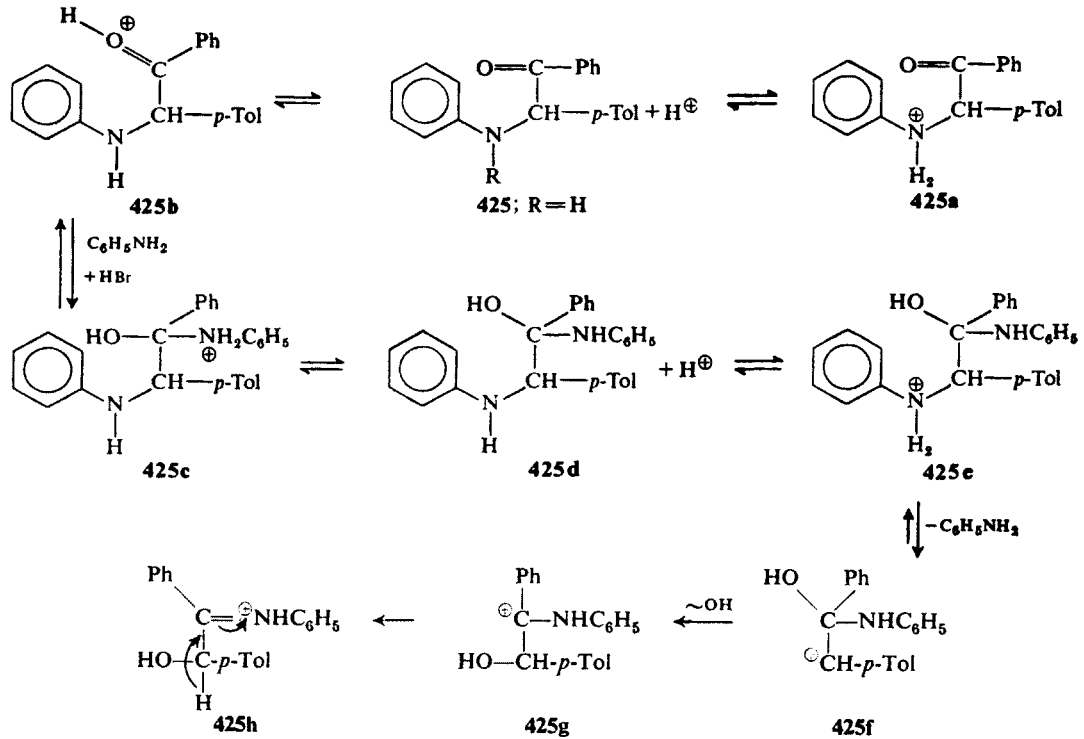
(*4*). Isomer **424** (R = H) is cyclized directly to the indole by acid catalysts at higher temperature while **425** (R = H) first isomerizes to **424** which then cyclizes.

(*5*). Compound **424** (R = CH_3 or C_2H_5) and Compound **425** (R = C_2H_5) always give direct (normal) cyclization with an acidic catalyst, but **425** (R = CH_3) cyclizes "directly" only with alcoholic zinc chloride and forms the *rearranged* product with zinc chloride at higher (fusion) temperatures.

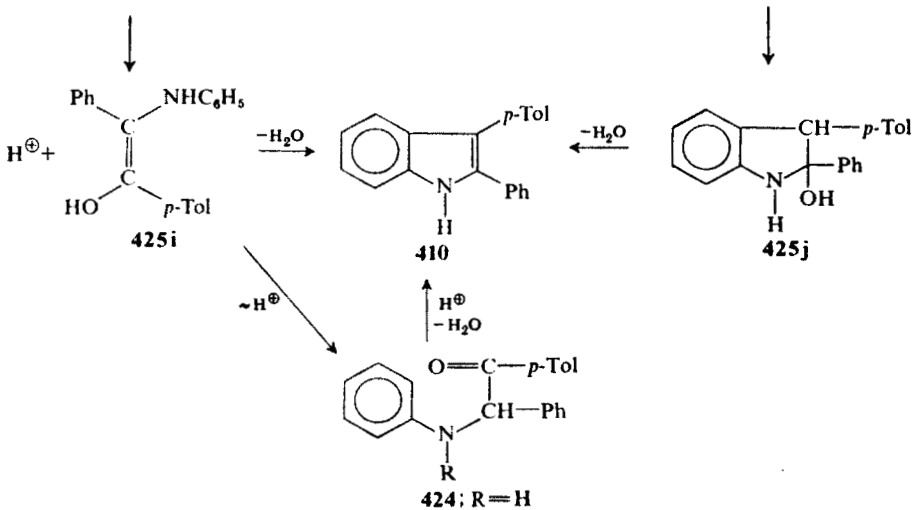
The mechanistic sequence proposed by Brown and Mann is illustrated in Scheme 42 using α-*p*-tolylphenacyl anilide (**425**, R = H) and showing how it is converted to the isomer α-phenyl-*p*-methylphenacyl anilide (**424**; R = H).

Brown and Mann[291] consider that the acid-catalyzed isomerization of **425** to **424** (R = H) is a fundamental problem in the Bischler reaction. If this is a general phenomenon, then the formation of 2-phenylindole (**352**) from phenacyl anilide (**359**) takes place by the initial conversion of phenacyl anilide to its isomer α-phenyl-α-phenylaminoacetaldehyde which would then cyclize directly (Eq. 146).

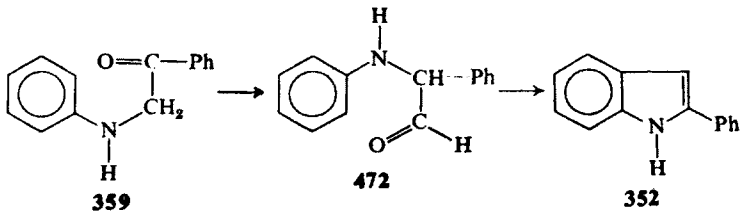
Since both **424** and **425** in the pure state are stable when heated to 200°, it is clear that certainly for this pair of isomeric α-arylaminoketones an acid catalyst is necessary to effect reaction. Protonation of **425** could occur either on the nitrogen or on the oxygen atom. If the nitrogen atom is protonated the inactive salt **425a** is formed. This does not isomerize when pure and dry. The presence of some free arylamine would permit reversible proton transfer from the nitrogen to the oxygen atom to provide **425b**. The work of Brown and Mann[291] has shown that the combination of an arylamine with some halogen acid is a better catalyst than is the halogen acid alone. The protonated species **425b** then adds an arylamine to form **425c**. Proton transfer, possibly aided by the added arylamine, first forms the neutral intermediate **425d** which then is converted to **425e**. The species **425e** loses


425b
425; R=H
425a
$C_6H_5NH_2$
+HBr
425c
425d
425e
$-C_6H_5NH_2$
425h
425g
425f

Scheme 42



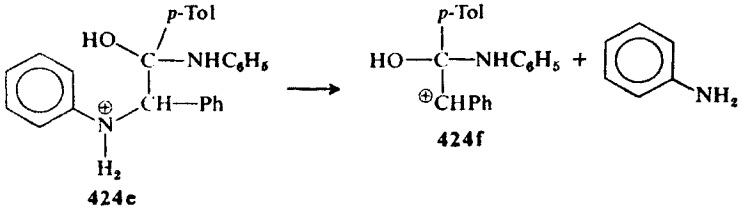
Scheme 42 (continued)



(146)

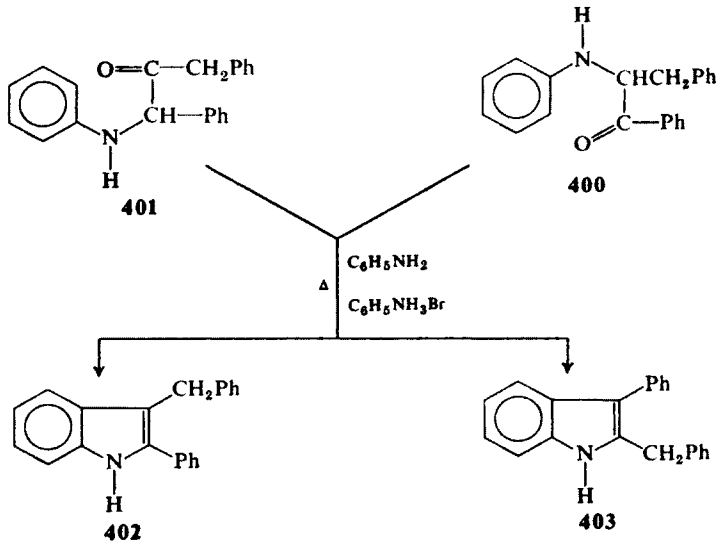
aniline, possibly anchimerically assisted by the hydroxy[318] or arylamino group on the adjacent nitrogen to form the carbonium ion **425f**. Under appropriate conditions, possibly that of higher temperature, this positively charged species could cyclize directly to the indoline **425j** which by loss of water would provide the indole **410**. Under milder conditions **425f** experiences an intramolecular rearrangement of the hydroxy group to form **425g** which then could form the enol **425i** via **425h**. By a prototropic shift, **425i** would form the isomeric α-arylamino ketone **424** (R = H). At higher temperatures and in the presence of an acid catalyst **424** could cyclize directly to the indole **410**, or first enolize to **425i**, then cyclize to **410**.

The fact that **425** (R = H) isomerizes to **424** (R = H) but the reverse has not been observed implies that **425e** loses aniline to form the carbonium ion **425f** much more readily than the alternate intermediate **424e** would lose aniline to form **424f** as part of a similar sequence which could be written for a possible conversion of **424** to **425** (R = H) (Eq. 147). This point has been



(147)

rationalized[291] on the basis of enhancement of the stability of the positive charge in **425f** due to participation of the *para* methyl group. Such additional stabilization of the positive charge in **424f** is lacking. It has been suggested[291] that the effect of other substituents should be examined in this regard. In cases where the isomeric α-arylaminoketones are both formed and both provide their respective indoles, then both must form positively charged species analogous to **424f** and **425f** which have similar stability. This might well be the situation with respect to α-anilino dibenzylketone (**401**) and its isomer α-anilino-β-phenylpropiophenone (**400**), either of which when heated with aniline containing aniline hydrobromide provides both 3-phenyl-2-benzylindole (**403**) and 2-phenyl-3-benzylindole (**402**)[290] (Scheme 43).



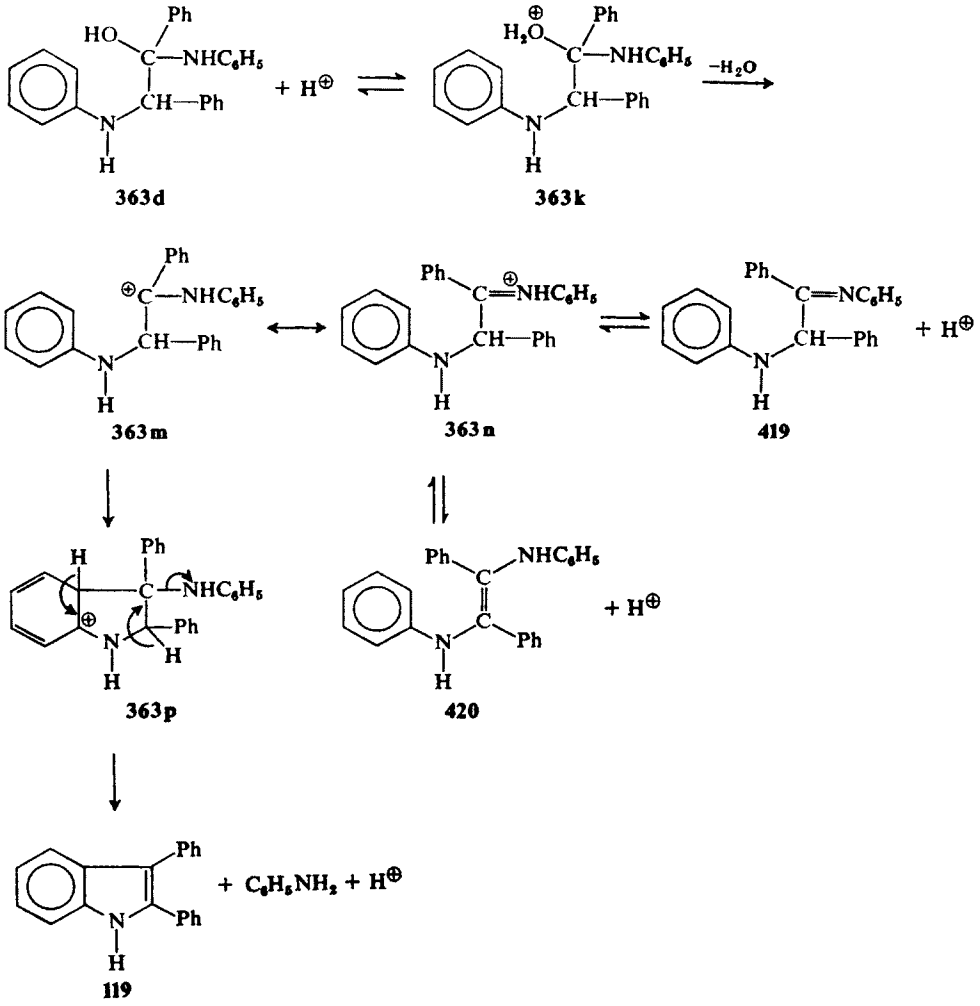
Scheme 43

The failure of the *N*-alkylated homologs to isomerize has been interpreted[291] on the basis of the finding[326] that the basic strength of *N*-methylated anilines increases in the order $C_6H_5NH_2 < C_6H_5NHCH_3 < C_6H_5N(CH_3)_2$, and that the difference in basic strength between *N*-methylaniline and *N*-ethylaniline is considerably greater than that between aniline and *N*-methylaniline. In the light of this information it is reasonable to assume that the equilibrium between **425** and **425a** is much more in favor of **425a** when the nitrogen is alkylated. The more stringent conditions necessary to convert **425a** to **425b** when the nitrogen is alkylated, and hence to initiate the sequence **425b** → **425i** → **424**, would also be sufficient to promote *direct* cyclization of **425** (and also **424**) to the respective indoles **427** and **426** (R = CH_3 or C_2H_5). This may also explain why **425** (R = CH_3) but not **425** (R = C_2H_5) isomerized to **424** (R = CH_3) and then cyclizes to 1-methyl-2-phenyl-3-*p*-tolylindole (**426**, R = CH_3) when fused with zinc chloride.

Julian et al.[290] had actually obtained from the controlled reaction of aniline with desylaniline (**363**) a product which analyzed correctly for either the aniline anil **419** or the enediamine **420**, and which could be converted to 2,3-diphenylindole (**119**) when heated in refluxing aniline containing some hydrochloric acid. Campaigne and Lake[295] have also obtained evidence that an anilino anil can be obtained from the Bischler reaction. Accordingly, any mechanism advanced for the Bischler reaction must accommodate these facts. Weygand and Richter[292] have pointed out that in the sequence of steps **425** → **425b** → **425i** → **424** proposed by Brown and Mann,[291] one perceives

a diamine or anilino anil **425d** which has retained a molecule of water. It is quite possible that under controlled conditions and with a molecule of appropriate structure, an intermediate such as **425d** could lose water to form the diamine, which in turn upon treatment with acid would cyclize to the indole. This is illustrated in Scheme 44, with the adduct **363d** of desyl-aniline **363** and aniline as examples.

It is conceivable that structure **363d** could be protonated on the oxygen atom by aniline hydrobromide acting as the proton transfer agent. The protonated species **363k** would then lose water quite readily to form the



Scheme 44

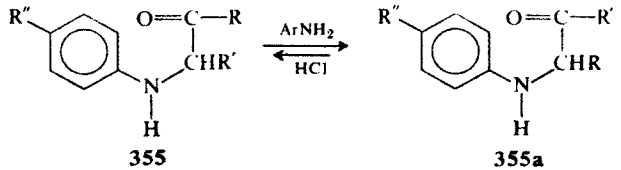
carbonium ion **363m** which is stabilized by electron contribution from both the phenyl and anilino moieties. Proton loss could then occur from **363n** to form either the anilino anil **419** or the enediamine **420**. It is quite clear that protonation of either **419** or **420** could produce the species **363n** which could either add water and form **363d**, or under more stringent conditions could cyclize directly to form 2,3-diphenylindole, probably through the intermediate **363p**. Thus the mechanism of Brown and Mann also accommodates the formation and subsequent indolization of the anilino anil or enediamine.

In their tracer experiments, Weygand and Richter[292] had found that a mixture of equimolar quantities of phenacyl anilide and ^{14}C-labeled aniline, heated for a few minutes at 180° in the presence of aniline hydrobromide, gave 2-phenylindole and aniline with the ^{14}C-activity equally divided between these two products. Of more significance was their second observation that when the above mixture was heated to only 100° for a short time, the phenacyl anilide which was obtained as the only product had undergone some arylamine exchange, in one case to the extent of 59% and in another to the extent of 32%. These findings can be explained by either the C—N cleavage and the "ortho shift"[288, 289] or the α-arylaminoketone isomerization and direct cyclization mechanism.[291] In order for this to be so it must be assumed that steps **425** to **425f** in Brown and Mann's mechanism[291] must be rapid and reversible. This could easily be so in the case of the reaction of phenacyl anilide (**359**) with aniline shown in Scheme 45 (**359** to **359f**).

More stringent conditions would then continue the reaction, possibly through the steps suggested, **359f** → **359i**, to the 2-phenylindole (**352**).

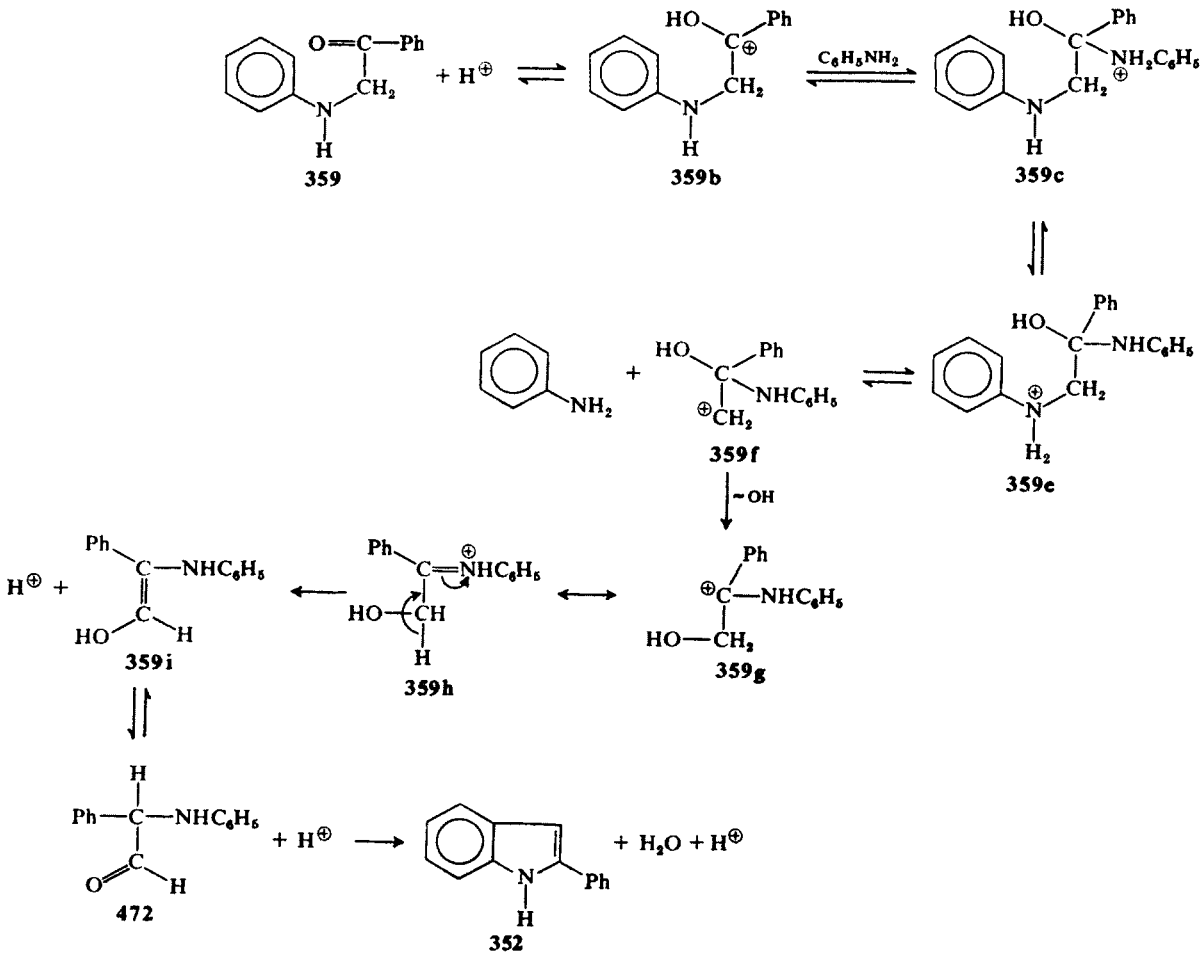
2. *Effect of Substituents on the Course of the Bischler Reaction*

a. Substituents Attached to the Carbonyl Group and/or the α-Carbon of the α-Arylaminoketone. It has already been shown in the previous discussion (pp. 330–332) that the substituents R and R′ in the α-arylaminoketone **355** have a pronounced effect in some cases on the position of the equilibrium between the two isomers **355** and **355a** (Eq. 148). When



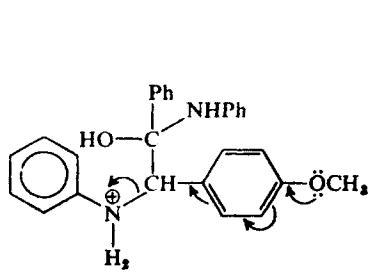
355 **355a** (148)

R is phenyl, R″ is H, and R′ is either *p*-tolyl[291] or *p*-anisyl,[319] or when R is *p*-chloro(or bromo)phenyl, R″ is chlorine or bromine, and R′ is *p*-anisyl,[318] the equilibrium attained by heating **355** in the presence of the appropriate

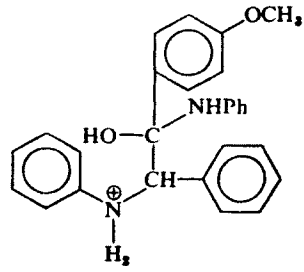

359
359b
359c
359e
359f
359g
359h
359i
472
352
$C_6H_5NH_2$
$-OH$
$+ H^{\oplus}$
$+ H_2O + H^{\oplus}$

Scheme 45

arylamine and an halogen acid lies well to the right and thus the chief indolic product obtained when the temperature of the reaction mixture is increased is that which appears to arise from direct cyclization of **355a**. This agrees with step **425e** → **425f** (pp. 354–355) of Brown and Mann's mechanism[291] in which separation of the arylamine from the ketone moiety is easier when R′ in **355** is a phenyl group with an electron-donor substituent (CH_3 or CH_3O) in the *para* position with the phenyl group R being unsubstituted, e.g., **473**, than in the case of the isomer **474**.

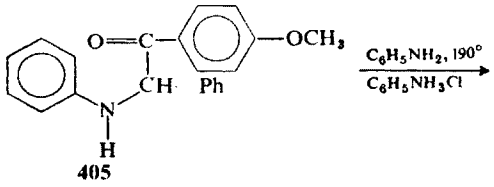


473



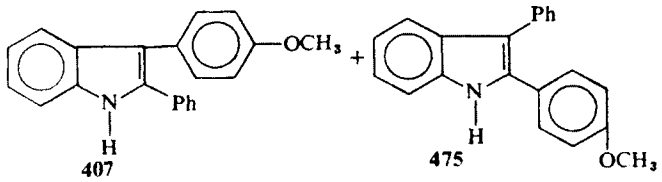
474

The apparently exclusive formation of 3-*p*-anisyl-2-phenylindole (**407**) from the reaction of aniline with 4-methoxybenzoin heated in excess aniline containing aniline hydrochloride[327] also illustrates this point. The isolation of both 3-*p*-anisyl-2-phenylindole (**407**) and 2-*p*-anisyl-3-phenylindole (**475**) in the ratio 4:1, respectively, when α-phenylamino-4-methoxydeoxybenzoin (**405**) was heated in aniline containing aniline hydrochloride[328] is another example (Eq. 149). This latter case shows as well that although the equilibrium favors **405**, the isomer α-(*p*-anisyl)phenacyl anilide (**404**) is formed to some extent and that both isomers appear to cyclize directly to the respective indoles **407** and **475**. This indicates that in the two cases previously cited



405

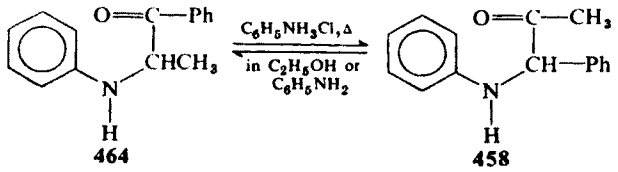
(149)



407 **475**

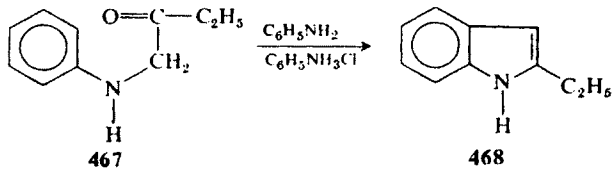
(Refs. 291 and 327) both isomeric α-arylaminoketones might in fact be present and form the respective isomeric indoles but that the minor component could not be isolated.

On the basis of the reasoning provided by Brown and Mann,[291] the equilibrium between α-phenylaminopropiophenone (**464**) and its isomer α-phenylaminobenzyl methyl ketone (**458**) should lie well towards **464** (Eq. 150). Two reports[290, 293] have shown that either isomer **464** or **458**, when



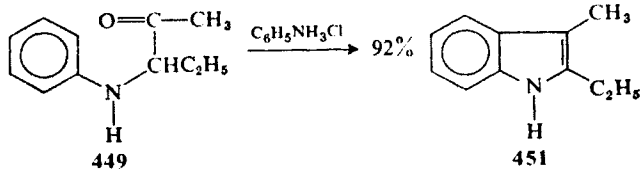
464 **458** (150)

heated for 2 hr in boiling ethanol or in aniline at 100° in the presence of aniline hydrochloride, was converted partly to the alternate isomer (**458** or **464**). Unfortunately, the yields of isolated materials were generally quite low, hence no definite statement can be made regarding the real proportion of the two products **464** and **458** in this case, except that both isomers are much more alike in stability than is the case for the isomeric pair **405** and **404**[319] cited above or for the isomeric α-phenylaminoketones **424** and **425** (R = H) of Brown and Mann.[291] However, when either isomer **464** or **458** is heated in boiling aniline containing aniline hydrochloride, apparently the only indole obtained is 3-methyl-2-phenylindole (**398**), the product of the direct cyclization of **458**. This suggests that the electronic and/or steric environment about the carbonyl group is important in determining the ease of cyclization. In this case, a methyl substituent attached to a carbonyl group (e.g., **458**) results in more facile cyclization than occurs when a phenyl group is attached to the carbonyl moiety (e.g., **464**). Such factors may account for (*1*) the observation that ethyl phenylaminomethyl ketone **467**, heated with excess aniline containing aniline hydrochloride, provided only 2-ethylindole (**468**)[307] (Eq. 151); (*2*) the finding that 3-phenylamino-2-pentanone (**449**) heated with aniline hydrochloride gives an excellent

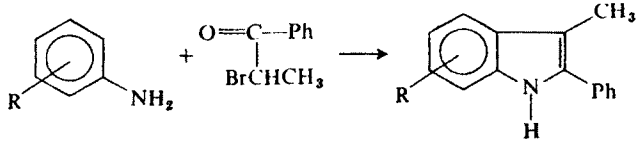


467 **468** (151)

yield of 2-ethyl-3-methylindole (**451**)[314] (Eq. 152); and (*3*) the apparent production of only the 3-methyl-2-phenylindoles when substituted anilines were heated with α-bromopropiophenone[329] (Eq. 153).

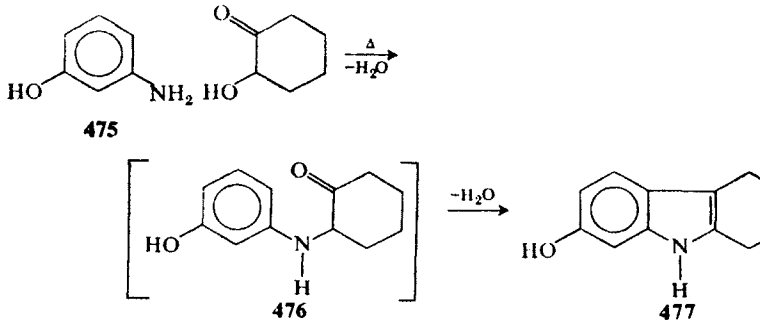


449 451 (152)



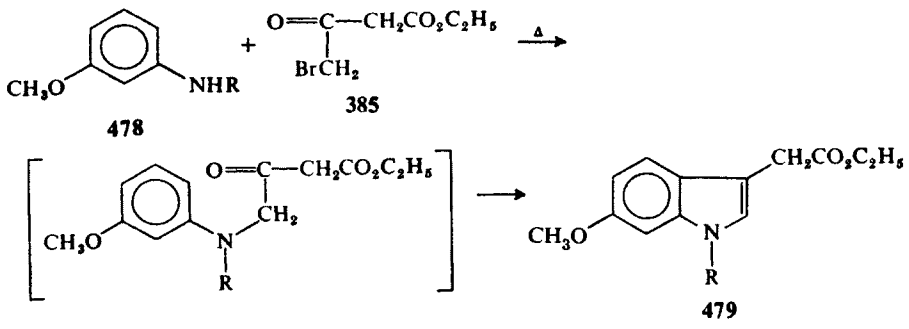
(153)

b. SUBSTITUENTS IN THE AROMATIC RING OF THE ARYLAMINE. The presence of electron-donor substituents in the benzene ring of the arylamino group of α-arylaminoketones appears to enhance the ease of cyclization to the indolic product. The compound *m*-aminophenol (**475**) reacts exceptionally easily with 2-hydroxycyclohexanone without the aid of an acid catalyst to provide 7-hydroxy-1,2,3,4-tetrahydrocarbazole (**477**) (Eq. 154). None of the



(154)

intermediate compound, 2-(*m*-hydroxyanilino)cyclohexanone (**476**), was obtained.[330, 331] The isomeric *o*-hydroxyaniline also reacted very easily with 2-hydroxycyclohexanone but produced a compound $C_{12}H_{15}O_2N$ which was not the expected 8-hydroxy-1,2,3,4-tetrahydrocarbazole.[330] *N*-Methyl-*m*-anisidine (**478**, R = CH_3) can be condensed with ethyl γ-bromoacetoacetate (**385**) and the resulting α-arylaminoketone cyclized to ethyl 1-methyl-6-methoxy-3-indolylacetate (**479**, R = CH_3) merely by heating the reactants **478** (R = CH_3) and **385** in boiling benzene or in boiling ethyl alcohol[297] (Eq. 155). An 85% yield of ethyl 1-benzyl-6-methoxy-3-indolylacetate (**479**, R = $C_6H_5CH_2$) is readily obtained from the reaction of *N*-benzyl-*m*-anisidine (**478**, R = $C_6H_5CH_2$) with **385**.[332] The fact that *p*-benzyloxy-*N*-methylaniline and the bromoester **385** heated with zinc chloride, failed to provide an isolable indole was believed due to the sensitivity of the benzyloxy group to zinc chloride since the same two reactants, merely heated in refluxing



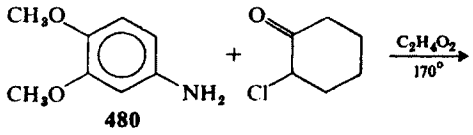
478 385 479

(155)

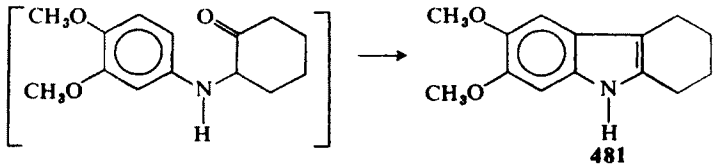
dry ethanol gave ethyl 5-benzyloxy-1-methyl-3-indolylacetate which could be hydrolyzed to the free acid in 40% yield.[297]

This increased ease of reaction might be attributed to one or more of the following factors. The first is that the electron donor (OH or CH_3O) increases the ease of electrophilic attack on the ring, particularly *para* to the substituent. This would facilitate any cyclization that occurs either by direct ring closure of **476** or by ring closure by the route involving participation of a second molecule of arylamine (Ref. 291, see also pp. 355–357 and 360 of this article). The second factor is that, if the latter process involving participation of a second molecule of arylamine is actually the route by which reaction occurs, then the presence of an electron-donor group in the arylamine ring would enhance the nucleophilicity of the amine and facilitate attack on the carbonyl group. Furthermore, an electron-donor substituent would increase the basicity of the arylamine and hence a higher concentration of the protonated species **425e** would be present (pp. 355, 356) in the mechanistic sequence of Brown and Mann,[291] with a consequent increase in the rate of loss of the arylamine moiety from the α-arylaminoketone. The rate-determining step of the Bischler reaction is not known, and no kinetic work has been reported to assist in the analysis of the mechanism. However, since it is known that α-arylaminoketones can isomerize under relatively mild conditions prior to cyclization[290, 291, 293, 318, 319] and because the work of Julian et al.[290] has shown that the formation of the anilino anil (or enediamine) might be a step in the Bischler reaction *following* any isomerization of the α-arylaminoketone and *preceding* its cyclization, and also because cyclization to the indole requires more stringent conditions than those employed to obtain the anilino anil,[290] it is quite likely that the rate-determining step for the over-all reaction of indole formation involves the electrophilic attack by the protonated carbonyl group or its equivalent on the arylamino ring.

The reaction of 4-aminoveratrole (**480**) with 2-chlorocyclohexanone heated to 170° in the presence of dry acetic acid, providing only 6,7-dimethoxy-1,2,3,4-tetrahydrocarbazole (**481**) in 40% yield, may be another example of



(156)

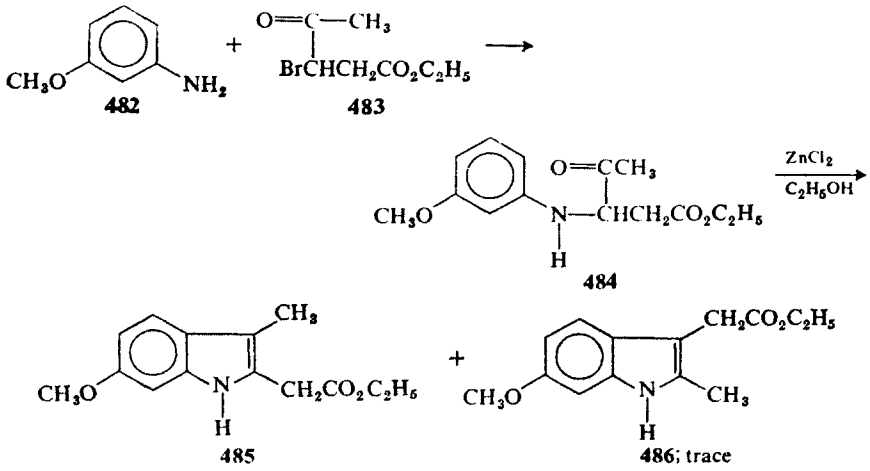


enhanced ease of reaction caused by the two methoxy substituents[333] (Eq. 156).

The introduction of one or more alkyl groups into the arylamino ring should also facilitate the Bischler reaction. However, the reported yields of indoles, ranging from 2.5 to 85%, give no clear indication that this is so. Certainly, from consideration of yields alone, without the benefit of rate studies, no conclusion can be drawn concerning the relative ease of reaction. The following examples illustrate the kind of results obtained.

The reaction of excess 4-amino-*o*-xylene and of excess 2-amino-*p*-xylene with 2-chlorocyclohexanone[294] gave 6,7-dimethyl-1,2,3,4-tetrahydrocarbazole and 5,8-dimethyl-1,2,3,4-tetrahydrocarbazole in 13 and 37% yield, respectively. The low yields, particularly of 6,7-dimethyl-1,2,3,4-tetrahydrocarbazole, are believed due to the extreme ease with which this compound absorbs a mole of oxygen during crystallization from light petroleum, presumably to form a hydroperoxide.[294] Further loss of yield might be due to a reaction of the arylamine with 2-chlorocyclohexanone to form the dehydrohalogenated molecule cyclohex-2-en-1-one.[334] It has been found that *p*-anisidine, *p*-phenetidine, and *p*-toluidine, heated at 145–155° with 2-hydroxycyclohexanone with a catalytic amount of hydrochloric acid as initially advocated,[315] failed to give the expected tetrahydrocarbazole but provided instead the 2-*p*-alkoxy (or methyl) anilinocyclohexanone.[335] However, if phosphorus oxytrichloride was used as catalyst instead of hydrochloric acid, the condensation and cyclization did occur at 150–160° to form the corresponding 6-substituted-1,2,3,4-tetrahydrocarbazoles but only in yields of 10–30%.[335] The reaction of benzoin, either with *m*- or *p*-acetaminoaniline in hot nitrobenzene containing some *p*-toluene-sulfonic acid or with *m*- or *p*-phenylenediamine in refluxing xylene containing the same acid catalyst, has provided the corresponding 6- and 5-acetamino- (or amino-) 2,3-diphenylindoles in fair to good yield.[336] Cyclization of phenacyl *m*-toluidide has given 6-methyl-2-phenylindole in 43% yield.[311] The reaction of α-bromopropiophenone, heated at 180° with an excess of aniline, or aniline substituted

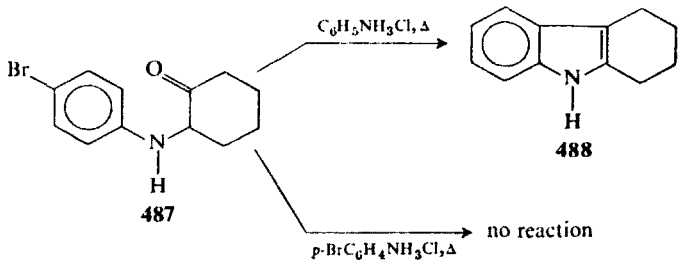
in the *para* or *meta* positions by CH_3 or CH_3O, provides in 50–84% yield the corresponding 5- or 6-substituted-3-methyl-2-phenylindoles.[329] The room temperature reaction of excess *m*-anisidine (**482**) with ethyl β-bromolevulinate (**483**) readily provided the corresponding ethyl β-(*m*-methoxyanilino)levulinate (**484**). This α-arylaminoketone was highly unstable in air, hence was not isolated but instead heated with zinc chloride in boiling ethyl alcohol and formed ethyl 3-methyl-6-methoxyindolyl-2-acetate (**485**) as the major product but only in fair yield (Scheme 46). Paper chromatography



Scheme 46

indicated that at least a minute amount of the isomer **486** was also formed.[337] A somewhat better yield of **485** was obtained when the amine **482** and the bromoester **483** were heated together in refluxing xylene.[337] Similar reactions were obtained with 2,4-dimethylaniline, *N*-methylaniline, *o*-toluidine, 2,5-dimethylaniline, and 2,3-dimethylaniline, but none of the indole-2-acetate could be isolated when *p*-toluidine, *p*-anisidine, *p*-bromoaniline, and *N*-ethylaniline were used.[337]

One would expect that electron-withdrawing substituents in the arylamine ring would *decrease* the ease of the Bischler reaction. Some cases have been reported that supports this view. Both *o*- and *p*-bromoaniline failed to react with 2-chlorocyclohexanone to produce the expected tetrahydrocarbazoles.[294] The difficulty must lie in the portion of the Bischler mechanistic sequence involving the reaction of the second molecule of arylamine and/or the electrophilic attack on the halogenated ring since 2-(*p*-bromoanilino)-cyclohexanone (**487**) when heated with aniline hydrochloride reacts to form 1,2,3,4-tetrahydrocarbazole (**488**) though in small yield, but fails to react at all with *p*-bromoaniline hydrochloride under similar conditions[294] (Eq. 157). Certainly the nucleophilicity of *p*-bromoaniline is expected to be lower than



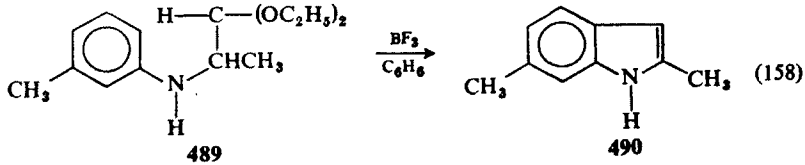
(157)

that of aniline. The failure of 3-(*p*-bromoanilino)-2-butanone to cyclize to 5-bromo-2,3-dimethylindole has also been reported.[321] Likewise, 2-(*p*-bromoanilino)cyclohexanone could not be cyclized with magnesium chloride and *p*-bromoaniline. Only tars were obtained.[295] When 2-(*p*-bromoanilino)-cyclohexanone was heated with *aniline* and magnesium chloride, a small amount of 1,2,3,4-tetrahydrocarbazole was formed. Apparently the *para*-chloro analog reacts more readily since 2-(*p*-chloroanilino)cyclohexanone, heated with *p*-chloroaniline under the same conditions, gave 6-chloro-1,2,3,4-tetrahydrocarbazole in 22% yield.[295] However, if 2-(*p*-bromoanilino)-cyclohexanone is heated with excess *p*-bromoaniline in the presence of *p*-bromoaniline *sulfate*, 6-bromo-1,2,3,4-tetrahydrocarbazole can be obtained in 60% yield, and under these conditions the 6-chloro analog is formed in 90% yield.[295] The reaction of 2-chlorocyclohexanone with methyl anthranilate and methyl *p*-aminobenzoate gave methyl 1,2,3,4-tetrahydrocarbazole-8-carboxylate (in 34% crude yield) and methyl 1,2,3,4-tetrahydrocarbazole-6-carboxylate (30% yield).[294] The reaction of *p*-aminobenzoic acid with 2-chlorocyclohexanone was unsuccessful though *m*-aminobenzoic acid did provide 1,2,3,4-tetrahydrocarbazole-7-carboxylic acid in 2.5% yield.[294]

Thus, from an examination of the reported reactions of α-arylaminoketones containing electron-withdrawing substituents in the anilino ring, the impression is gained that the Bischler reaction is retarded. Here again this conclusion can be substantiated only by comparative rate studies.

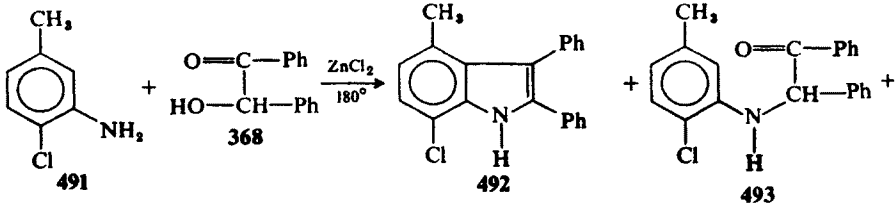
Of considerable interest is the strong preference for α-arylaminoketones with substituents in the *meta* position of the arylamino ring to cyclize by ring closure at the position *para* to the substituent, thus providing 6-substituted indoles or 7-substituted-1,2,3,4-tetrahydrocarbazoles as the chief or the sole indolic product. A number of the reactions noted in the paragraphs immediately above illustrate this effect. The finding that *m*-aminophenol reacts with 2-hydroxycyclohexanone to produce only 7-hydroxy-1,2,3,4-tetrahydrocarbazole with no discernible trace of the 5-hydroxy isomer[330] was challenged by workers who stated that the product obtained was really 5-hydroxy-1,2,3,4-tetrahydrocarbazole.[338] However, the original claim was later substantiated.[339] The isolation from the reaction of 4-amino-*o*-xylene

with 2-chlorocyclohexanone of only 6,7-dimethyl-1,2,3,4-tetrahydrocarbazole (13%) with no trace of the 5,6-dimethyl isomer[294] agrees with the observation that only one trimethylindole was obtained from the reaction of *m*-toluidine with 3-bromo-2-butanone although two isomers are possible.[321] Only 7-chloro-1,2,3,4-tetrahydrocarbazole was obtained from the reaction of *m*-chloroaniline with 2-chlorocyclohexanone[294] in agreement with Bischler's observation[340] that only one product was obtained from the cyclization of phenacyl *m*-chloroaniline hydrochloride. The reaction of *m*-toluidine and of *m*-anisidine with α-bromopropiophenone gave only 3,6-dimethyl-2-phenylindole and 3-methyl-6-methoxy-2-phenyl indole, respectively, with no indication of the presence of the 4-isomer.[329] Also, treatment of a benzene solution of 2-(*m*-toluidino)propionaldehyde diethylacetal (**489**) with boron trifluoride gave 2,6-dimethylindole (**490**)[286](Eq. 158). This strong tendency for *meta*-substituted α-anilinoketones to form the pyrrole ring by attack at the position



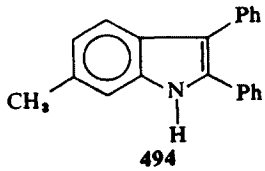
489 **490** (158)

in the arylamine ring *para* to the substituent is further illustrated by the reaction of 6-chloro-*m*-toluidine (**491**) with benzoin (**368**) heated to 180° with powdered dry zinc chloride. The products obtained were not only the expected 7-chloro-4-methyl-2,3-diphenylindole (**492**) and some uncyclized α-arylaminoketone **493**, but also 6-methyl-2,3-diphenylindole (**494**), a product arising from loss of the halogen atom[202] (Eq. 159).



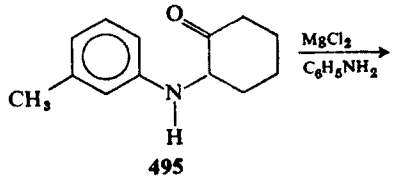
491 **368** **492** **493**

(159)



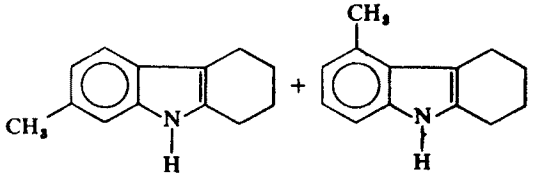
494

There is evidence that *both* isomers might be produced, with the 6-substituted indole preferred over the 4-isomer, or the 7-substituted-1,2,3,4-tetrahydrocarbazole preferred over the 5-isomer. The failure to detect and obtain both isomers is no doubt a problem of analysis and separation. When 2-(*m*-toluidino)cyclohexanone (**495**) was heated in cellosolve containing magnesium chloride and aniline, there was obtained a 3:1 mixture of 7-methyl-1,2,3,4-tetrahydrocarbazole (**496**) and 5-methyl-1,2,3,4-tetrahydrocarbazole (**497**) from which the former crystallized readily, but the latter could not be separated in the pure state either by crystallization or chromatography[295] (Eq. 160).



495

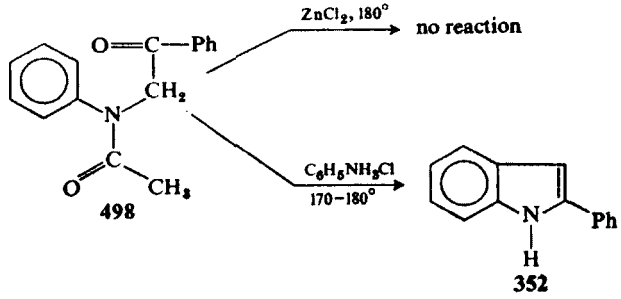
(160)



496 **497**

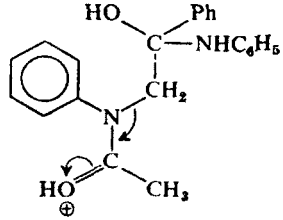
Since all of the above examples of *meta*-substituted anilines contained either an alkyl, an alkoxy group, or an halogen atom as the substituent, all of which are known to favor electrophilic substitution at the position in the aromatic ring *para* to themselves, this directive effect in the Bischler reaction supports the view that the ring closure occurs by an ionic rather than free radical mechanism. However, a steric effect may also play a prominent part and direct the attack on the least encumbered position of the arylamine ring. This gains some support from the observation that *m*-aminobenzoic acid reacts with 2-chlorocyclohexanone to provide 1,2,3,4-tetrahydrocarbazole-7-carboxylic acid as the only isolable product though only in 2.5% yield.[294]

c. Substituents on the Nitrogen Atom of the Arylamine Although phenacyl anilide heated with zinc chloride readily provides 2-phenylindole (**352**),[67] the *N*-acetyl derivative **498**, heated with zinc chloride to 180°, remained unchanged[289] (Eq. 161). But if phenacyl *N*-acetylanilide (**498**) is heated with aniline hydrochloride, 2-phenylindole (**352**) is obtained.[341] It is considered[341] that this might arise by a preliminary deacetylation followed

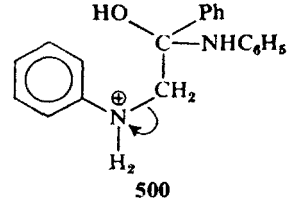


498 352 (161)

by the usual cyclization according to the Bischler reaction.[288a] However, it is possible that aniline could react with the carbonyl group and initiate the elimination of the acetanilide moiety, possibly by anchimeric assistance from the α-hydroxyl or α-arylamino group in the species **425d** (see pp. 355–357) of the Brown and Mann mechanism[291] or by transient epoxide formation (see pp. 331–332) according to Nelson's view.[293, 318] The acetanilide moiety should be a better leaving group than the unacetylated amine, although the latter would be more readily protonated because it is a stronger base (compare **499** and **500**).



499



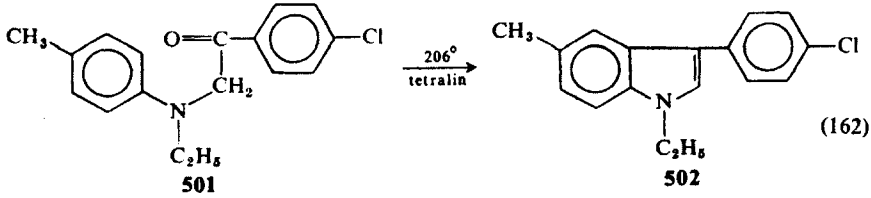
500

Alkyl groups attached to the nitrogen atom of α-arylaminoketones are reported to increase the resistance of the α-arylaminoketone to isomerization[291] and also cause indolization to occur preferentially by a direct ring closure process. However, this peculiarity depends to a large extent on the structure of the ketone. The discussion on pp. 334–335, 349–350 provides information in this regard. Several cases are reported in which the alkyl group on the nitrogen of the α-arylaminoketone apparently offers no serious hindrance to cyclization. The reaction of ethyl γ-bromoacetoacetate with *N*-methyl-*p*-anisidine provides 5-methoxy-1-methyl-3-indolylacetic acid in 26% yield whereas with *N*-methyl-*o*-anisidine, the isomer 7-methoxy-1-methyl-3-indolyl-acetic acid, is obtained in only 1.5% yield. The analogous *N*-methyl-*o*-toluidide under the same conditions forms 1,7-dimethyl-3-indolylacetic acid in 20% yield.[297] The reaction of ethyl 5-bromo-3-methyllevulinate and of ethyl 5-bromo-3,3-dimethyllevulinate with several secondary arylamines with or without an alkyl or an alkoxy substituent in the aryl ring also provide

the corresponding 3-indolylacetic acids in fair yield.[297] Stroh and Beitz[337] have reported a difference in the ease of reaction between *N*-methylaniline and *N*-ethylaniline. The former reacts with ethyl β-bromolevulinate to produce ethyl 1,3-dimethyl-2-indolylacetate whereas the latter fails to provide the analogous indole.

3. *Thermal Cyclization in the Bischler Reaction*

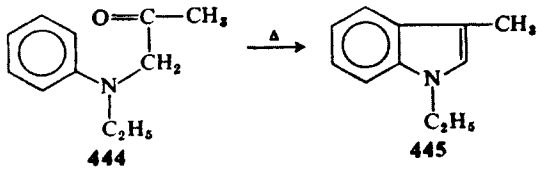
Although Bischler[302, 303] had suggested that the reaction of α-phenylaminoketones to form indoles required the intervention of a second molecule of arylamine, later work[288a, 289, 291, 309-312] clearly showed that an acid catalyst also appeared to be necessary (see pp. 323–325). However, it has been shown[289] that the conversion of *p*-chlorophenacyl *N*-ethyl-*p*-toluidide (**501**) to 1-ethyl-3-*p*-chlorophenyl-5-methylindole (**502**) could be accomplished not only by heating **501** with zinc chloride in boiling ethyl alcohol or by fusion of the arylaminoketone with zinc chloride, but also by merely heating **501** in boiling



501 **502** (162)

tetralin (Eq. 162). Because of this and also because it is known that the Fischer indole synthesis can be effected without the intervention of acidic catalysts by simply heating the arylhydrazones in high boiling solvents (Ref. 162, cf. also Ref. 163), the possibility of similar thermal reaction of α-arylaminoketones to form indoles was examined.[320] The α-secondaryarylaminoketones were chosen for study since they were reported to be stable to heat in the absence of acidic catalysts whereas the α-*primary*arylaminoketones, when heated strongly, suffer extensive decomposition.[289, 291]

When 1-(*N*-ethylanilino)-2-propanone (**444**) was heated without a solvent, only a small amount of 1-ethyl-3-methylindole (**445**) was obtained (Eq. 163).

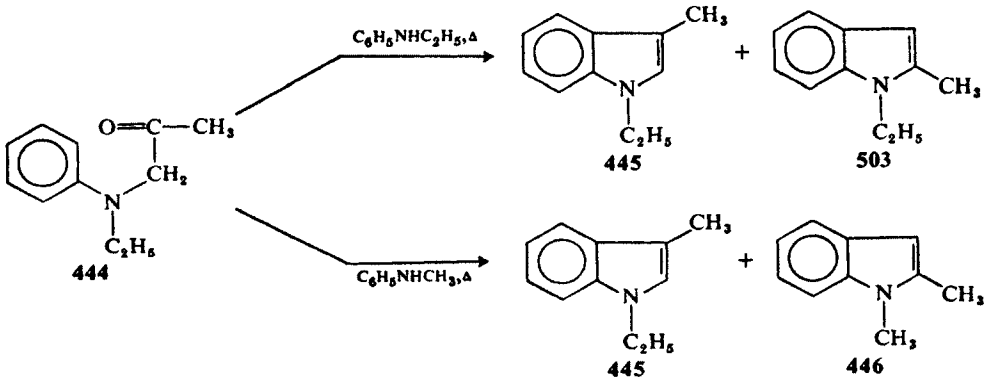


444 **445** (163)

Results obtained when **444** was heated in a number of solvents indicated the existence of a "solvent effect." Heating **444** for 3 hr in decalin at 190° or in

nitrobenzene at 160–170° or for 24 hr in boiling dimethylaniline gave no indole. However 3 hr in quinoline at 185° gave a 28% yield of **445** while 17 hr in acetic anhydride at 140° produced **445** in 53% yield. In boiling dimethylformamide (18 hr) a 15% yield of the indole was obtained. The glycols were particularly effective since a 70% yield of **445** was obtained when the α-arylaminoketone **444** was heated for 24 hr in refluxing ethylene glycol. Diethylene glycol gave no better results. In each of these cases, no rearrangement occurred and apparently **444** cyclized directly to the indole with simultaneous loss of water. Similar results were obtained with 1-(*N*-methylanilino)-2-propanone, 3-(*N*-methylanilino)-2-butanone, 3-(*N*-methylanilino)-2-pentanone, 2-(*N*-methylanilino)acetophenone, and 1-(*N*-methylanilino)-1-phenyl-2-propanone and provided the corresponding indoles in yields of 77, 69, 55, 88, and 92%, respectively.

When **444** was heated for 3 hr in boiling *N*-ethylaniline a mixture of 1-ethyl-3-methylindole (**445**) and 1-ethyl-2-methylindole (**503**) was obtained



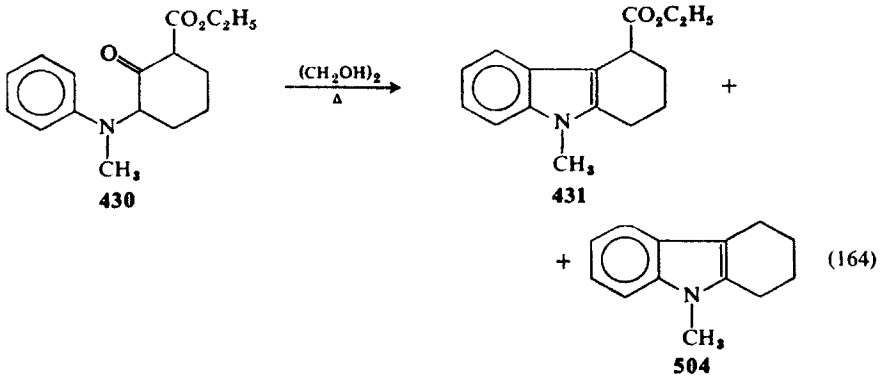
Scheme 47

in 45% yield, identified by comparison of the ir spectrum with that of an authentic mixture. When **444** was heated in boiling *N*-methylaniline, a 90% yield of **445** and 1,2-dimethylindole (**446**) was obtained (Scheme 47). These were separated and identified. Similar results were obtained by heating 1-(*N*-methylanilino)-2-propanone in boiling *N*-methylaniline.

It is thus apparent that these α-secondaryarylamines, heated in refluxing ethylene glycol, provide the direct cyclization product, whereas when heated in a secondary arylamine both the direct cyclization product and displacement-rearrangement product are obtained. This shows that thermal conditions, without the aid of an acid catalyst, are sufficient to effect the Bischler reaction.

The α-secondaryarylaminoketones containing a carbethoxy group α or β to the carbonyl moiety also cyclize when heated in boiling ethylene glycol,

but a portion of the product suffers loss of the carbethoxy moiety. Thus 2-(*N*-methylanilino)-6-carbethoxycyclohexanone (**430**) provides both 4-carbethoxy-9-methyl-1,2,3,4-tetrahydrocarbazole **431** and 9-methyl-1,2, 3,4-tetrahydrocarbazole (**504**), the former in 20% yield after saponification to the acid, and the latter in 20% yield (Eq. 164).

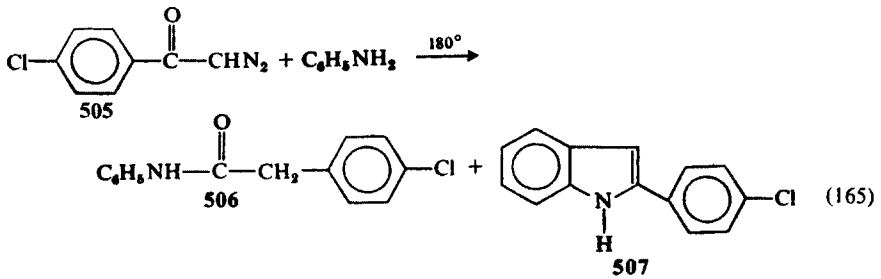


(164)

The same study[320] showed that the α-*primary*arylaminoketone when heated for 24 hr in refluxing ethylene glycol, also cyclized to the indole, but provided 2,3-dimethylindole in only 8% yield.

4. *Extension of the Bischler Reaction*

a. The Reaction of Diazoketones with Arylamines. In a study of the Wolffe rearrangement involving the reaction of *p*-chlorophenyl diazomethyl ketone(**505**) with aniline to produce *p*-chlorophenylacetanilide (**506**),[287] it was found that only a small amount of the expected anilide **506** was formed while the major product, obtained in 20–28% yield, was 2-*p*-chlorophenylindole (**507**) (Eq. 165). It was noted that indole formation was due to

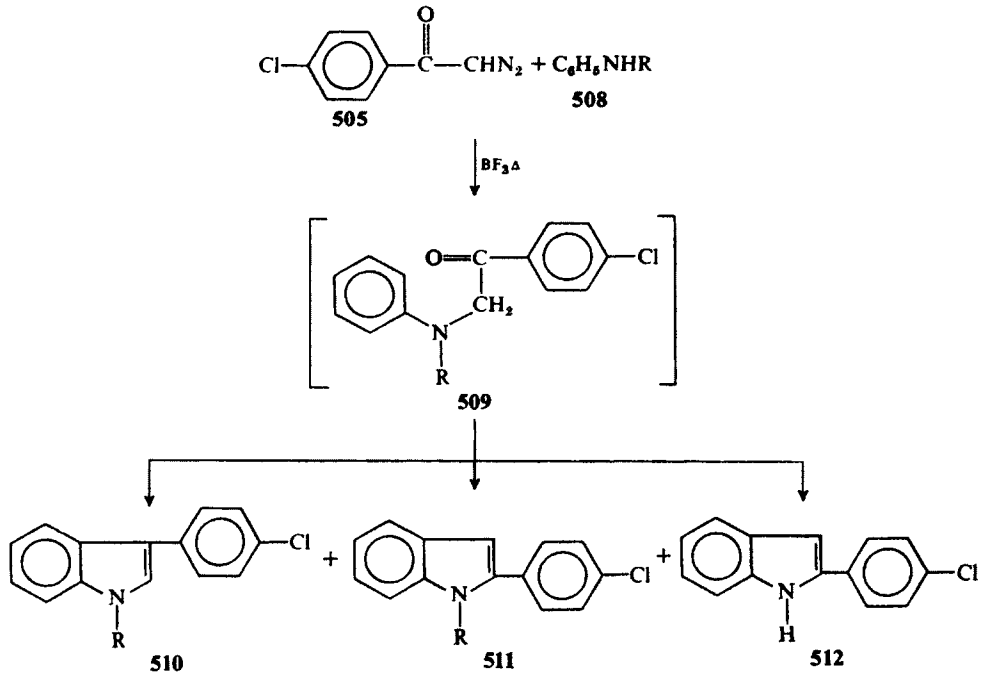


(165)

the presence of halogen acid as well as the arylamine, and that if the diazoketone was heated at 180–200° for 5 hr in aniline containing an equivalent

of either aniline hydrochloride or boron trifluoride etherate, an 82% yield of the indole **507** could be obtained. The reaction was fast, since a 65% yield of **507** was obtained after only a 3-min reaction period. This reaction was found to be applicable to several aryl diazomethyl ketones in which the aryl group was phenyl, *p*-methoxyphenyl, *p*-tolyl, 4-biphenylyl, and 1- or 2-naphthyl. The yields were generally greater than 60%, and often better than those obtained by the Fischer indole synthesis. *p*-Nitrophenyl diazomethyl ketone gave only a 3% yield of 3-*p*-nitrophenylindole, and then only if the time of heating was brief. *n*-Propyl diazomethyl ketone provided 2-*n*-propylindole in 23% yield. This low yield was thought to be due to the difficulty of isolation of the indole since no indole could be isolated at all from the reaction of 1-phenylamino-2-pentanone with aniline and aniline hydrobromide.[323] In all of the above cases only the 2-substituted indole was obtained.

The reaction of *p*-chlorophenyl diazomethyl ketone (**505**) with *secondary* arylamines **508** in the presence of an equimolar amount of boron trifluoride etherate gave a mixture of three indoles **510**, **511**, and **512** (Scheme 48) in each case. When R is methyl, the yields of these products were 40, 18, and



Scheme 48

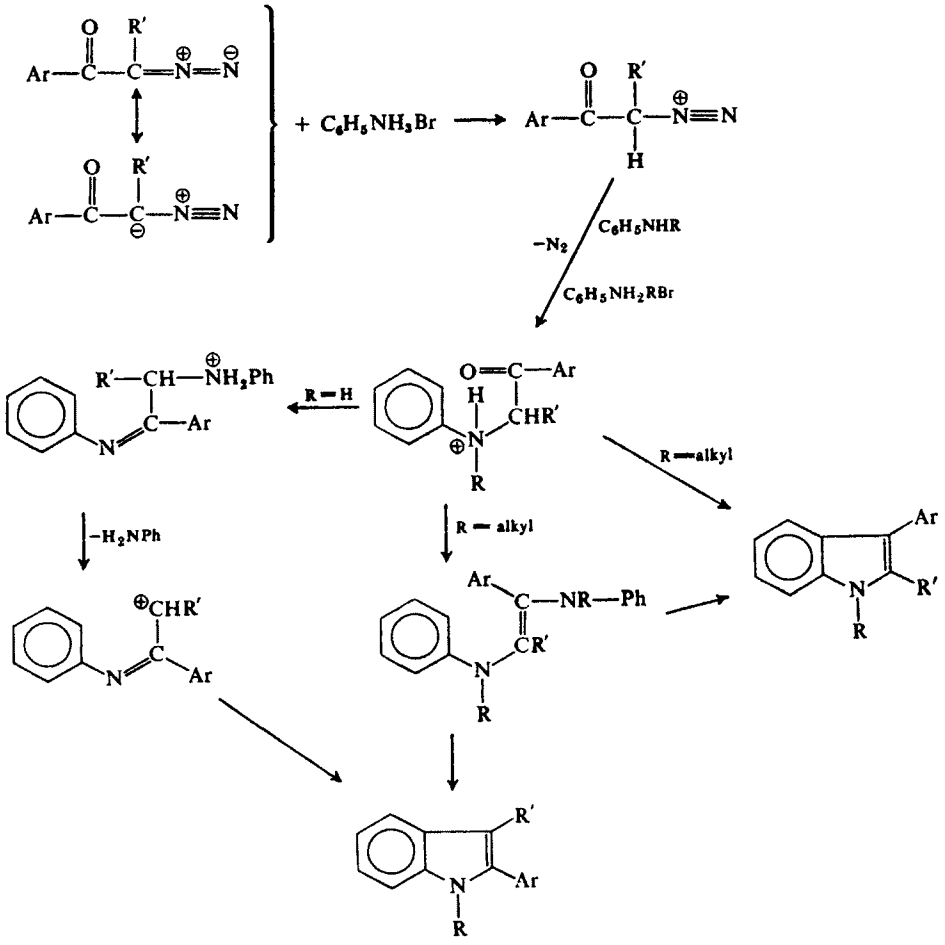
8%, respectively. If R is ethyl, a larger proportion (55–64%) of the 3-substituted indole **510** is produced, accompanied by only a trace (1–4%) of **511** and even less of **512**. This difference suggests that the greater steric requirements of the *N*-alkyl groups favor "direct cyclization of the intermediate presumed to be the anilinoketone **509** rather than indirect cyclization via an anilino-anil required to give the 2-aryl derivative." However, the relative base strengths of aniline, *N*-methylaniline, and *N* ethylaniline may be the significant factor in this regard as Brown and Mann[291] have suggested (see pp. 359, 360).

The formation of a small amount of the dealkylated compound 2-*p*-chlorophenylindole (**512**) is analogous to a similar loss of the alkyl group from the nitrogen in the Bischler reaction of *N*-ethylaniline or *N*-methylaniline with *p*-chloro- (or methyl-) phenacyl bromide[291] and is considered to occur[287] by attack of the *N*-methylaniline on the *N*-methylaniline hydrobromide, or possibly on the anilinoketone hydrobromide **509** · HBr, at the high temperature employed for the reaction, to produce dimethylaniline and aniline. The latter then reacts with **509** to form **512**. Brown and Mann envisage methyl transfer to occur from the protonated species **509** · HBr with a resulting loss of methyl bromide which alkylates the *N*-methylaniline to form *N*,*N*-dimethylaniline, a compound they isolated in small amount.

α-Diazoethyl ketones give similar reactions with aniline in the presence of halogen acid or boron trifluoride, but in somewhat lower yields (32–53%). The 3-methyl-2-arylindoles obtained were less stable and more difficult to isolate than were the 2-arylindoles. The lower yields could be due to these reasons and/or to a competitive side reaction which appears to occur with α-diazoethyl or α-diazopropyl ketones but not with diazomethyl ketones.[287]

Since the results obtained from the reaction of the α-diazoketones with primary and secondary arylamines paralleled those obtained by the Bischler reaction of *p*-chlorophenacyl bromide with arylamines,[289] the suggestion was made[287] that the mechanisms would be similar in that they would both form the common intermediate α-arylaminoketone **509** or its salt, from which the observed products could be obtained. This is shown in Scheme 49. Primary arylamines are considered to react by formation of the anilino anil which by loss of the *original* arylamine and formation of a carbonium ion would cyclize to the 2-substituted indole. The secondary arylamines, unable to form the anilino anil, could instead be converted to the enamine, which then would cyclize by two alternative routes to form the 2-substituted and/or 3-substituted indoles.

Attempts to isolate an α-arylaminoketone, e.g., **509**, were unsuccessful although unstable mixtures were obtained which could be converted to indoles. However, that such an α-arylaminoketone might be formed by the reaction of α-diazoketones with arylamines is supported by the isolation of



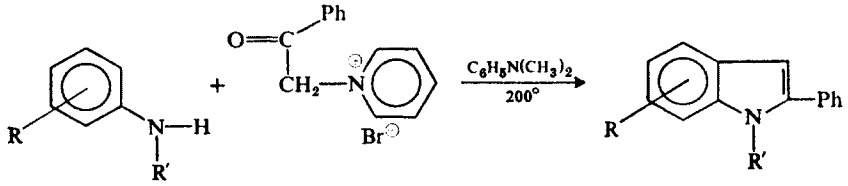
Scheme 49

an arylamino ketone from the reaction of α-diazoacetophenone with aniline in the presence of copper[342] and the formation of *N*-phenacylpyridinium chloride in 84% yield from the reaction of α-diazoacetophenone with pyridine hydrochloride.[343] It was shown that α-diazoacetophenone, heated in ethanol with 4-picoline hydrobromide, gave 1-phenacyl-4-picolinium bromide in 92% yield.[287] This quaternary salt, when heated with aniline, gave 2-phenylindole in 69% yield.[287]

b. THE REACTION OF PHENACYLPYRIDINIUM SALTS WITH ARYLAMINES. Little work has appeared involving the reaction of phenacyl quaternary salts with arylamines to produce indoles. This may be due to the realization that indole formation by this route requires the additional step of formation

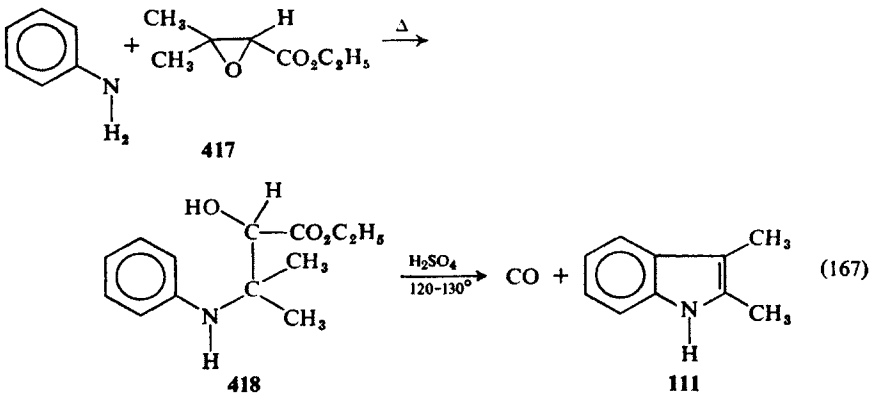
of the quaternary salt. The more direct reaction of phenacyl halides with primary or secondary arylamines would be the preferred approach.

Following the report that α-diazoacetophenone reacted with pyridine hydrochloride in ethanol to provide *N*-phenacylpyridinium chloride in excellent yield,[343] Blades and Wilds[287] prepared *N*-phenacyl-4-picolinium bromide by a similar method and then showed that this salt gave 2-phenylindole in 69% yield when heated in aniline at 185°. A later report[285] described the preparation of 5-chloro-, 5-methyl-, and 7-methyl-2-phenylindole and also 1-methyl-2-phenylindole by the reaction of *N*-phenacylpyridinium bromide with the appropriately substituted anilines in dimethylaniline at 200° (Eq. 166).



(166)

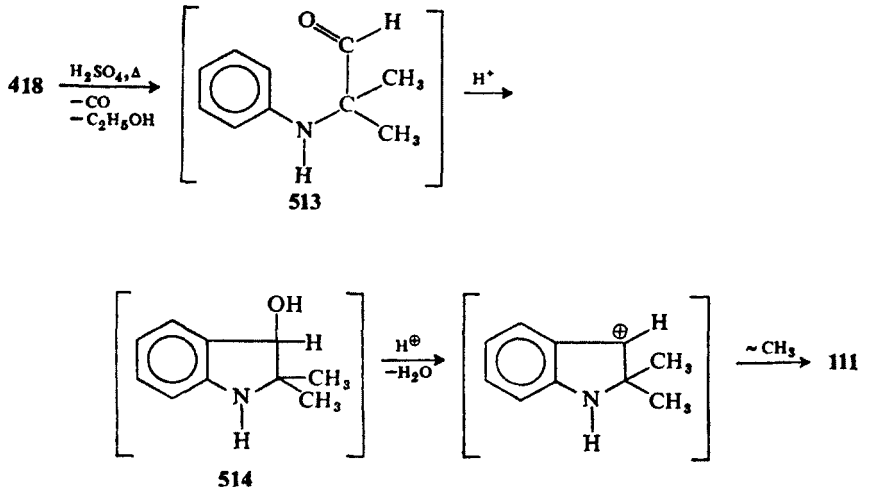
c. The Reaction of Arylamines with Glycidic Acid Esters. The acid-catalyzed decomposition of β-arylamino-α-hydroxycarboxylic acid esters provides a convenient route to indoles[283, 284] but has been explored only to a limited extent. When ethyl 3,3-dimethylglycidate (**417**) is heated with aniline, the isolable ethyl α-hydroxy-β-phenylaminoisovalerate (**418**) is obtained in



(167)

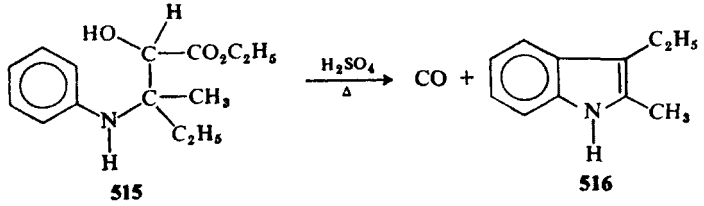
excellent yield (Eq. 167). Treatment of **418** with hot concentrated sulfuric acid produces 2,3-dimethylindole (**111**) in 90% yield along with carbon monoxide (Eq. 167). The evolution of carbon monoxide proves that the hydroxyl group must have been located on the α-carbon of the ester **418** and hence that the oxirane ring of **417** was broken at the carbon-oxygen bond

remote from the carbethoxy substituent. The sulfuric acid probably converts the α-hydroxycarboxylic acid ester to the aldehyde **513** which could then cyclize to the 3-hydroxy-2,2-dimethylindoline (**514**). Under the strong acid conditions and elevated temperature **514** would dehydrate and rearrange via



(168)

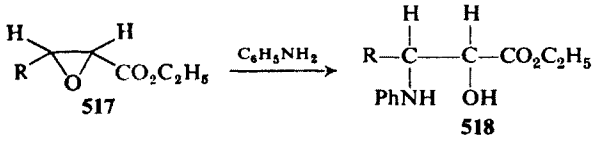
a retropinacol rearrangement to the observed product 2,3-dimethylindole (**111**) (Eq. 168). The glycidic ester **417** reacts with substituted arylamines such as *o*- and *p*-toluidine and with 2-aminopyridine to produce the α-hydroxy-β-arylamino ester corresponding to **418** in yields of 50–60%. These then cyclize with concentrated sulfuric acid to provide the respective indoles in very high yield. It is interesting that the homologous ester **515** under these conditions appears to provide only 3-ethyl-2-methylindole (**516**), a product obtained by the preferential migration of the ethyl group[344] (Eq. 169).



(169)

The reactivity of the epoxide ring declines sharply if highly branched groups are attached to the epoxide ring of the glycidic acid ester[284] with a consequent increase in the reaction of the arylamine with the ester group to form the anilide. Thus, if an *n*-propyl or isopropyl group is attached to the

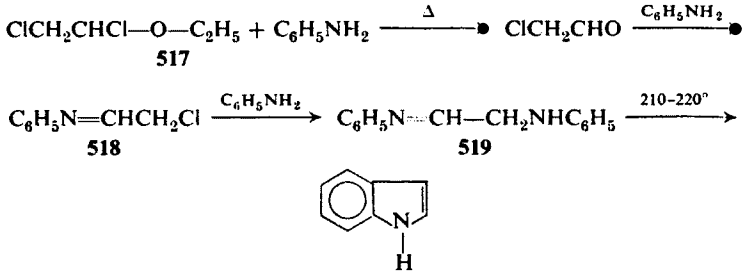
β-carbon of the glycidic acid ester (**517**; R = *n*-C_3H_7 or *i*-C_3H_7), a 50% yield of the α-hydroxy-β-phenylamino ester **518** is obtained (Eq. 170).



(170)

If R is *t*-butyl, the yield of ester **518** drops to 28%.

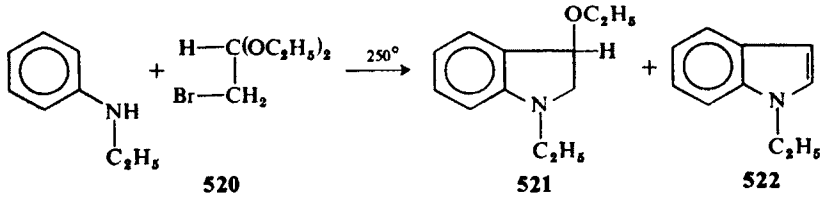
d. The Cyclization of α-Arylaminoaldehyde Dialkylacetals. Early reports have described the synthesis of the indole nucleus by the reaction of aniline with chloroacetaldehyde,[345, 346] chloroacetaldehyde diethylacetal,[345–348] or with α,β-dichloroethyl ethyl ether.[346–348] The reaction of α,β-dichloroethyl ethyl ether (**517**) with aniline was believed to occur by the sequence of reactions given in Scheme 50.[346] In this scheme the *N*-phenyl-α-chloroethylidine



Scheme 50

imine (**518**) reacted with a second molecule of aniline to form *N*-phenyl-α-phenylaminoethylidine imine (**519**). Both **518** and **519** were obtained and the latter was shown to cyclize to indole when heated to 210–220°.[346] However, subsequent attempts to repeat this work have all met with failure (Ref. 4, p. 25; 286).

It has also been reported[349] that a 2:1 molar mixture of *N*-ethylaniline and bromoacetaldehyde diethylacetal (**520**), heated to 250° gave 1-ethylindole (**522**) in 36% yield along with a small amount of the presumed intermediate 1-ethyl-3-ethoxyindoline (**521**) (Eq. 171). This reaction was found to be successful with secondary but not with primary arylamines.[349] Here again, later attempts to repeat the reaction met with failure,[286, 325, 350] although the room temperature reaction of excess *N*-ethylaniline with bromoacetaldehyde diethylacetal did provide a small amount of *N*-ethyl-*N*-phenylaminoacetaldehyde diethylacetal. The reaction of chloroacetaldehyde diethylacetal with aniline in the presence of sodamide in ether[351] did produce *N*-phenylaminoacetaldehyde diethylacetal, but efforts to cyclize this product to the indole,



520 521 522

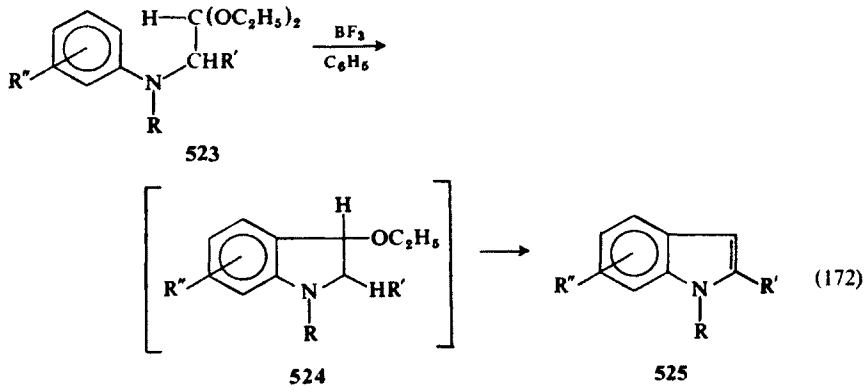
(171)

using 10% hydrochloric acid or 70% sulfuric acid, gave only an amorphous mass with no evidence of indole formation. Similar results were found in attempts to cyclize *N*-phenylaminoacetaldehyde diethylacetal by the use of arylamine hydrochloride, zinc chloride, or cuprous chloride,[325] catalysts which are known to promote the Bischler reaction. Similarly, only resins were obtained when a 2:1 molar mixture of aniline and chloroacetaldehyde dimethylacetal was heated[352] or 2,5-dimethoxyphenylaminoacetaldehyde diethylacetal was heated in the presence of acid.[353]

It is of interest in this connection that attempts to prepare 2-methylindole from the reaction of monochloroacetone with aniline have been unsuccessful[322, 354, 355] although *N*-methylaniline does react when heated with chloroacetone[322] or with chloroacetone diethylketal[355] to form 1,3-dimethylindole.

Chastrette[286] has recently reported an extensive study of the cyclization of α-arylaminoaldehyde dialkylacetals in which it was shown that such acetals could be cyclized to indoles under certain conditions, but only if an alkyl substituent was attached to the α-carbon of the aldehyde moiety. This provided a convenient route to 2-substituted indoles. The failure of primary- or secondaryarylaminoacetaldehyde dialkylacetals to cyclize to the indole upon treatment with acid was found to be due to the much faster reaction of the methylene group of the aldehyde moiety with the liberated carbonyl group to form polymeric material (crotonization). But if one of the α-hydrogen atoms in the α-arylaminoacetaldehyde dialkylacetal is replaced by an alkyl substituent and the arylamine group is either primary or secondary (**523**; R = H or alkyl, R′ = methyl or ethyl), then, in dry benzene solution and in the presence of boron trifluoride, polymerization or "crotonization" is minimized or eliminated and a 29–53% yield of the corresponding indole **525** is readily obtained. The presumed intermediate **524** could not be isolated (Eq. 172).

The reaction has also been accomplished successfully if a methyl substituent R″ is in the benzene ring either in the *o*-, *m*-, or *p*-position with respect to the amino group, and with R = H and R′ = methyl or ethyl. It is noteworthy that when the methyl group (R″) is in the *meta* position in **523** only



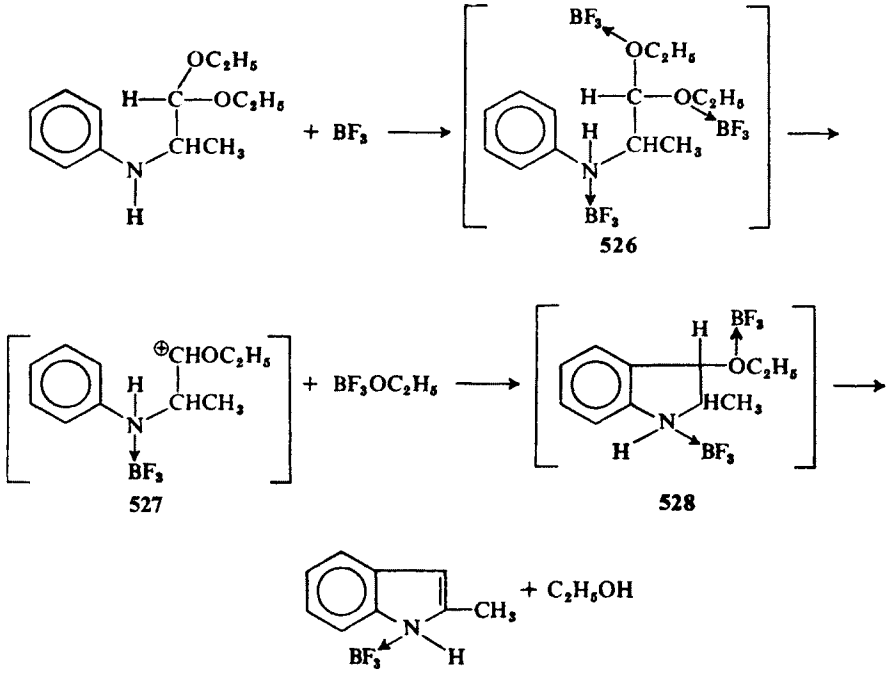
(172)

the corresponding 6-methylindole **525** is obtained, although the 4-methyl isomer is theoretically possible.

Since an alkyl substituent on the α-carbon of the aldehyde group was necessary to inhibit polymerization, Chastrette[286] heated a mixture of aniline and α-bromopropionaldehyde diethylacetal at 120° for 7 hr and obtained 2-methylindole though only in 18% yield. Application of this "direct" method to mixtures of *o*-, *m*-, or *p*-toluidine with α-bromopropionaldehyde diethylacetal gave 10–15% yields of the corresponding 2,7-, 2,6-, and 2,5-dimethylindoles. But *N*-alkylanilines, treated similarly with the same α-bromoacetal, failed to react at all, in spite of the report[349] that a 2:1 mixture of *N*-ethylaniline and bromoacetaldehyde diethylacetal provided a reasonable yield of the 1-ethylindole.

An attempt to cyclize α-phenylaminopropionaldehyde diethylacetal to 2-methylindole by heating the former with aniline hydrobromide at 130–140° met with failure even though alcohol was formed in 90% of theory.[286]

Chastrette suggested a possible course of indole formation by the reaction of a benzene solution of α-arylamino-α-alkyl aldehyde acetals with boron trifluoride which involves a preliminary association of boron trifluoride with the nitrogen *and* oxygen functions. This complex **526** then loses an ethoxy group to form a carbonium ion **527** which forms the intermediate indoline **528** by electrophilic attack on the aryl ring. Under the influence of the Lewis acid, boron trifluoride, the indoline **528** loses ethyl alcohol to form the indole (Scheme 51). That acetals in the presence of boron trifluoride can provide an electron-deficient species has been shown by the addition of acetaldehyde diethylacetal to ethyl vinyl ether under the influence of boron trifluoride.[356] Chastrette stated[286] that the requirement of an alkyl group in the α-position of the acetal moiety (R′ in **523**) to promote cyclization to the indole, whereas an alkyl group only on the nitrogen or in the ring (R or R″ = alkyl, R′ = H in **523**) fails to bring about cyclization is difficult to explain on

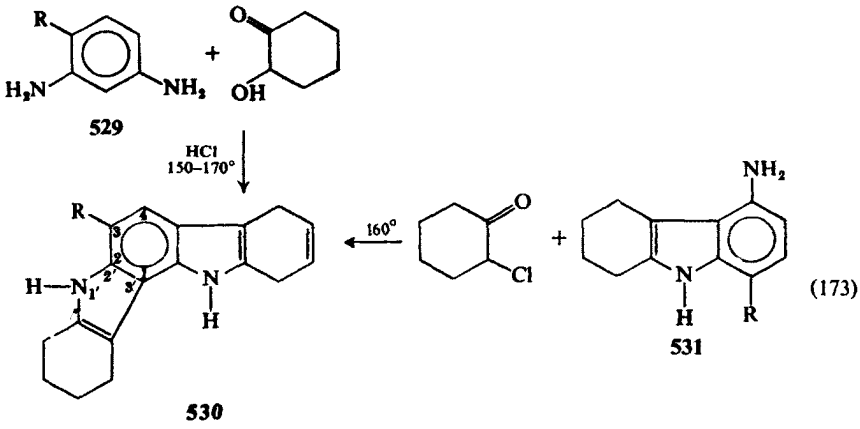


Scheme 51

an electronic basis. However, the effect may be due to steric factors since models show that an alkyl group R′ (**523**) restrains the mobility and favors a conformation in which the geminal dioxy group approaches the aryl nucleus. There may be a relation between the observation above and the reports that aniline and monochloroacetone do not provide indole.[322, 354, 355] whereas 3-phenylamino-2-butanone cyclizes readily to 2,3-dimethylindole.[321]

5. *Indolocarbazoles*

The Bischler reaction has provided a convenient route for the preparation of fused indolocarbazole ring systems. The reaction of the *m*-phenylenediamine **529** (R = H or CH_3) with 2-hydroxycyclohexanone, when treated with two drops of concentrated hydrochloric acid and then heated, gave the angular structure 5,6,7,8,4′,5′,6′,7′-octahydroindolo[3′,2′-1,2]carbazole **530** (R = H or CH_3)[315] (Eq. 173). This procedure was simpler and more productive than was the preparation of **530** (R = H) by the Fischer reaction using biscyclohexanone *m*-phenylenehydrazone.[141, 357] In fact, by the Fischer procedure, compound **530** (R = CH_3) could not be obtained.[141] However, the

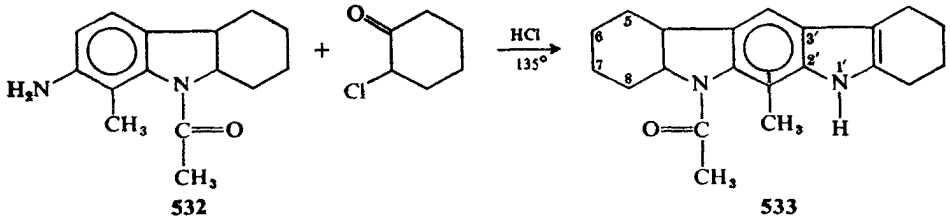


(173)

Bischler reaction of 2-hydroxy- (or chloro-) cyclohexanone with *o*- and *p*-phenylenediamine failed to provide any octahydroindolocarbazole.[315]

Compound **530** (R = H) was also obtained by the reaction of 2-chlorocyclohexanone with 5-amino-1,2,3,4-tetrahydrocarbazole **531** (R = H).[357]

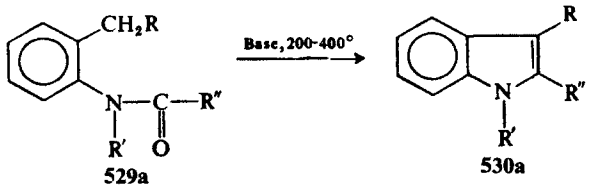
The tendency to form the angular rather than the linear fused ring system can be stopped if a substituent is suitably situated to block such a reaction. This is illustrated by the formation of 9-acetyl-5,6,7,8,12,13,4',5',6',7'-decahydro-1-methylindolo[2',3'-2,3]carbazole (**533**) from the reaction of 2-hydroxycyclohexanone with 7-amino-9-acetyl-8-methyl-1,2,3,4,10,11-hexahydrocarbazole (**532**)[358] (Eq. 174).



(174)

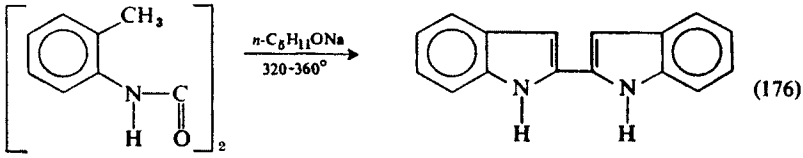
C. The Madelung Indole Synthesis

The intramolecular cyclization of *N*-acylated-*o*-alkylanilines in the presence of a strong base and at elevated temperatures is known as the Madelung indole synthesis. The reaction was first employed by Madelung[359] who found that *o*-acetotoluidide (**529a**, R = R' = H, R'' = CH_3) or *o*-benzotoluidide (**529a**, R = R' = H, R'' = C_6H_5), heated to 360–380° with a 2-molar equivalent of sodium ethoxide in the absence of air gave the corresponding 2-methyl- and 2-phenylindole (**530a**, R = R'' = H, R'' = CH_3 or C_6H_5) (Eq. 175).



529a 530a (175)

The same report[359] noted that better yields of indoles were obtained by using salts of longer chain alcohols, and that by this method it was possible to condense *o*-oxalyltoluidide (**531a**) in the presence of the sodium salt of *n*-amyl alcohol to 2,2-biindole (**532a**) in 26% yield[360] (Eq. 176). Alkali hydroxides



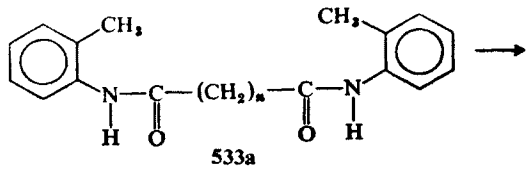
531a 532a (176)

failed to provide indoles, but instead promoted hydrolysis of the amides to regenerate the *o*-alkylanilines.[359] Madelung was unable to obtain indole from the reaction of sodium ethoxide with *o*-formotoluidide (**529a**, R = R′ = R″ = H).[359]

It was later found by Verley that sodamide in 1.5 molar excess also was a suitable reagent to effect the conversion of *o*-acetotoluidide to 2-methylindole[361] and that this modified method could be applied generally to acylated *o*-toluidines **529a** where R = R′ = H and R″ = ethyl, *n*-propyl, and isobutyl.[362] These conditions were unsuitable for the conversion of *o*-formotoluidide to indole itself, but could be made to form indole if the reaction was moderated by the use of an inert diluent.[361] A modified and improved version of Verley's procedure has been devised which converts *o*-acetotoluidide to 2-methylindole in 80–83% yield.[363]

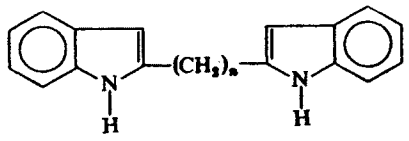
The Verley modification of the Madelung reaction has been used to convert malonyl di-*o*-toluidide (**533a**, *n* = 1) to diindolyl-2,2′-methane (**534**, *n* = 1)[364] and the bis-*o*-toluidides of adipic, pimelic, and sebacic acids (**533a**; *n* = 4, 5, 8) to the corresponding diindolyl products **534** in ~50% yield,[365] although the reaction with succinoyl bis-*o*-toluidide (**533a**, *n* = 2) failed[365] (Eq. 177).

The Madelung reaction, using sodium ethoxide, has been applied to aceto-*m*-4-xylidide from which 2,5-dimethylindole has been obtained in 40% yield.[366] The reaction is apparently not generally applicable to all acylated *m*-4-xylidines since 2,4-xylylsuccinamic acid **535** when subjected to these conditions gave only β-2,4-xylylpropionic acid **536**[366] (Eq. 178). However, it is possible to prepare 2-(α-dimethylamino-γ-hydroxy)-*n*-propylindole (**538**) from *o*-(α-dimethylamino-γ-phenoxy)butyrotoluidide (**537**) by the Madelung

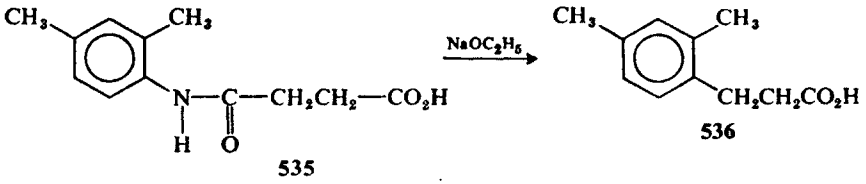


533a

(177)



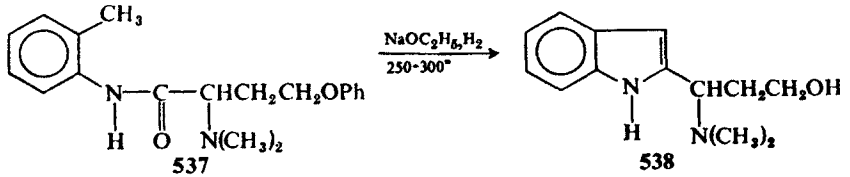
534



535 536

(178)

reaction[367] although in this case simultaneous loss of the phenyl group occurs (Eq. 179). A similar loss of the methyl group from the ether function occurs

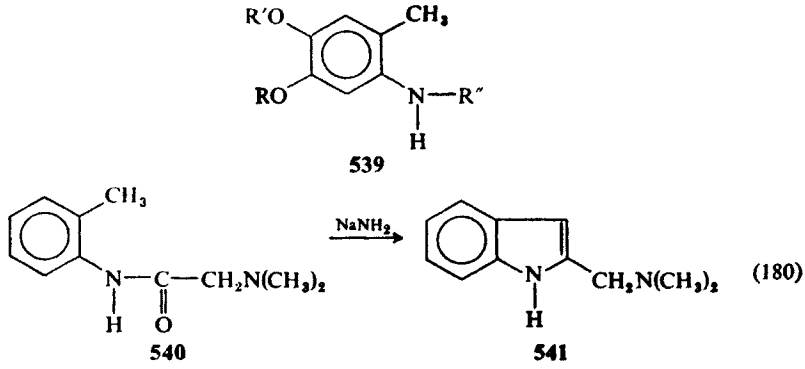


537 538

(179)

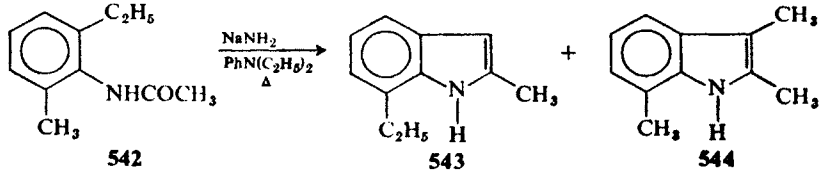
when 4-methoxy-2-methylaniline is converted to the bis-*p*-methoxy-*o*-toluidide of dicarboxylic acids, such as adipic, pimelic, or sebacic acids, and the product treated with sodamide at 240°.[365] The Madelung reaction with *p*-benzyloxy-*o*-formotoluidide failed completely, apparently due to the sensitivity of the benzyloxy group to such drastic conditions.[103] However, a small yield of the expected indole was obtained when *p*-methoxy-*o*-formotoluidide was subjected to the Madelung cyclization,[368] though attempts to prepare 7-methoxyindole by the Madelung reaction were unsuccessful.[369] The more complicated compound 2-amino-4,5-dihydroxytoluene (**539**, R = R′ = H), when converted to the triacetyl derivative (R = R′ = R″ = CH_3CO) or the *N*-formyl or *N*-acetyl di-*O*-benzyl derivative and then subjected to cyclizing conditions with potassium-*t*-butoxide, gave only black amorphous material.[370] *o*-Dimethylaminoacetotoluidide (**540**) is readily converted in 66% yield to 2-dimethylaminomethylindole (**541**) providing sodamide rather than sodium ethoxide[371] is used as catalyst. Treatment of

540 with potassium *t*-butoxide, potassium amide, or lithium amide apparently gives less than 20% conversion to **541** (Eq. 180).



(180)

The Madelung reaction has been extended successfully to *N*-acylated-*o*-ethylanilines.[364, 372–376] It has been reported that 2,3-dimethylindole is formed by treatment of *N*-acetyl-*o*-ethylaniline with sodamide.[372] or in 43.5% yield from the reaction of this anilide with potassium *t*-butoxide,[368] a base advocated by Tyson.[377] Following Tyson's procedure, *N*-formyl-*o*-ethylaniline has been converted to 3-methylindole in 68% yield.[368] The yield of 3-methylindole is increased to 80% if the mixture of *N*-formyl-*o*-ethylaniline and potassium *t*-butoxide is heated with carbon monoxide at 60 atm.[376] The highest yields of the 3-methylindole, substituted or unsubstituted at position 2, are generally obtained by using potassium *t*-butoxide as condensing agent.[368, 373, 374, 376] When 2-ethyl-6-methylacetanilide (**542**) is heated with sodamide in diethylaniline[375] both possible products 7-ethyl-2-methylindole (**543**) and 2,3,7-trimethylindole (**544**) are obtained in the proportion 85.5:2.5, respectively (Eq. 181). The large preponderance of **543** can be explained on



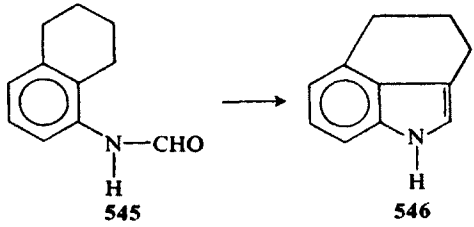
(181)

the basis of relative acidities of the α-hydrogen atoms on the alkyl substituents and/or on the basis of steric considerations. Inert diluents such as dimethylaniline and tetrahydronaphthalene have been used advantageously by other workers.[361, 364]

The Madelung reaction, with the base either potassium ethoxide or potassium *t*-butoxide, has been applied to the preparation of *N*-methylindoles[368, 378] though in poor yield. *N*-Methyl-*o*-ethylacetanilide, treated with

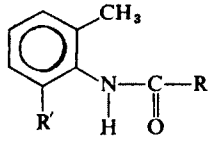
potassium *t*-butoxide, gave a 14.5% yield of 1,2,3-trimethylindole, while under the same conditions *N*-methyl-*o*-formotoluidide gave in 10% yield a mixture of indolic material from which 1-methylindole was isolated as its picrate and in which indole was found, a product resulting from the loss of the *N*-methyl group.[368] The reaction of base with *N*-acyl-*o*-alkylanilines is considered to occur by simpler and more definitely discernible stages, in contrast to the apparently more complicated reaction of the *N*-alkyl-*N*-acyl-*o*-alkylanilines because the latter gives a mixture of products among which not only is the indole lacking the alkyl group on the nitrogen but also the alkali salt of the *N*-alkyl-*o*-alkylaniline.[368]

A variety of mono-, di-, and trialkylindoles have been prepared from the appropriate ring alkylated *N*-acylanilines using either potassium ethoxide or *t*-butoxide[378–380] or sodamide.[375, 381–383] The yields vary from poor to good for 4-methylindole,[378, 379] 5-methylindole,[378] 6-methylindole,[378–380] 2,4-,[378] 2,5-,[364, 366, 381, 383] 2,6-,[378, 383] 2,7-,[364, 381, 383] 4,6-, 5,6-, 1,4-, 1,5-, and 1,6-dimethylindole,[378] and 2,5,7-[381] and 2,3,7-trimethylindole.[375] The base-catalyzed ring closure of 5-*n*-amyl-*o*-formotoluidide to 6-*n*-amylindole has been reported to occur only in low yield.[384] The conversion of *N*-formyl-5,6,7,8-tetrahydronaphthylamine (**545**) to 1,3,4,5-tetrahydrobenz[*c*,*d*]indole (**546**) has been accomplished with potassium *t*-butoxide in yields of 5[385] and 11%[386] (Eq. 182).



545 **546** (182)

Piozzi and Langella[387] have made an extensive examination of the synthesis of polyalkylated indoles by the Madelung reaction. They also studied the influence of the alkyl component R of the *N*-acyl group on the ease of cyclization of *N*-acylated *o*-toluidines **547** *in terms of isolated yields* of the respective indoles **548** (Eq. 183). Some of the results are shown in Eq. (183). Their results may be summarized as follows: (*1*). Lengthening of the unbranched carbon chain R influences the yields moderately. When R is C_1 to C_5 the yields of indoles are 80–85%. When R contains more than five carbon atoms the yield shows a progressive moderate decrease. (*2*). Branching on the α-carbon of R causes a marked drop in yield and this lowering is augmented by a simultaneous increase in chain length. (*3*). The presence of alkyl groups R′ at C-6 in **547** causes a small decrease in yield of the respective indole **548** if R′ is unbranched and small, but a pronounced drop in yield if



547 548

R	% yield
n-amyl	85
isoamyl	70
n-C_6H_{13}	70
n-C_9H_{19}	50
t-butyl	45
t-amyl	30
t-C_6H_{13}	20

(183)

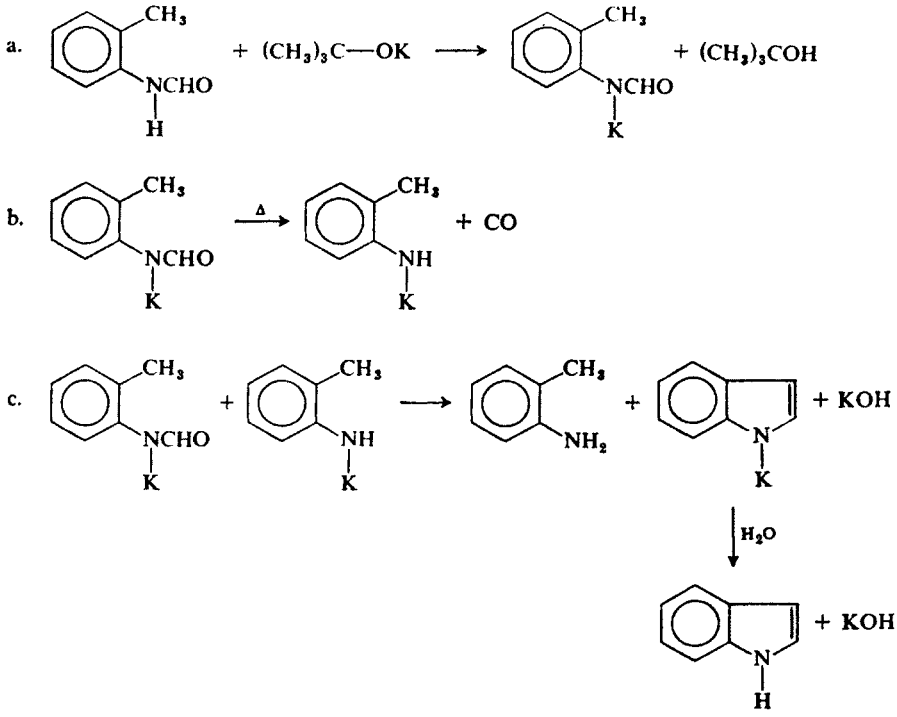
R′ is branched. These results point to the existence of a steric effect which influences the ease of cyclization.

Attempts to effect the Madelung reaction with acylamino-*o*-anilines containing ring substituents such as the nitro group[368] or halogens[388] have all failed.

Although numerous reports have appeared in which the Madelung reaction has been utilized to prepare indoles, few have been devoted to the examination of the mechanism of the reaction and accordingly it is not yet firmly established. Madelung noted that a one-molar excess of sodium alkoxide was necessary for satisfactory conversion of *o*-acetotoluidide to 2-methylindole and therefore suggested that the first molar equivalent of base converted *o*-acetotoluidide to the sodium salt while the second mole of base was required to effect the intramolecular condensation to the indole.[359] Furthermore, he observed that alkali hydroxides failed to cause indole formation but hydrolyzed the amides to the free amines.[359] From this it can be assumed that hydroxides, formed during any phase of the reaction, would destroy a portion of the cyclizable species.

The report that *o*-formotoluidide could not be converted to indole[359] and the lack of details concerning the claim that sodamide could bring about this conversion[361] prompted Tyson to examine the Madelung reaction.[377] He found that sodamide, sodium oxide, or sodium alkoxides were quite ineffective, but that potassium amide, potassium metal in liquid ammonia, or potassium alkoxides all were able to form indole from *o*-formotoluidide. Potassium *t*-butoxide was particularly effective and provided 0.4 mole of indole per mole of *o*-formotoluidide. Since this was the maximum yield obtainable, it was stated that 2 moles of the *o*-acyltoluidide were required to produce 1 mole of the indole.[377] A copious evolution of gas, primarily a mixture of hydrogen and carbon monoxide, was also noted.[377] These observations led to the proposal of the mechanism given in Scheme 52.[389]

Stage *c* of this mechanism implies an intramolecular Claisen condensation caused by the potassium *o*-toluidide, or the potassium salt of *o*-formotoluidide itself, though it is expected that the former would be the more effective entity responsible for the cyclization since it is the stronger base, considering the extent of delocalization of negative change in the two respective anions. That potassium (or sodium) *o*-formotoluidide itself



Scheme 52

could be an effective base is shown by the report that this salt, first formed from the reaction of a slight excess of potassium (or sodium) hydroxide with *o*-formotoluidide in boiling benzene under conditions which remove water by azeotropic distillation[390] or prepared by the reaction of sodium or potassium metal on the *o*-acylotoluidides,[391] when isolated and fused at ~300° provided indole in 17–21% yield along with carbon monoxide.[390, 391] Furthermore, the reaction of an alkali metal with *o*-acetotoluidide in an inert solvent (diethylaniline or tetrahydronaphthalene) produced the alkali salt which when heated to the usual temperature was converted to 2-methylindole.[364] In this case copper or copper bronze could be added as catalyst.[364]

It has been stated that this mechanism cannot be applied to the cyclization of *o*-acylaminoalkylbenzenes possessing an alkyl substituent on the nitrogen atom to form 1-alkylindoles.[368] If indeed the important step for indole formation is the intramolecular Claisen condensation, then Stages *a* and *b* may not be necessary. Formation of the potassium salt of the *o*-formyltoluidine (Stage *a*) will certainly occur and can be considered as an inevitable side reaction. Stage *a* should really be represented as an equilibrium between the two possible salts. Although carbon monoxide has been observed as one of the products, it is not yet established that under the reaction conditions it

arises only from the decomposition of the potassium *salt* of *o*-formotoluidide (Stage *b*). This then may be a second side reaction which leads to loss of cyclizable species. The multiplicity of products as well as the low yield of indole observed in the Madelung reaction applied to *N*-methyl-*o*-acylaminoalkylbenzenes may be the result of the more competitive side reactions occurring under the conditions of the reaction.

The reaction of sodium alkoxides with *o*-formotoluidide was reexamined and found to provide indole in 6% yield, but if either dry potassium acetate or potassium sulfate is added to the reaction mixture prior to fusion of the toluidide, the yield of indole is raised to 34–37%.[392] The function of the anhydrous potassium acetate or sulfate was not determined, although it was suggested that it might act as a "catalyst." Here also, in agreement with Tyson's view,[377, 389] it was stated that 2 moles of the *o*-formotoluidide were required to form 1 mole of indole.

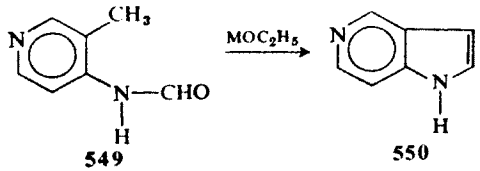
A subsequent study of the cyclization of *o*-formotoluidide[393] provided the following observation. (*1*). Potassium or sodium *o*-toluidide and sodium anilide were all very effective catalysts, the best being potassium *o*-toluidide. (*2*). Excess potassium *o*-toluidide was more effective than was potassium amide or a potassium alkoxide since 0.68 mole of indole per mole of *o*-formotoluidide was obtained. The base sodium *o*-toluidide gave 0.58 mole of indole per mole of *o*-formotoluidide. (*3*). The addition of excess anhydrous (fused) potassium formate (0.4 mole) to a mixture of *o*-formotoluidide (0.1 mole), sodium *o*-toluidide (0.6 mole), and *o*-toluidine (0.1 mole) resulted in a yield of 1.07 moles of indole for 1 mole of *o*-formotoluidide. It was believed that under the reaction conditions (270–290°) the potassium formate decomposed to liberate carbon monoxide which in turn reacted with the sodium *o*-toluidide to form sodium *o*-formotoluidide (the reverse of Stage *b* of Tyson's mechanism), thus leading to an increase in the yield of indole. Support for this latter view was obtained from the observation that a mixture of potassium formate and sodium or potassium *o*-toluidide, containing no *o*-formotoluidide,[393] or, a mixture of sodium *o*-toluidide and carbon monoxide under pressure,[394] provided indole in good yield.

In a later study of the Madelung reaction[395] some of Tyson's work[393, 394] was repeated and the results obtained were found to differ from those previously reported.[393, 394] A mixture of sodium *o*-toluidide, *o*-formotoluidide, and fused, dry potassium formate, heated to 300° under Tyson's conditions,[393] provided a mixture of carbon monoxide and hydrogen and an 80–83% yield of indole based on the *o*-formotoluidide employed. However, the reaction of sodium *o*-toluidide with *o*-formotoluidide or with potassium formate both failed to give any indole, in sharp contrast to previous findings.[393, 394] Furthermore, the reaction of a mixture of *o*-formotoluidide labeled with ^{14}C in the formyl group, inactive freshly fused potassium formate, and sodium

o-toluidide gave an 80% yield of indole with specific ^{14}C activity in the α-carbon nearly the same as that present in the starting material, *o*-formotoluidide. The carbon monoxide obtained from this reaction showed no activity. The remainder of the ^{14}C-activity was found in the tarry residue. A parallel reaction of inactive *o*-formotoluidide, inactive sodium *o*-toluidide, and ^{14}C-labeled potassium formate provided an 87% yield of indole which contained only 2% of the activity. The carbon monoxide evolved contained no more than 1% of the activity. The residue which was not volatile with steam possessed nearly all of the ^{14}C-activity.

It appears quite clear from this work that potassium formate does not decompose into carbon monoxide at the temperature employed (300°) but requires at least 400° for such decomposition.[395] Furthermore, potassium formate does not enter into the reaction to form additional *o*-formotoluidide (the reverse of Stage *b*), certainly not under the conditions of Tyson's reaction as employed by Pichat et al.[395] The fact that potassium formate facilitates the formation of indole is quite definitely established but its particular role is not yet clarified. It is suggested[395] that its role is similar to that of the dry potassium acetate or potassium sulfate which enhance the yield of indole from the reaction of *o*-formotoluidide with sodium alkoxides.[392]

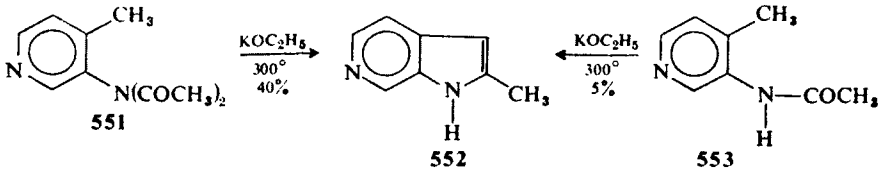
The Madelung reaction has been extended to the formation of several azaindoles from the appropriate acylaminopicolines. This is of particular advantage since the acid-catalyzed Fischer cyclization of pyridylhydrazones gives fair results at best, but only for those compounds which can be cyclized easily,[164, 396] although the thermal cyclization of pyridylhydrazones has been considerably more successful.[164–166] The preparation of 5-azaindole (**550**) by the reaction of sodium or potassium ethoxide with 4-formamido-3-picoline (**549**) has been unsuccessful[397] (Eq. 184). However, the fused



549 **550** (184)

mixture of sodium anilide, sodium formate, and 4-formamido-3-picoline (**549**) provided **550** in 21% yield,[164] considerably higher than that (3%) obtained with sodium ethoxide.[398] The same procedure[164] was employed to to prepare 6-methyl-7-azaindole and 4-methyl-7-azaindole in yields of 24 and 13%, respectively,[399] and is reported to provide 7-azaindole in 51% yield.[400] Attempts to prepare 6-azindole from 3-formamido-4-picoline and involving a number of modifications of the Madelung reaction have met with failure.[401]

It is interesting that 3-diacetamido-4-picoline (**551**), heated with potassium ethoxide at 300° gave a 40% yield of 2-methyl-6-azaindole (**552**) while 3-monoacetamido-4-picoline (**553**) under the same conditions gave **552** in only 5% yield,[401] even though it has been reported[402] that **553** provides **552** in 23% yield (Eq. 185). The fact that 3-diacetamido-4-picoline (**551**), a

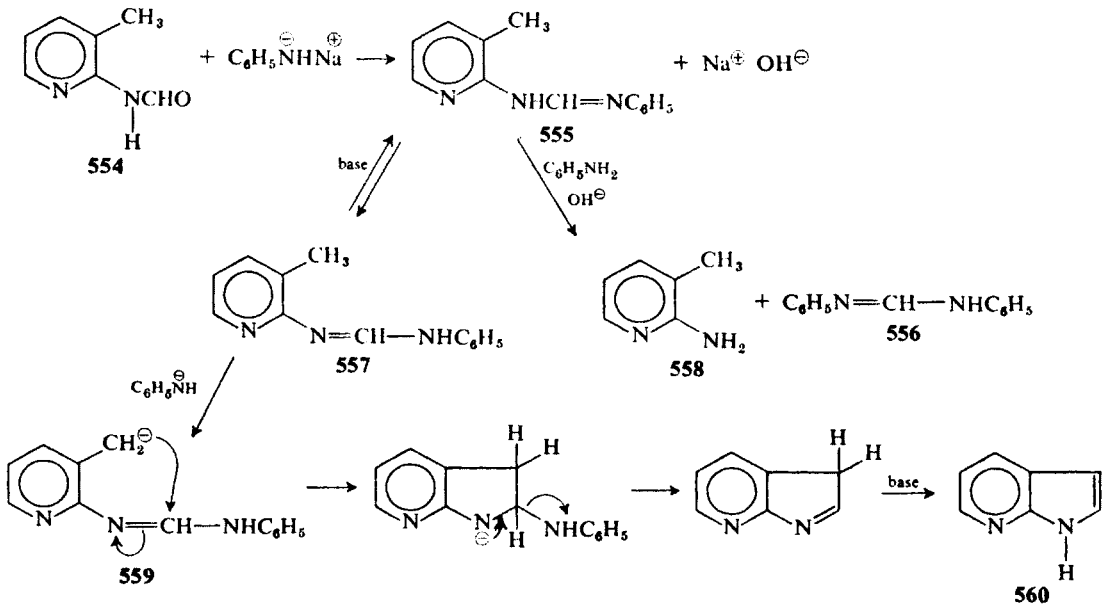


551 **552** **553**

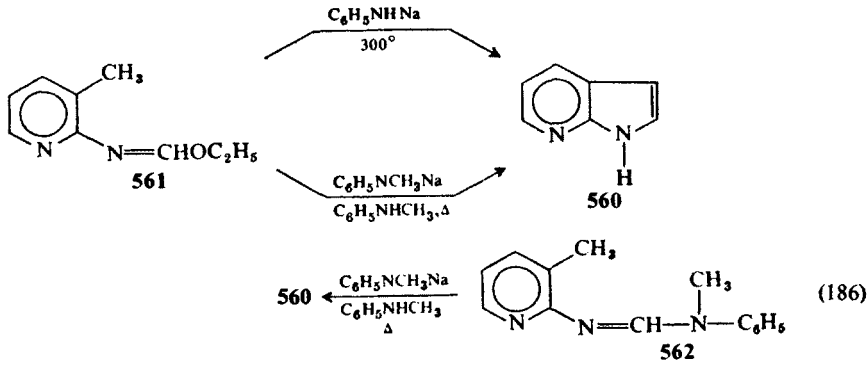
(185)

compound not expected to form a salt according to Tyson's mechanism (Stage *a*), gave a 40% yield of the 2-methyl-6-azaindole (**552**) was thought to provide evidence that the important function of the base was to remove a proton from the methyl group and thus initiate the intramolecular Claisen reaction.[401] A good yield of 2-methyl-4-azaindole was obtained from the reaction of 3-diacetamido-2-picoline with potassium ethoxide at 350°.[397] The 3-diformamido-4-picoline, analogous to the diacetamido compound **551**, could not be formed,[401] hence it is not known whether the same advantage occurs as is found for the cyclization of the diacetamido picolines.

A recent report[403] concerning the preparation of 7-azaindole has provided information that appears to be significant with respect to the mechanism of the Madelung reaction. During unsuccessful attempts[403] to repeat the reported procedure[400] for the preparation of 7-azaindole (**560**) from 2-formamido-3-picoline (**554**), it was noted that a considerable quantity of *N*,*N*′-diphenylformamidine (**556**) was obtained as a by-product. A possible route to its formation could be by base-catalyzed replacement by aniline of the 2-amino-3-picoline (**558**) from *N*-(3-methyl-2-pyridyl)-*N*′-phenylformamidine (**555**) which in turn could be formed by condensation of 2-formamido-3-picoline (**554**) with sodium anilide (Scheme 53). On the assumption that one of the routes, if not *the* route, to the formation of 7-azaindole could involve base-catalyzed cyclization of the formamidine **555** or its tautomer **557** via **559** (Scheme 53), ethyl *N*-(3-methyl-2-pyridyl)formimidate (**561**), a good precursor for **557**, was heated to 300° with sodium anilide in mineral oil. A 40% yield of 7-azaindole (**560**) was obtained. If **561** was heated with sodium *N*-methylanilide in boiling *N*-methylaniline (200°), the yield of **560** was raised to *52*% (Eq. 186). A reaction temperature of 300° in this latter case lowered the yield of 7-azaindole to 38%, thus confirming the observation that 7-azaindole is unstable at higher temperatures.[404] If *N*-(3-methyl-2-pyridyl)-*N*′-methyl-*N*′-phenylformamidine (**562**) (the product expected to form first

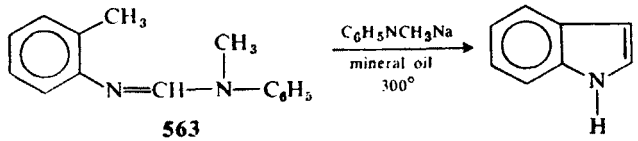

CH3
NCHO
H
554
+ C6H5NHNa
NHCH=NC6H5
555
+ Na OH
base
C6H5NH2
OH
CH3
N=CH—NHC6H5
557
CH3
NH2
558
+ C6H5N=CH—NHC6H5
556
C6H6NH
CH2
N=CH—NHC6H5
559
NHC6H5
base
560

Scheme 53



(186)

when **561** reacts with sodium *N*-methylanilide) is prepared and heated with sodium *N*-methylanilide in boiling *N*-methylaniline, the yield of 7-azaindole is increased to 80%. By this latter method *N*-(2-tolyl)-*N'*-methyl-*N'*-phenylformamidine (**563**), heated to 300° in mineral oil with sodium *N*-methylanilide, gave indole in 76% yield (Eq. 187). At 200° the reaction apparently was



(187)

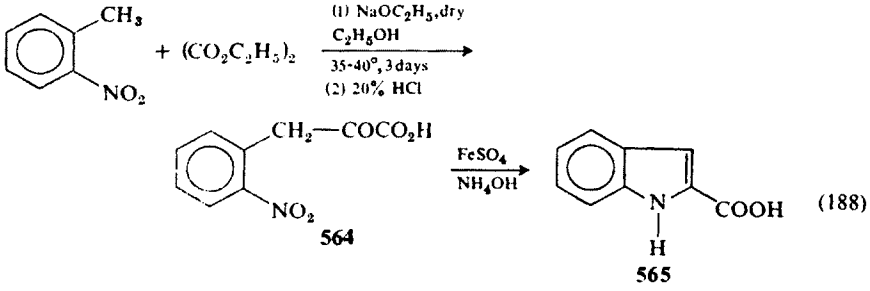
considerably less productive. Good yields of both 6-methyl- and 7-methylindole were obtained similarly from the respective amidines.

This work suggests that, as expected for the actual cyclization step, the base (sodium anilide in this case) is required to remove the proton from the methyl group as the essential step in the cyclization. However, competitive reactions such as condensation of the base with the formyl group could lead to the formamidine **555** which could lose the methylated aryl ring to form **556** and hence decrease the quantity of cyclizable material. Further loss of base could occur by reaction of the sodium anilide with the formamidine **555** or its tautomer **557** to form the respective salt, which is not expected to cyclize readily. If now such competitive reactions are eliminated by prior formation of the formamidine **562** or **563**, which contain no active hydrogen other than those on the ring methyl group, then the probability of intramolecular Claisen cyclization is greatly increased.

D. The Reissert Indole Synthesis

In a study of the base, catalyzed condensation of diethyl oxalate with *o*- and *p*-nitrotoluene to form the respective *o*- and *p*-nitrophenylpyruvic acids,[405] Reissert found that when the *o*-nitrophenylpyruvic acid (**564**) was

reduced with ferrous sulfate and ammonia, the resulting amine immediately cyclized under the reaction conditions to produce indole-2-carboxylic acid (**565**) (Eq. 188). This reaction has become known as the Reissert indole synthesis and provides a convenient method for the preparation of indole as well as indoles containing substituents in the aryl ring.



(188)

Reissert's original procedure employed sodium ethoxide in a 20-fold excess of dry ethanol as the condensing system, and the subsequent treatment with 20% aqueous hydrochloric acid led to the isolation of *o*-nitrophenylpyruvic acid (**564**) in 55% yield. The same procedure provided 2-nitro-5-methylphenylpyruvic acid in 30% yield from the reaction of diethyl oxalate with 4-nitro-*m*-xylene.[406] The procedure was improved by the use of potassium ethoxide in dry ether[407] which permitted the isolation of the pyruvic acid **564** as its ethyl ester in 80% yield and the isolation of ethyl 2-nitro-5-methylphenylpyruvate in 85% yield.[408] The base sodium ethoxide failed to condense 2-nitro-6-methoxytoluene with diethyl oxalate, but the stronger base potassium ethoxide in dry ether gave satisfactory results.[409] The latter method has been used with fair to excellent results by many investigators,[60, 63, 384, 410–415] while the cheaper sodium ethoxide in dry ethanol was found by others to be quite satisfactory in many cases.[388, 413, 416–418] Potassium ethoxide in dry ethanol has been found quite effective.[419] In some cases a mixture of toluene, potassium in ethanol, and absolute ether[420, 421] or a mixture of anhydrous benzene and potassium ethoxide[422] has been found advantageous. Better yields of the *o*-nitrophenylpyruvic acid were obtained if the diethyl oxalate was redistilled before use.[61]

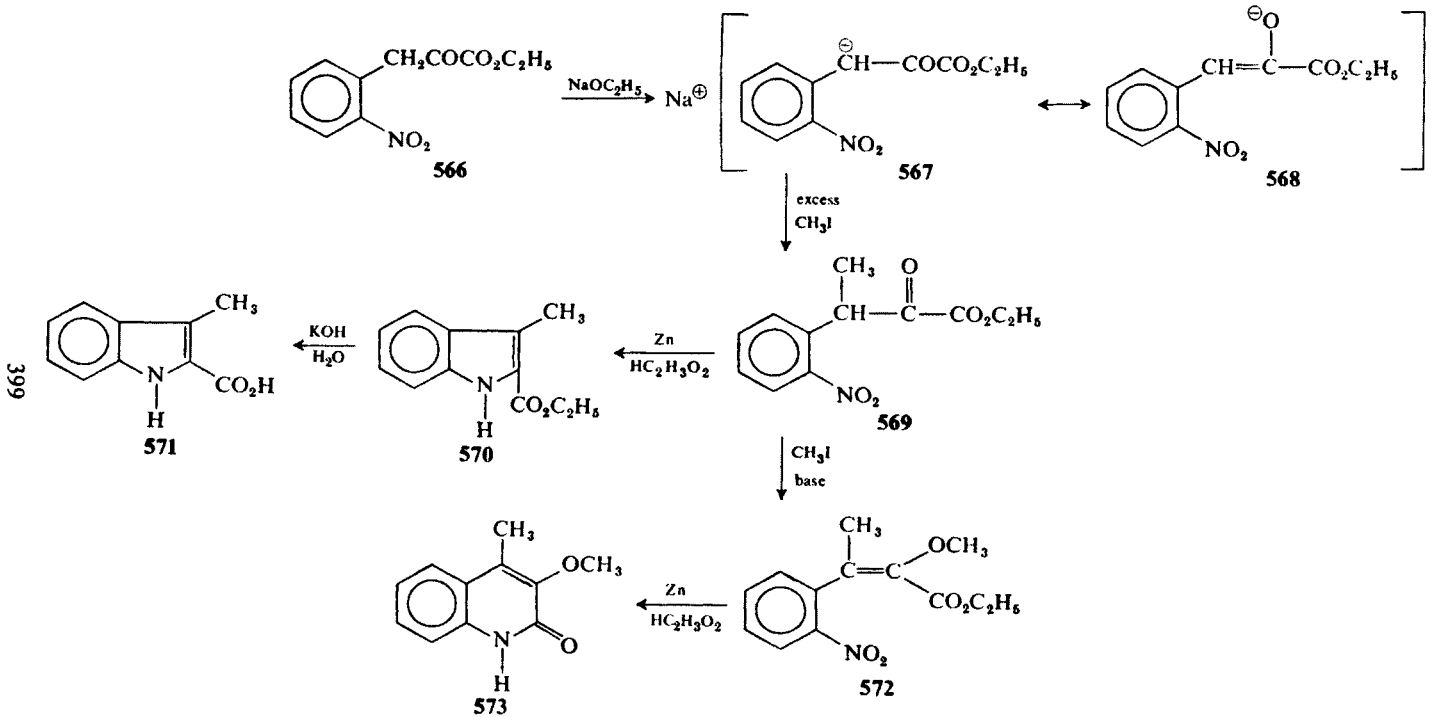
The yields of the *o*-nitrophenylpyruvate are often increased if the condensation of the *o*-nitrotoluene with diethyl oxalate is allowed to proceed at room temperature, or slightly above room temperature, for several days. The condensation of 4- and 5-benzylthio-2-nitrotoluene with diethyl oxalate in dry ethanol containing sodium ethoxide took place rapidly, and after 1 hr at reflux temperature provided a good yield of 4- and 5-benzylthio-2-nitrophenylpyruvic acid. The same conditions applied to the 3- and 6-benzylthio-2-nitrotoluenes gave only small quantities of the corresponding

pyruvic acids.[418] However, the stronger base potassium ethoxide in ethanol diluted with ether, along with a reaction period of 6 days at room temperature with diethyl oxalate, converted 6-benzylthio-2-nitrotoluene in 94% yield to the highly colored (red) potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate. This accumulated as a precipitate. The condensation of 3-benzylthio-2-nitrotoluene with ethyl oxalate under the same conditions required 16 days to form the orange potassium enolate of ethyl 3-benzylthio-2-nitrophenylpyruvate in 68% yield.[418]

The reductive cyclization of *o*-nitrophenylpyruvic acid or its ethyl ester to the corresponding indole-2-carboxylic acid, or its ester, is usually accomplished quite satisfactorily by treatment with hot ferrous sulfate heptahydrate in ammonium hydroxide.[63, 123, 130, 278, 413, 414, 417–419, 423–427] In the preparation of 5,6-dimethoxyindole-2-carboxylic acid by the ammoniacal ferrous sulfate reduction of ethyl 2-ntiro-4,5-dimethoxyphenylpruvate,[423] the yield of the indole acid could be increased substantially if a higher concentration of ammonia was used, and if the ferric hydroxide sludge was washed repeatedly with dilute aqueous ammonia. The addition of ethanol to the mixture of ferrous sulfate and ammonium hydroxide was found to be advantageous, no doubt due to the greater solubility of the organic substrate in the ethanol–water mixture.[384, 422] Satisfactory reductive cyclization has been achieved with iron powder suspended in an acetic acid–ethanol mixture,[123, 420, 428] iron filings and hydrochloric acid,[415] iron filings in acetic acid–ethanol,[429, 430] zinc dust and acetic acid,[61, 217, 405, 408] and sodium hydrosulfite (sodium dithionite).[388, 416, 421, 431, 432]

It is interesting that if the reduction of *o*-nitrophenylpyruvic acid is carried out with sodium amalgam, 1-hydroxyindole-2-carboxylic acid is obtained (Ref. 5, p. 18).

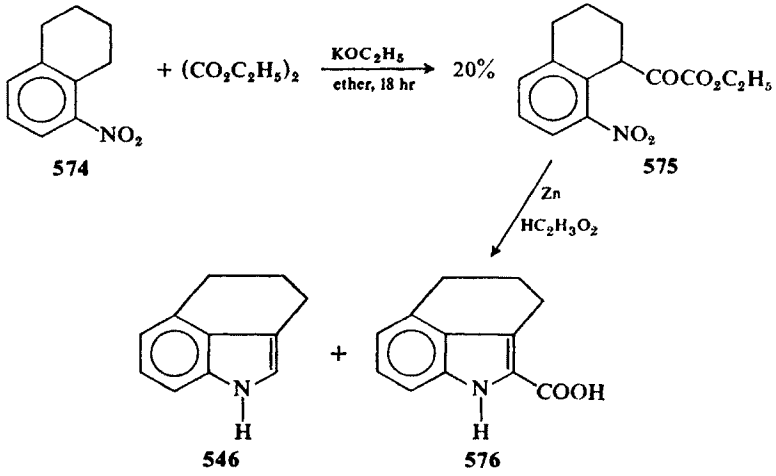
Although the particular value of the Reissert indole synthesis is in the preparation of indoles substituted at specific positions in the benzene ring, the adaptation of Reissert's method to the production of 3-substituted indoles has been examined briefly.[278] The reaction of the sodium salt **567–568** of ethyl *o*-nitrophenylpyruvate (**566**) with a half-molar excess of methyl iodide gave an exothermic reaction which no doubt provided a mixture of methylated products, e.g., **569** and **572**, since reduction of this material with zinc and acetic acid gave not only ethyl 3-methylindole-2-carboxylate (**570**) (in unstated yield) but a 2% yield of 3-methoxy-4-methyl-2-quinolone (**573**) (Scheme 54). The indole ester **570** was readily hydrolyzed to 3-methylindole-2-carboxylic acid (**571**). The formation of byproducts during the C-alkylation apparently limits the utility of this method. However, it merits further investigation. Better yields (63–71%) of 3-methylindole (skatole) and 3-methylindole-2-carboxylic acid can be obtained by heating indole or indole-2-carboxylic acid with methanol and sodium methoxide to 210–220° in an


CH2COCO2C2H5
NO2
566
NaOC2H5
Na⊕
CH—COCO2C2H5
NO2
567
CH=C—CO2C2H5
NO2
568
excess
CH3I
CH3
O
CH—C—CO2C2H5
NO2
569
Zn
HC2H3O2
CH3
N
H
CO2C2H5
570
KOH
H2O
CH3
N
H
CO2H
571
CH3I
base
CH3
OCH3
C=C
CO2C2H5
NO2
572
Zn
HC2H3O2
CH3
OCH3
N
H
O
573

Scheme 54

autoclave.[432] Using the appropriate alcohol, along with its sodium salt, either indole or indole-2-carboxylic acid can be converted to the product in which the 3-substituent is methyl, ethyl, *n*-propyl, *n*-butyl, *n*-heptyl, benzyl, or 3-γ-phenylpropyl. The reaction of secondary alcohols plus their salts with indole-3-carboxylic acid was unsuccessful, but indole itself was found to react and provide 3-isopropylindole while 7-methylindole gave 3-cyclohexyl-7-methylindole with isopropyl alcohol and cyclohexanol, respectively, along with their sodium salts.[432] The tertiary alcohols did not react with indole under these conditions.

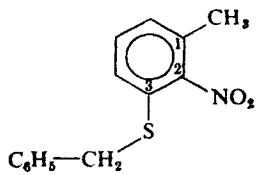
In contrast to the facile condensation of *o*-nitrotoluene with diethyl oxalate in the presence of potassium ethoxide in ether–alcohol solution, *o*-nitroethylbenzene fails to react at all.[407] It has been suggested[433] that this might be due to a steric effect caused by the methyl moiety of the ethyl group, since 1-nitro-5,6,7,8-tetrahydronaphthalene (**574**) does react with diethyl oxalate in the presence of potassium ethoxide and ether to give a 20% yield of ethyl 1-nitro-5,6,7,8-tetrahydronaphthyl-8-oxalate (**575**), a compound which can be reductively cyclized with zinc and acetic acid to give a mixture of 1,3,4,5-tetrahydrobenz[*c*,*d*]indole (**546**) and 1,3,4,5-tetrahydrobenz[*c*,*d*]indole-2-carboxylic acid (**576**)[386] (Eq. 189). Since the sterically hindered 2-nitrotoluenes having the C-6 substituent, such as iodo,[419] methyl or chloro,[434]



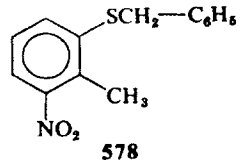
(189)

methoxy,[409] and benzylthio,[418] do react with diethyl oxalate in the presence of base, though with some difficulty, it may be that the important factor preventing the reaction of *o*-nitroethylbenzene is the electron-donor property of the methyl group on the α-carbon which decreases markedly the ease of proton removal from the α-carbon.[435] It has been suggested[418] that a reason why 3- and 6-benzylthio-2-nitrotoluenes (**577** and **578**) find more difficulty

in reacting with diethyl oxalate in the presence of base than do the 4- and 5-benzylthio isomers is the lower degree of activation which the methyl group can experience due to the *o*-nitro group. If coplanarity of the nitro group with the ring is responsible, at least in part, for the activation of the methyl group to permit proton removal and formation of the carbanion, it is readily seen that the groups in the two positions *ortho* to the nitro group in 3-benzylthio-2-nitrotoluene (**577**) and the buttressing effect of the benzylthio group upon the methyl substituent in 6-benzylthio-2-nitrotoluene (**578**) would indeed cause a marked restriction in the coplanarity of the nitro group with the ring as compared with that attainable in the 4- and 5-benzylthio-2-nitrotoluenes. In support of this it has been found that the

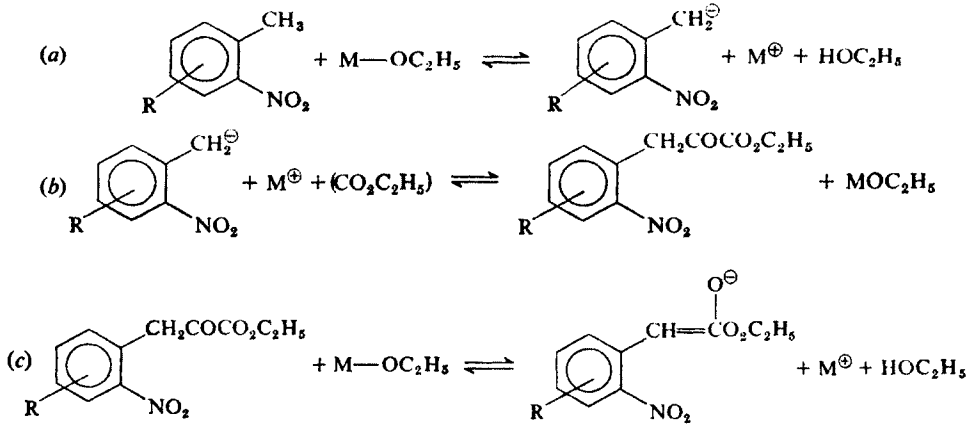


577



578

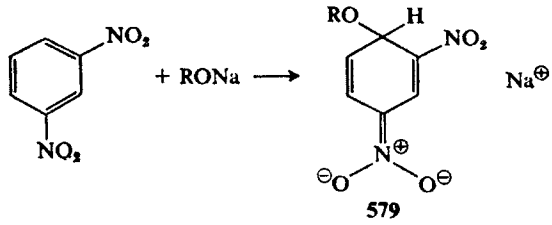
position of the absorption bands in the ir spectrum characteristic of the nitro group in these nitrotoluenes resemble those for the aliphatic nitro group in nitromethane to a progressively greater degree in the order 3-benzylthio-2-nitrotoluene > 6-benzylthio-2-nitrotoluene > 4-benzylthio-2-nitrotoluene. The order of apparent ease of condensation of these toluenes with diethyl oxalate is 4-benzylthio- > 6-benzylthio- > 3-benzylthio-2-nitrotoluene in agreement with this view. The same report[418] indicated that the poor reaction of 3- and 6-benzylthio-2-nitrotoluene with diethyl oxalate in the presence of sodium ethoxide in ethanol might also be due in part to an unfavorable shift in the equilibria shown in Scheme 55.



Scheme 55

The requirement of a stronger base (KOC_2H_5) to shift the equilibrium to the right, as well as solvent conditions (ether or ether + alcohol) to promote precipitation of the highly colored (red) enolate salt (Eq. *c*) thus explains why 3- and 6-benzylthio-2-nitrotoluene will provide a 68 and 94% yield of the enolate, respectively, if potassium ethoxide and ether are used and the reaction is allowed to proceed for 6 to 16 days.[418]

Since activation of the methyl group by the nitro group due to its electronegative nature is required for successful base-catalyzed reaction of the *o*-nitrotoluene with diethyl oxalate, electron-donor substituents in *o*-nitrotoluene are expected to retard the reaction, whereas electron-withdrawing substituents should enhance the ease of proton removal to form the carbanion. This is supported by the finding that 4-benzyloxy-2-nitrotoluene fails to condense satisfactorily with diethyl oxalate in the presence of sodium ethoxide and ethanol, but the stronger base potassium ethoxide along with the addition of ether provides the 4-benzyloxy-2-nitrophenylpyruvate in 40% yield.[427] Moderately electron-withdrawing substituents such as the halogens appear to give satisfactory condensation of the halogenated *o*-nitrotoluenes with diethyl oxalate in the presence of sodium ethoxide in ethanol. The compound 4-cyano-2-nitrotoluene reacted with diethyl oxalate in ethanolic sodium ethoxide to provide ethyl 4-cyano-2-nitrophenylpyruvate.[436] However, 2,4-dinitrotoluene could not be condensed with diethyl oxalate in the presence of strong base.[436, 437] Only a blue solution was obtained rather than the red color of the salt of the expected enolate, and this solution soon turned black and tarry. It is well known that *m*-dinitrobenzene does react with strong bases to form a complex believed to have the structure **579** (Eq. 190).



579

(190)

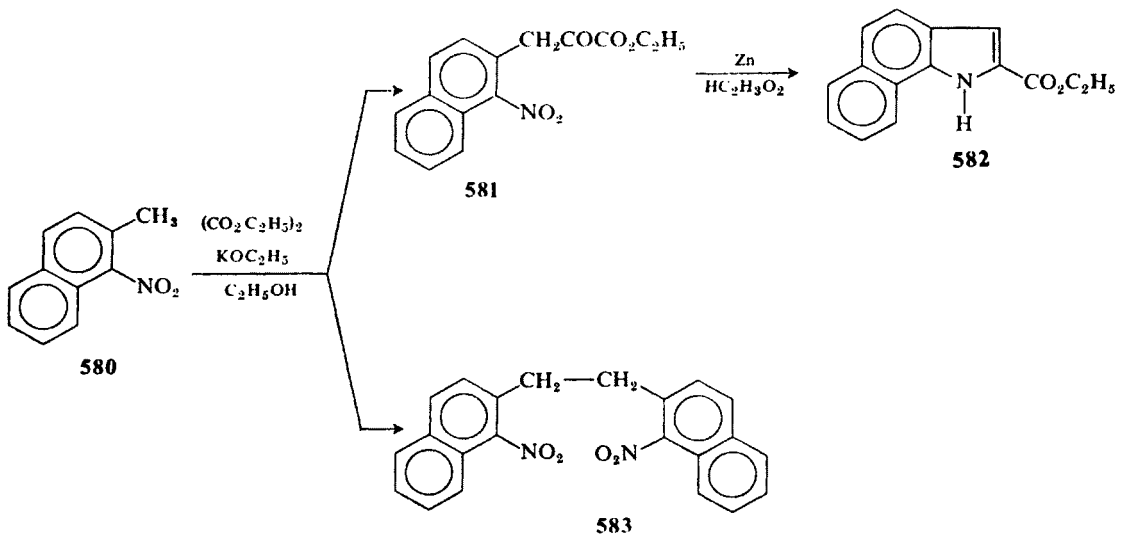
This may take precedence over the expected proton removal from the methyl group of 2,4-dinitrotoluene by sodium or potassium ethoxide. However, it has been shown that if lithium ethoxide is used as base, 2,4-dinitrotoluene does react with diethyl oxalate in ethanol to form ethyl 2,4-dinitrophenylpyruvate in good yield.[437]

Some caution should be observed regarding concentration of reactants used in the Reissert synthesis. Reissert[405] had obtained, along with the expected pyruvate, small quantities of bimolecular condensation products

from the reaction of *o*-nitrotoluene with diethyl oxalate when the concentration of the reactants was high (~0.5–1 molar). Both 4,4′-dinitrobibenzyl and 4,4′-dinitrostilbene were obtained in small amounts from side reactions during the condensation of *p*-nitrotoluene with diethyl oxalate.[407] The reaction of 2-methyl-1-nitronaphthalene (**580**) with diethyl oxalate in the presence of potassium ethoxide[438] gave the expected ethyl 1-nitro-2-naphthylpyruvate (**581**), which when reduced gave ethyl 6,7-benzindole-2-carboxylate (**582**) (Eq. 191). Along with the expected product **581** there occurred the coupling product 1,2-bis(1-nitro-2-naphthyl)ethane (**583**). When the concentration of the potassium ethoxide used in the condensation was doubled, **583** became the chief product.

Although the Reissert reaction has been widely used for the preparation of indoles, little work has appeared that deals with the mechanistic aspect of this reaction. The essential step of the Reissert indole synthesis is that involving the condensation of diethyl oxalate with the *o*-nitrotoluene to provide the *o*-nitrophenylpyruvic acid or its ethyl ester. Reissert found that both *o*- and *p*-nitrotoluene condensed readily with diethyl oxalate in the presence of sodium ethoxide in ethanol to form *o*- and *p*-nitrophenylpyruvate, whereas *m*-nitrotoluene could not be induced to react.[405] Furthermore, these *o*- and *p*-nitrophenylpyruvates, when left in the presence of base, reverted to the original reactants.[405] The reversible nature of this condensation has been corroborated.[418, 437] Vadekar[437] has shown that a solution of sodium ethoxide, *o*-nitrotoluene, and diethyl oxalate in ethanol, left for a period of time at room temperature, attained an equilibrium in which both *o*-nitrotoluene and ethyl *o*-nitrophenylpyruvate were present. The same equilibrium of *o*-nitrotoluene and ethyl *o*-nitrophenylpyruvate was obtained when a solution of ethyl *o*-nitrophenylpyruvate and sodium ethoxide in ethanol was allowed to stand for a period of time. Theoretical concentrations of reactants were made the same in both cases. Piers et al.[418] found that in attempts to convert the potassium enolate of ethyl 6-benzylthio-2-nitrophenylpyruvate to the pyruvic acid by treatment with aqueous base, some 6-benzylthio-2-nitrotoluene was obtained. Furthermore, pure 4-benzylthio-2-nitrophenylpyruvic acid left in 95% ethanol (a solvent used for its crystallization) for 4 weeks at room temperature was converted largely to 4-benzylthio-2-nitrotoluene. Thus the base-catalyzed reaction of *o*- and *p*-nitrotoluenes with diethyl oxalate seems to resemble the Claisen condensation.[439] Ingold has stated[439] that although there is no kinetic evidence for the Claisen condensation, all other available evidence points to a reversible reaction involving carbonium formation as the rate-determining step.

In order to obtain information which might explain the variable results reported for the Reissert reaction, a kinetic study has been made of the base catalyzed reaction in ethanol of diethyl oxalate with *o*- and *p*-nitrotoluene



580 581 582 583

(191)

and several 4-substituted *o*-nitrotoluenes.[437] The reaction was followed by photometric measurement of the concentration of ethyl *o*-nitrophenylpyruvate as its highly colored enol salt in excess alkoxide. An examination of the initial portion of the reaction in which the reverse reaction was negligible and in which all the reactants and products were completely soluble gave the following results:

(1). The condensation of diethyl oxalate with *o*-nitrotoluene in the presence of sodium alkoxide is a reversible reaction.

(2). The over-all reaction is fourth order; first order in both the nitrotoluene and diethyl oxalate and apparently second order in sodium or potassium ethoxide.

(3). The relative rate of reaction using potassium ethoxide or sodium ethoxide under otherwise identical conditions was found to be 1.47/1.00.

(4). The relative rate of reaction for *o*-, *p*-, and *m*-nitrotoluenes under the influence of sodium ethoxide was found to be 0.560/1.04/0.0.

(5). The relative rates k^R/k^H of condensation of *o*-nitrotoluenes containing a substituent R in the position *para* to the methyl group are shown in Table I (k^H is the rate of unsubstituted *o*-nitrotoluene). For comparison the relative rate for 3-bromo-2-nitrotoluene is also shown. The Hammett σ plot gave a large positive value (3.7) for ρ.

TABLE I

R	k^R/k^H
H	1.00
CH_3	0.443
F	1.61
Cl	7.03
Br	8.09
I	9.32
3-Br	1.53

(6). A substantial positive primary salt effect was observed.

(7). As the solvent ethanol was gradually replaced by benzene, the rate of reaction increased as shown in Table II. The per cent conversion to product at equilibrium is shown for each of these solvents. The per cent conversion increases as the proportion of benzene increases. For benzene/ethanol proportions of 80/20 or greater, the product began to precipitate at the per cent conversion indicated. Diethyl oxalate as solvent as well as reactant gave a higher rate of condensation than was found in pure benzene, but because the

TABLE II

Benzene/ethanol (v/v)	Relative rates	% Conversion to product at equilibrium	
0/100	1.0	3.2	
30/70	1.2	5.8	
70/30	2.1	9.1	
80/20	3.6	28	Product precipitation occurred at this conversion
90/10	5.6	—	
100/0	96	11.2	

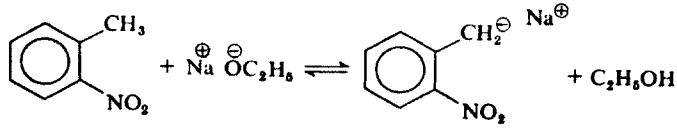
product precipitated almost immediately, the reaction could not be followed kinetically.

(8). An approximate 40-fold increase in rate occurred when the reaction temperature was changed from 35 to 76° for the reaction of *o*-nitrotoluene in the presence of sodium ethoxide in ethanol.

The high positive value of 3.7 for ρ clearly indicates that formation of a carbanion is involved prior to or in the rate-determining step of the reaction.

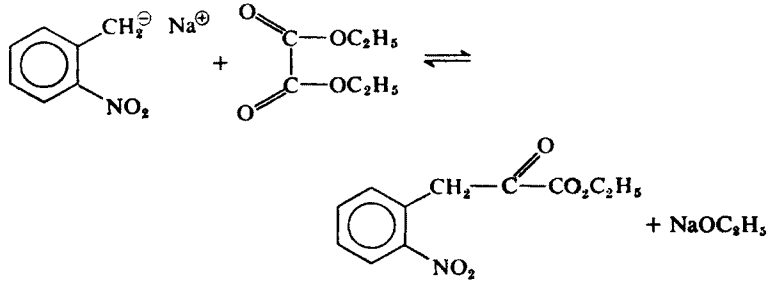
The marked increase in rate when ethanol is replaced by benzene as solvent can be due to one or more of the following factors. The reaction of *o*-nitrotoluene with sodium ethoxide is no doubt an equilibrium (Eq. *a*)

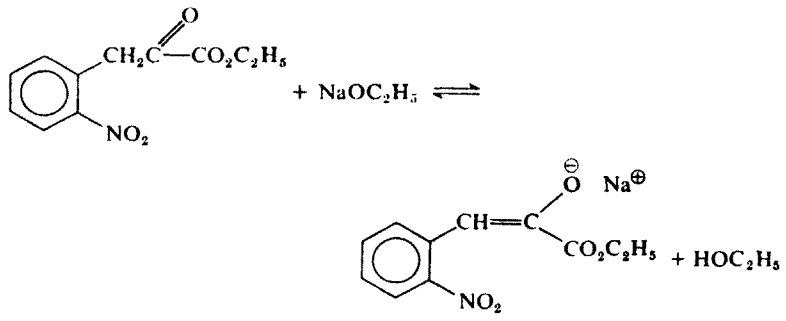
(*a*)



which would be forced to the left by ethanol as solvent, thus decreasing the concentration of the species that reacts with diethyl oxalate. If the solvent is benzene this reverse shift is minimized. In the aprotic solvent benzene, the ethoxide anion is not solvated to the same extent as in ethanol, hence it is a stronger base. In addition, the equilibria (*b*) and (*c*) would be shifted to the right as the sodium enolate, less soluble in benzene than in ethanol, precipitates from the benzene solution. These arguments would also apply if ether

(*b*)

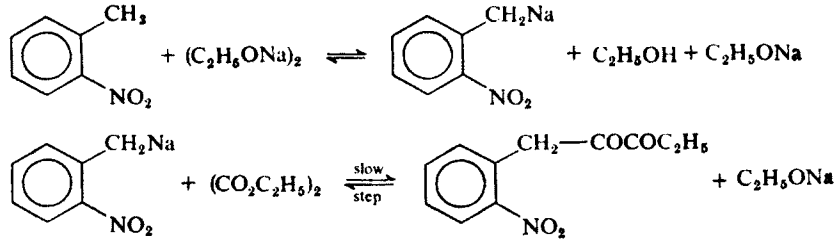


(c) 

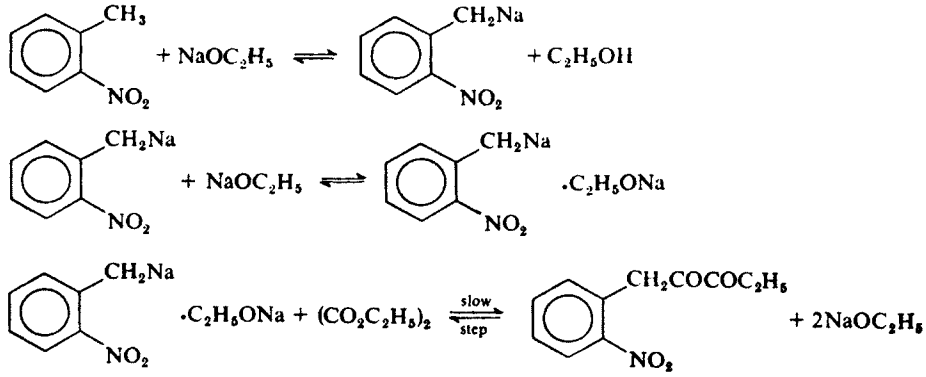
were used as solvent and would explain the favorable effect on the reaction observed when ether is added to the ethanol solution, or replaces ethanol as solvent.

The effect of substituents on the rate of reaction of the *o*-nitrotoluene with diethyl oxalate corroborates the previous observation that electron-donor substituents retard the reaction, particularly if they are situated *para* to the methyl group since they would increase the difficulty of proton removal from the methyl moiety. That the fluorine atom increases the rate of reaction much less than does bromine, though it is more electro-negative than is bromine, is no doubt due to the fact that electron donation to the aryl ring is greater for the fluorine atom because its small size permits better overlap of the *p*-orbitals of fluorine with those of the benzene ring system. The drop in relative rate of reaction from 8.09 to 1.53 when the bromine substituent is changed from position 4 to position 3 in the 2-nitrotoluene reflects the development of steric repression of attainment of coplanarity of the nitro group with the ring in order to activate the methyl group.

A number of mechanisms were suggested[437] to explain the fourth-order kinetics; however, the observation of second-order dependence upon base was difficult to interpret. It was clear, however, that the rate-controlling step must be the attack by an anionic species on the diethyl oxalate and not on a complex or addition compound of sodium ethoxide with diethyl oxalate since evidence[437, 440] showed that sodium ethoxide in ethanol does not complex with diethyl oxalate.

(A) 

(B)



Scheme 56

Plausible mechanisms suggested[437] are shown in Scheme 56. Mechanism A requires an "ion quadruplet" $(C_2H_5O^-Na^+)_2$ which presumably should react very much faster with the nitrotoluene than would the "ion pair" $C_2H_5O^{\ominus}Na^{\oplus}$. Evidence for such ion quadruplets has been advanced[441] in the studies of dioxane–water mixtures of dielectric constant 23 or less. The dielectric constant of ethanol is 24. Whether such aggregates do occur in ethanol is not known. Mechanism B also requires an "ion quadruplet" composed of one molecule of sodium ethoxide and one of the sodium salt of *o*-nitrotoluene. Ingold et al.[442] have postulated similar ion quadruplets in their study of the solvolysis of alkyl halides in benzene.

In Table III are summarized many of the substituted 2-nitrotoluenes that have been condensed with diethyl oxalate to form the substituted 2-nitrophenylpyruvic acids or their esters.

The reductive cyclization of *o*-nitrophenylpyruvic acids is the final step of the Reissert indole synthesis, and provides an indole containing a carboxylic acid group in the α-position. Usually it is necessary that this carboxylic acid group be removed. The indole synthesis by the Fischer cyclization of pyruvic acid phenylhydrazones[23] also requires final removal of carbon dioxide from the indole-2-carboxylic acid so formed. A variety of methods have been employed for such decarboxylations. A convenient and widely applicable method is that of heating the indole-2-carboxylic acid in quinoline containing copper chromite.[452] This has been found quite satisfactory for indole-2-carboxylic acids with aryl ring substituents as 4-, 5-, 6-, or 7-chloro,[130, 444] -fluoro,[429] 4-, 5-, 6-, or 7-methoxy,[53, 282] 7-nitro,[88] 6-alkyl,[384] 5-chloro and 6-methoxy,[415] 5- or 6-benzylthio,[418] 4-iodo,[453] or if 1-carboxymethyl or 1-carboxymethyl-3-methylindole-2-carboxylic acid is used.[454] It has been found advantageous to add small amounts of copper chromite catalyst periodically to the hot solution during the course of the decarboxylation.[446] Best results are obtained if the quinoline is redistilled and pure.[88, 130, 418] A

TABLE III

Substituents and their positions in the 2-nitrotoluene nucleus

3	4	5	6	Ref.
				405, 407
CH_3O				409, 426
	CH_3O			278, 426
		CH_3O		409
			CH_3O	409, 426
	CN			436
		CN		61
	$CO_2C_2H_5$			436
	$PhCH_2O$			412, 421, 427
		$PhCH_2O$		81, 421, 425, 427
			$PhCH_2O$	421
$PhCH_2S$				418
	$PhCH_2S$			418
		$PhCH_2S$		418
			$PhCH_2S$	418
	CH_3			405
		CH_3		406, 408
			CH_3	434, 450
	F			63, 429, 443
		F		443
			F	63
Cl				414
	Cl			130, 413, 433, 444, 445, 451
			Cl	130, 414, 434
Br				446
	Br			417
		Br		447, 448
			Br	388, 417
			I	419
	NO_2			437
	$(CH_3)_2N$			430
	1-Pentenyl			384
			SR	431
——Benz——				438
	OH	OH		123, 420, 428
		$PhCH_2O$	Cl	422
	CH_3O	Cl		415
	CH_3O	CH_3O		423, 449

nitrogen atmosphere is beneficial.[415] Heating the indole-2-carboxylic acid in quinoline containing copper powder has provided a good yield of indole-3-acetic acid,[50] β-indole-3-propionic acid,[69] and γ-indole-3-butyric acid.[113] The addition of cuprous iodide as well as copper powder to the quinoline solution of 4-iodoindole-2-carboxylic acid has produced 4-iodoindole in 50–70% yield[419] in contrast to the extensive decomposition that occurs when 4-iodoindole-2-carboxylic acid is merely heated above its melting point, a procedure that gives a 90% yield of 4-chloroindole from 4-chloroindole-2-carboxylic acid.[419] Hot quinoline containing cuprous chloride has been used successfully to decarboxylate 4- and 6-chloroindole-2-carboxylic acid.[111, 413] Barltrop and Taylor[388] were unable to decarboxylate 4- and 6-bromoindole-2-carboxylic acid using quinoline alone, or with quinoline containing cuprous bromide, cuprous oxide, or copper. Refluxing resorcinol also failed.[388] However, by the use of *pure* quinoline and cuprous bromide, carbon dioxide could be removed from 4- and 6-bromo[417, 445] as well as 5- and 7-bromoindole-2-carboxylic acid.[445]

The variable and sometimes poor results obtained in the decarboxylation of aryl ring-halogenated indole-2-carboxylic acids by the use of hot quinoline containing cuprous halide[111, 413] was found[130] to be due to contamination of the indole-2-carboxylic acid by sulfate ion arising from the preceding ferrous sulfate-ammonium hydroxide reductive cyclization step. If this sulfate ion is eliminated and particularly if the cuprous halide is replaced by copper chromite in the pure quinoline, then consistently good yields of 4, 5, 6, or 7-chloroindoles have been obtained from the respective chloroindole-2-carboxylic acids.[130]

Cuprous cyanide added to the quinoline solution of 5-bromo- or 7-chloroindole-2-carboxylic acid[414] or 4-chloro-5-benzyloxyindole-2-carboxylic acid[422] not only effects decarboxylation but also replaces the halogen by the cyano group, thus providing a route to the corresponding indole-4,5,6- or 7-carboxylic acids.

A mixture of quinoline and red cuprous oxide rather than copper powder is reported to cause smoother decarboxylation, effective at lower temperatures.[135] If diethylene glycol is used as the heating medium, along with one or two equivalents of quinoline, isolation of the product is facilitated because the decarboxylated product is more readily extracted from the tarry residues.[135] A hot solution of quinoline containing cupric oxide has provided 4-, 5-, 6-, and 7-nitroindoles in yields of 51, 71, 38, and 78%, respectively, from the corresponding nitroindole-2-carboxylic acid.[128]

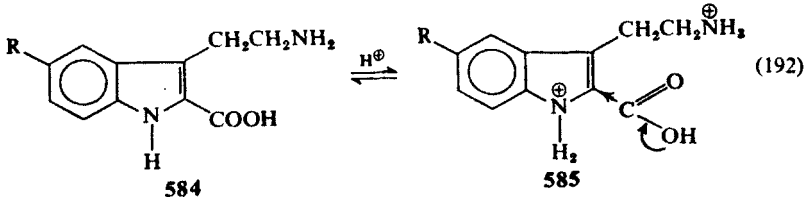
Copper powder in hot quinaldine readily decarboxylates 5,6-dialkoxyindole-2-carboxylic acid in 63% yield.[420] Hot glycerol is reported to effect smooth decarboxylation of 5,6-dimethoxyindole-2-carboxylic acid. Both 6- and 7-hydroxyindole-2-carboxylic acid readily lose carbon dioxide under

these conditions,[412] whereas only tar is obtained if boiling quinoline and copper bronze are employed.[412] 6-Dimethylaminoindole-2-carboxylic acid, when heated in glycerol, is converted to 6-dimethylaminoindole in 88.5% yield,[431] but quinaldine and copper powder is reported to be a better system for the decarboxylation of 4-, 5-, and 6-benzyloxyindole-2-carboxylic acid[421] than is hot glycerol.[427]

Merely heating the acid above its melting point is quite satisfactory in a number of cases. Molecules which are sensitive to high temperatures and to the more vigorous conditions of hot quinoline, are apparently more advantageously decarboxylated by heating them to or slightly above their melting point. The four aryl ring-fluorinated indoles are obtained in this manner from the corresponding fluoroindole-2-carboxylic acids.[63] The 6,7-benzindole-2-carboxylic acid loses carbon dioxide readily under these conditions.[84] An indole-3-carboxylic acid such as 5-hydroxy-2-methylindole-3-carboxylic acid is particularly easily decarboxylated by heating in this manner.[455] Usually a carboxymethyl group attached to the indole nucleus is much more resistant to the loss of carbon dioxide than is a carboxyl group directly attached to the ring system. However, it is reported[456] that 3,4- and 3,6-dicarboxymethylindole-2-carboxylic acid, when boiled in resorcinol, are converted to 3,4-and 3,6-dimethylindole, respectively.

The use of a small amount of the copper salt of the indole-2-carboxylic acid as catalyst has permitted satisfactory decarboxylation in hot quinoline of both 4- and 6-benzylmercaptoindole-2-carboxylic acid which with quinoline and copper chromite gave poor yields of the corresponding 4- and 6-benzylmercaptoindoles, accompanied by simultaneous loss of sulfur as H_2S.[418] A comparison[457] of decarboxylation in hot quinoline using (*1*) a small amount of the copper salt of the indole-2-carboxylic acid, (*2*) copper chromite, and (*3*) no catalyst at all showed that for all six substituted indole-2-carboxylic acids used, the first method gave high yields of product (61% or better) as good as, and in most cases very much better than, those obtained by either of the other two methods. The temperatures necessary to effect the loss of carbon dioxide were lower and the times required were shorter than those necessary for the other two methods. The use of the copper salt of the indole-2-carboxylic acids seems to be potentially useful as a general method of decarboxylation.

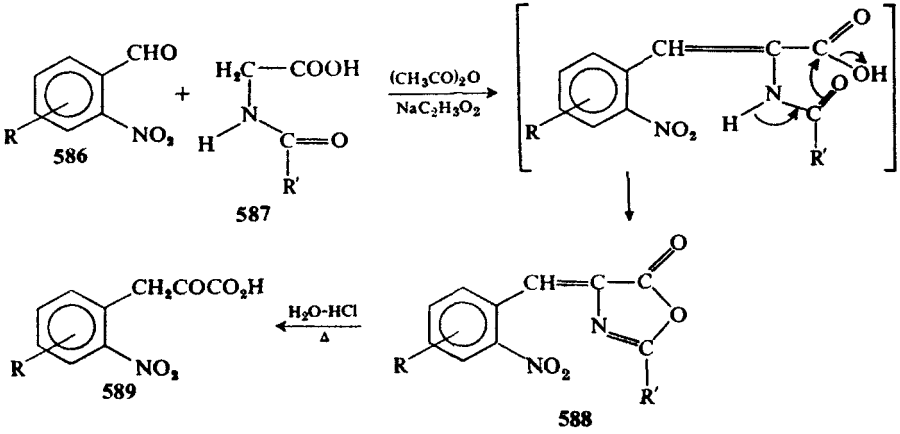
The reported failure[134] of 6-nitro-3-(β-aminoethyl)indole-2-carboxylic acid (**584**, R = NO_2) to lose carbon dioxide by any method led to a study[134] of the effect of the substituent R on the ease of decarboxylation of **584** in acid media (Eq. 192). It was found that the ease decreases in the order R = $CH_3O > CH_3 > H > Cl > NO_2$. This order is the reverse of that expected for decarboxylation since electron-attracting groups (e.g., NO_2) generally favor the heterolytic cleavage of the C—CO_2H bond.[458] To explain the results



(192)

it was suggested[134] that the first step of the decarboxylation is the protonation of the ring nitrogen **585**. The positive charge on this nitrogen would then attract electrons from C-2 and favor loss of carbon dioxide. The relative electronegativities of the substituents, increasing in the order $CH_3O < CH_3 < H < Cl < NO_2$, agree with the view that they would progressively decrease the electron availability of the pyrrole nitrogen for protonation. Hence, protonation of the ring nitrogen of **584** with $R = NO_2$ would probably not occur under the reaction conditions.

An interesting and useful route to the preparation of a number of ring substituted *o*-nitrophenylpyruvic acids is that involving condensation of an *o*-nitrobenzaldehyde **586** with either aceturic acid (**587**, $R' = CH_3$) or hippuric acid (**587**; $R' = Ph$) in the presence of acetic anhydride and sodium acetate.

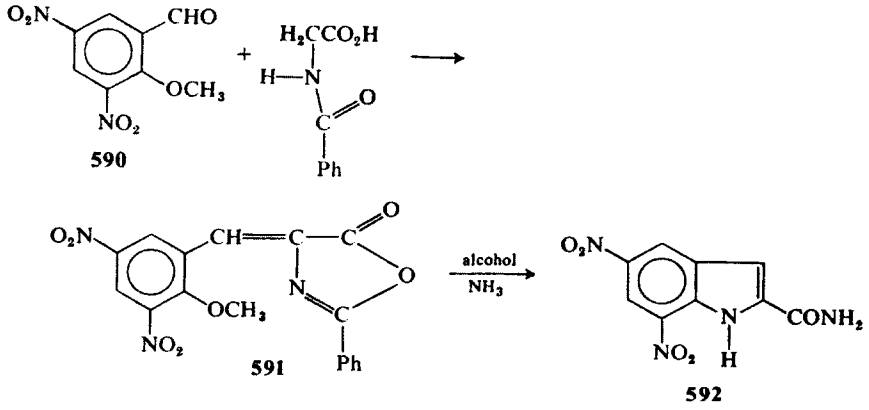


Scheme 57

The azlactone **588**, upon hydrolysis with dilute (~1%) hydrochloric acid, readily provides the 2-nitrophenylpyruvic acid **589** (Scheme 57). Aceturic acid is preferred to hippuric acid since difficulty has been encountered in the hydrolysis of the azlactone **588** ($R' = Ph$) [5-keto-2-phenyl-4-(2′-nitrobenzylidene)-4,5-dihydrooxazole, if $R = H$], to the 2-nitrophenylpyruvic acid **589**.[412, 459–461] By this method 4-hydroxy-3-methoxy-2-nitrobenzaldehyde was converted to 4-(4′-acetoxy-3′-methoxy-2′-nitrobenzylindole)-2-methyloxazol-5-one (**588**, R = 4-acetoxy and 3-methoxy, $R' =$ methyl) which was

then hydrolyzed to 4-hydroxy-3-methoxy-2-nitrophenylpyruvic acid and converted finally to 6-hydroxy-7-methoxyindole.[455] Similarly, 4,5-dihydroxy-2-nitrobenzaldehyde was converted to a monoacetate of the azlactone 4-(4′,5′-dihydroxy-2′-nitrobenzylidene)-2-methyl-4,5-dihydrooxazol-5-one which hydrolyzed to 4,5-dihydroxy-2-nitrophenylpyruvic acid.[123] This was acetylated and then reduced with iron and acetic acid to 5,6-diacetoxyindole-2-carboxylic acid which finally gave 5,6-dihydroxyindole.[123] A similar procedure provided 6-hydroxyindole.[412]

A reaction that resembles the Reissert synthesis involves the condensation of 2-methoxy-3,5-dinitrobenzaldehyde (**590**) with hippuric acid to provide the azlactone **591**.[462] The azlactone was converted, by treatment in a sealed tube with methanol and ammonia, to 5,7-dinitroindole-2-carboxamide **592** (Eq. 193). An attempt to prepare 5-nitroindole-2-carboxamide by the same

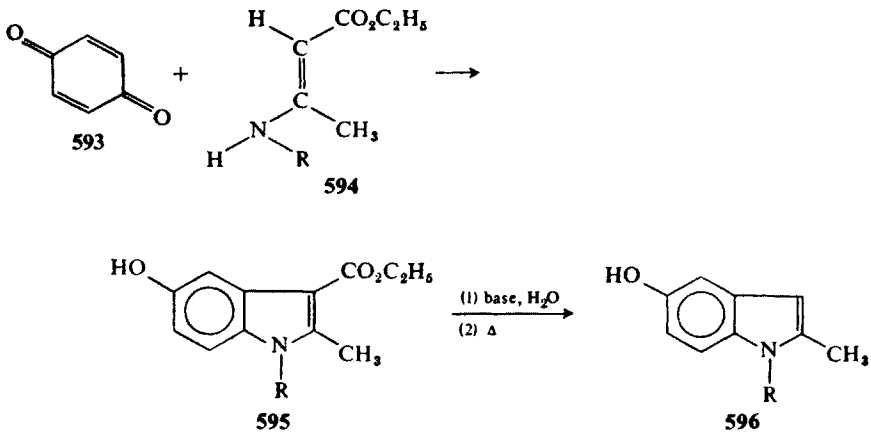


(193)

route[84] starting from 2-methoxy-5-nitrobenzaldehyde failed. The condensation of the aldehyde with hippuric acid to form the azlactone 4-(2-methoxy-5-nitrobenzylidene)-2-phenyl-4,5-dihydrooxazol-5-one was successful, but treatment of the latter with alcoholic ammonia failed to form the 5-nitroindole-2-carboxamide. Apparently activation by only one nitro group is not sufficient under these conditions to permit displacement of the methoxyl group by the ammonia and thus initiate the cyclization.

E. The Nenitzescu Indole Synthesis

The reaction of *p*-benzoquinone (**593**) with ethyl β-aminocrotonate (**594**, R = H) to produce ethyl 5-hydroxy-2-methylindole-3-carboxylate (**595**, R = H)[463] is known as the Nenitzescu indole synthesis (Eq. 194). Although



(194)

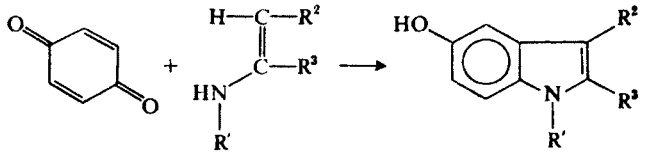
no support was given at the time[463] for the assignment of the structure **595**, subsequent work by Beer et al.[455] and many other investigators has proved it to be correct. Accordingly, this procedure provides a simple route to the 5-hydroxyindole-3-carboxylic acid esters which in turn are readily converted by hydrolysis and decarboxylation to 5-hydroxy-2-substituted indoles (**596**).

The reaction is generally carried out in refluxing dry ethanol[455, 464, 465] or acetone[455, 464–467] under nitrogen, or with somewhat better yields in the solvents benzene,[463, 468] chloroform,[468] methylene chloride,[469] or ethylene dichloride.[470–472] Acetic acid has been found effective[473] in certain cases that have failed to provide the indole in the solvents mentioned above. Condensation of the β-aminocrotonic acid ester **594** with a *p*-benzoquinone and cyclization to the 5-hydroxyindole has been successful when the substituent R on the nitrogen of the aminocrotonic acid ester **594** is methyl[465, 467, 474]; ethyl[475–479]; *n*-propyl, isopropyl, or *n*-butyl[477]; *n*-hexyl[465]; β-cyanoethyl[475]; β-hydroxyethyl[474, 477]; carbethoxymethyl[463, 480]; benzyl[465, 474, 476]; phenyl[463, 474, 476, 481]; *o*-tolyl[474]; dimethylaminopropyl[465]; γ-hydroxypropyl[482]; or $PhCH_2\underset{|}{C}HCO_2CH_3$.[483]

Additional variations of the enamine structure **597** that have been condensed satisfactorily with a *p*-benzoquinone to form 5-hydroxyindoles **598** are given in Table IV.

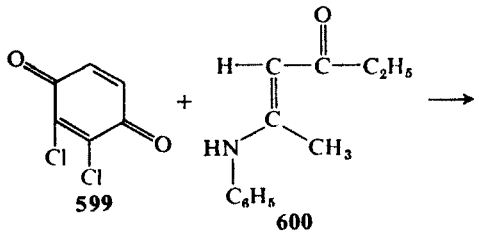
The reaction of 2,3-dichloro-*p*-benzoquinone (**599**) with the *N*-phenylimine (enamine tautomer) of propionylacetone **600** did not give the expected indole but lost aniline to form 6,7-dichloro-5-hydroxy-2-methyl-3-propionylbenzofuran (**601**)[487] (Eq. 195). Similarly, *p*-benzoquinone and acetylacetone-*N*-*n*-butylimine (**602**) produce 3-acetyl-5-hydroxy-2-methylbenzofuran (**603**) (Eq. 196) rather than the 5-hydroxyindole, while *p*-benzoquinone reacts

TABLE IV

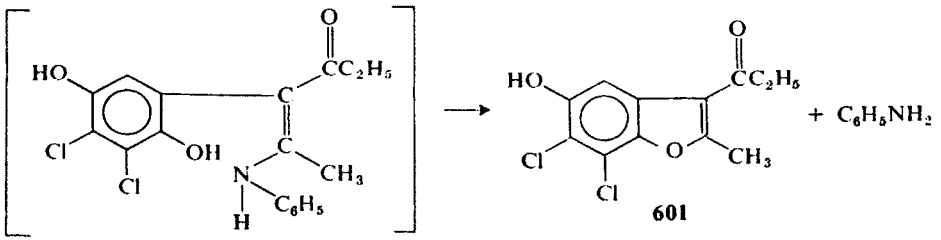


597 598

R^1	R^2	R^3	Ref.
C_2H_5	$CO_2C_2H_5$	C_2H_5	477
H	$CO_2C_2H_5$	OC_2H_5	466
H	$CO_2C_2H_5$	C_6H_5	473
Alkyl	$CO_2C_2H_5$	C_6H_5	485, 486
H	CN	C_6H_5	473
C_2H_5	$CONHC_6H_5$	CH_3	476
Alkyl or aryl	$COCH_3$	CH_3	471, 481
C_2H_5	$CO_2C_2H_5$	$CH_2CO_2C_2H_5$	484

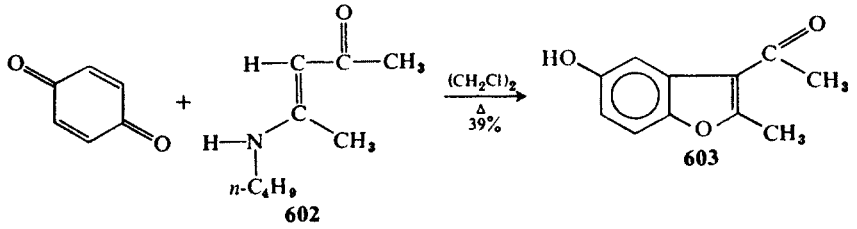


599 600



601

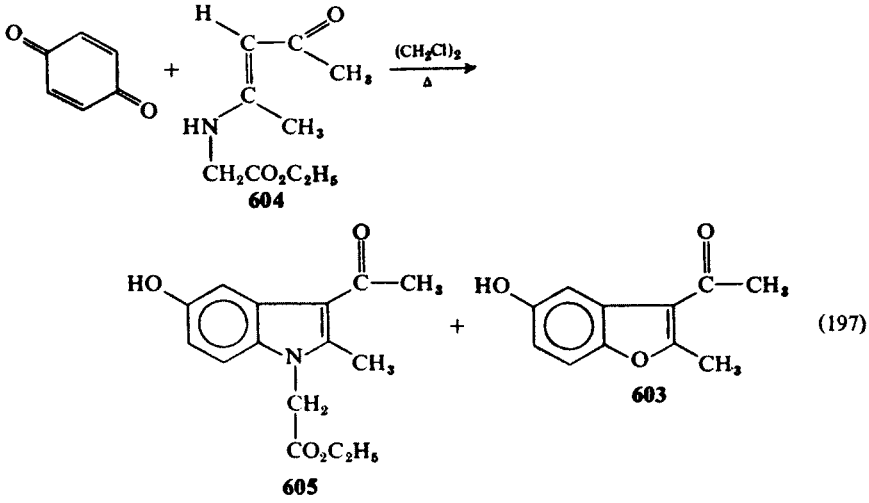
(195)



602 603

(196)

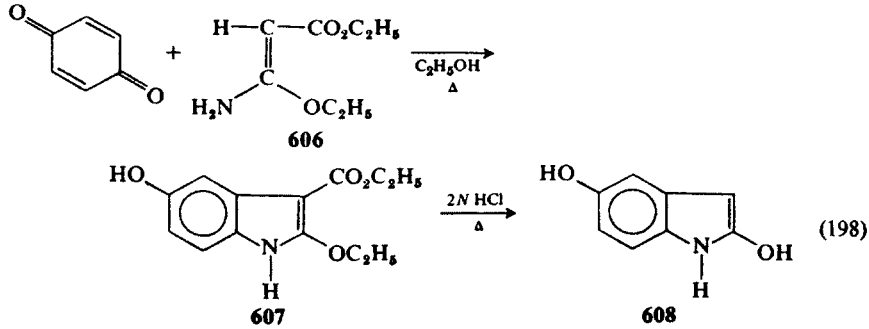
with acetylacetone-*N*-carbethoxymethylimine (**604**) to give the expected indole **605** along with the benzofuran **603**[471] (Eq. 197). If the carboethoxy-



(197)

methyl group on the nitrogen atom of **604** is replaced by groups such as *p*-tolyl, *p*-anisyl, *o*-anisyl, *p*-dimethylaminophenyl, or *p*-acetamidophenyl, then 12 to 58% of the corresponding 5-hydroxy-2-methyl-3-acetyl-1-substituted indole is formed, apparently unaccompanied by the corresponding benzofuran.[471]

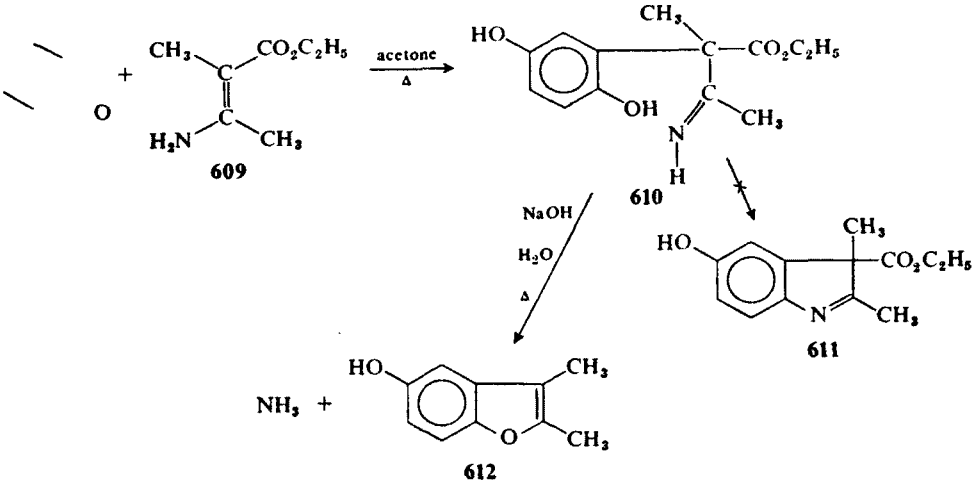
The reaction of ethyl β-amino-β-ethoxyacrylate (**606**) with *p*-benzoquinone provides ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate (**607**) which is surprisingly resistant to alkaline hydrolysis, giving only tars when vigorous conditions are employed[466] (Eq. 198). However, hydrolysis with 2 *N* hydrochloric acid proceeds smoothly to give 5-hydroxyoxindole (**608**).



(198)

Certain β-aminoacrylic acid esters either do not provide 5-hydroxyindoles or fail to react with *p*-benzoquinone. Ethyl β-amino-α-methylcrotonate (**609**) reacts with *p*-benzoquinone to give **610**, a rather unstable base, which does

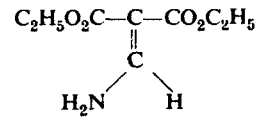
not cyclize to the ethyl 5-hydroxy-2,3-dimethylindolenine-3-carboxylate (**611**) as expected, but upon alkaline hydrolysis gives 5-hydroxy-2,3-dimethylbenzofuran (**612**) and ammonia[466] (Scheme 58).



609 610 611 612

Scheme 58

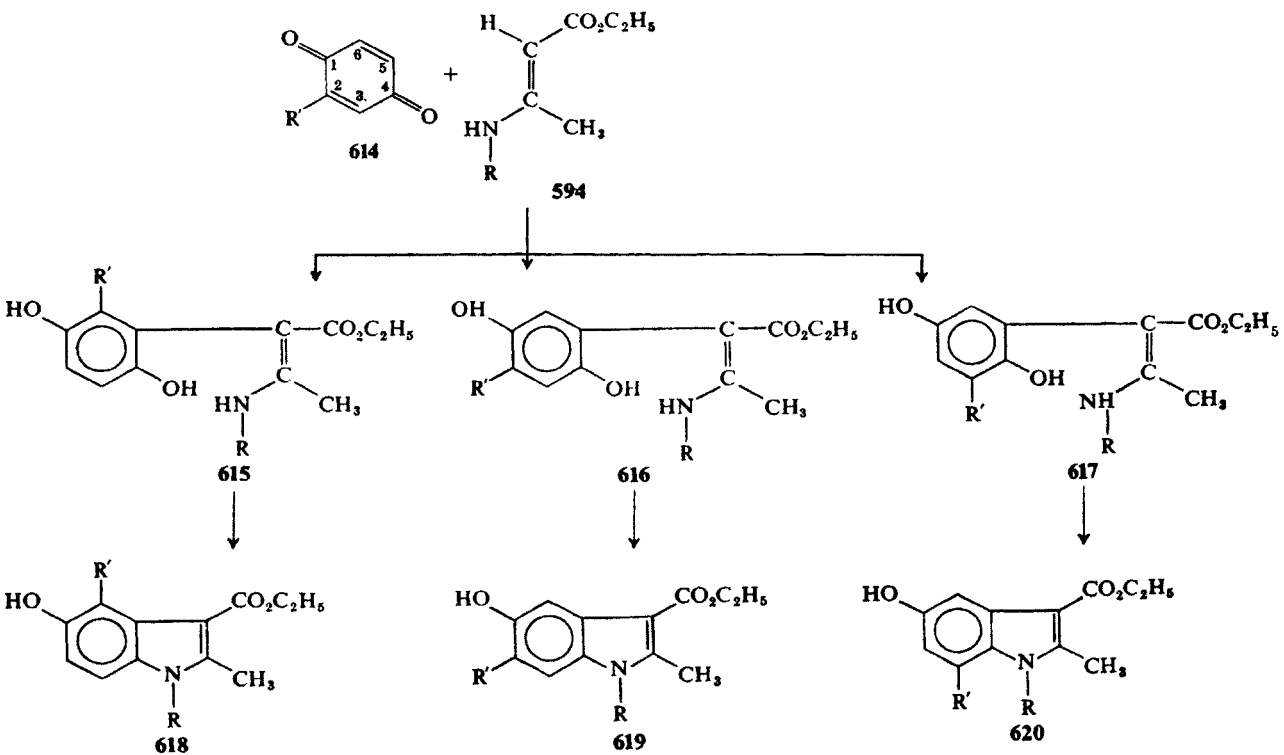
Although *N*-alkyl and *N*-aryl derivatives of ethyl β-aminocrotonate (**594**) react well with *p*-benzoquinone, the *N*-acetyl derivative does not react at all.[466] Diethyl aminomethylenemalonate (**613**) also fails to react with *p*-benzoquinone.[466]



613

Several substituted *p*-benzoquinones have been condensed quite satisfactorily with β-aminocrotonic acid esters or their analogs, thus providing 5-hydroxy-2-substituted indoles with additional substituents in the benzene ring. These substituted *p*-benzoquinones are 2-hydroxy,[455] 2-methoxy[455, 466, 477, 488]; 2-methyl[455, 464, 472, 477, 479, 485, 486, 488]; 2-chloro[467,489]; 2-fluoro, -iodo, or -bromo[489]; 2-ethyl[477, 478, 488]; 2-benzylthio[465]; 2-trifluoromethyl[489]; 2-carbethoxy or 2-acetyl[490]; 2,3-benz[467, 475, 485, 486]; 2,3-dimethyl[464]; 2-hydroxy-3,6-dimethyl[455]; 2-chloro-3-trifluoromethyl[489]; 2-chloro-5-trifluoromethyl[489]; and 2-methoxy-5-trifluoromethyl.[490]

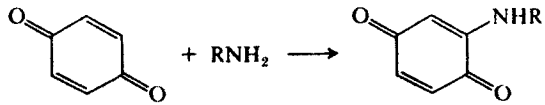
The early work involving the condensation of 2-substituted-*p*-benzoquinones with ethyl β-aminocrotonate indicated that the only indolic product obtained was ethyl 5-hydroxy-2-methyl-6-substituted indole-3-carboxylate.[455, 464-466] However, from the view[466, 478, 488] that the first step



Scheme 59

of the condensation is the formation of the 2,5-dihydroxyphenyl derivatives **615**, **616**, and **617** of the β-aminocrotonate (cf. **610**), it is clear that the three indolic products **618**, **619**, and **620** are possible[477, 488–490] (Scheme 59).

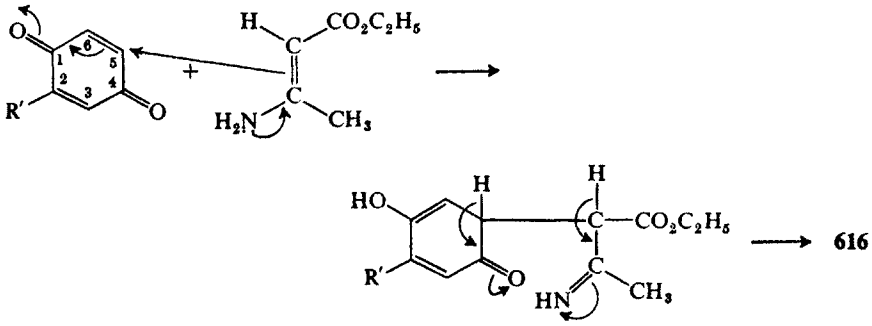
It is known that electron-donor substituents at C-2 in the *p*-benzoquinone ring activate the C-5 and C-6 positions of the ring to nucleophilic attacking agents while electron-withdrawing substituents at C-2 favor such attack at C-3.[491] Although amines are known to react with *p*-benzoquinone to give structures of the type **621**[492] (Eq. 199), enamines usually react at the terminal



(199)

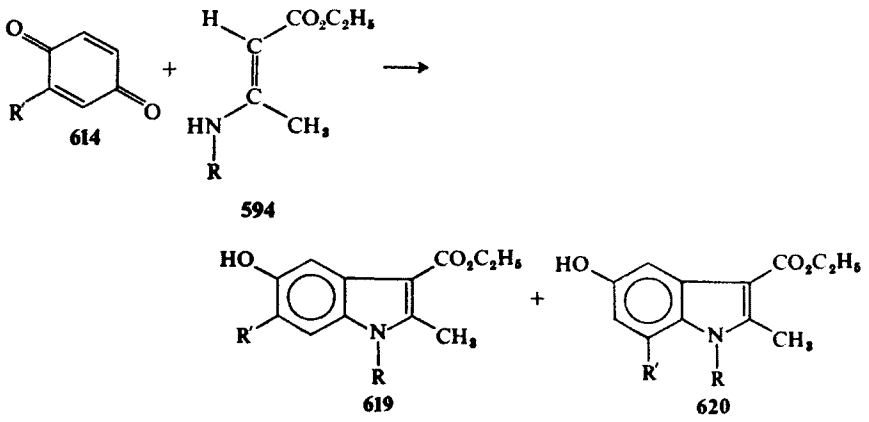
621

carbon[493–495] and thus by a Michael-type reaction[495] can form Structures **615**, **616**, and **617**, as shown in Eq. (200).



(200)

In a detailed study of the Nenitzescu reaction involving several 2-substituted-*p*-benzoquinones **614** (R′ = alkyl or alkoxy) with ethyl β-aminocrotonate and some of its *N*-alkylated derivatives **594**, Allen et al.[477, 488] found that the 6-substituted isomer **619** was produced as the major product, accompanied frequently by the 7-substituted isomer **620** usually in minor amount (Eq. 201). In only one case (R′ = CH_3, R = H) were the two products **619** and **620** obtained in nearly equal quantity. Yields were generally low. Table V, taken from the work of Allen et al.,[477, 488, 489] shows their results. No evidence could be obtained for the formation of the 4-substituted-5-hydroxyindole **618**. The table indicates that except for the case of the halogens, as the alkyl substituents R′ attached to C-2 of the *p*-benzoquinone and/or R attached to the nitrogen atom of the amine increased in size, the ratio **619**/**620** increased. Because of their weak electron donor (via resonance) property, the halogens also promoted attack by the β-aminocrotonic acid ester at the C-5 and C-6 positions of the 2-halo-*p*-benzoquinones to provide



614 594 619 620

(201)

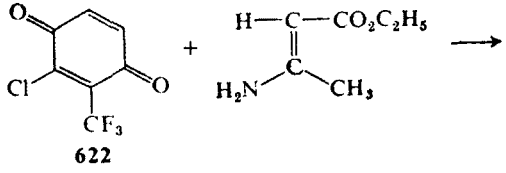
both the 6-halo- and 7-halo-5-hydroxyindoles **619** and **620** (R′ = halogen, R = H).[489] Here, however, increase of size of the halogen at C-2 of the *p*-benzoquinone gave a progressive decrease in the proportion **619/620**, and in the case of the 2-fluoro-*p*-benzoquinone only the 6-fluoro-5-hydroxyindole **619** was obtained. Apparently none of the four 2-halogenated-*p*-benzoquinones gave any of the 4-halo-5-hydroxyindole **618** (R′ = halogen, R = H).

The strongly electron-withdrawing trifluoromethyl substituent,[496, 497] in agreement with the general finding of Wilgas et al. (Ref. 491 and references

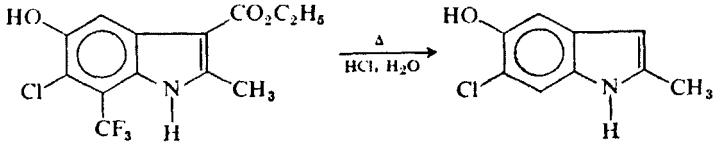
TABLE V

Substituents on **614** and **594**		Product, % yield		Ratio **619/620**
R′	R	**619**	**620**	
CH_3	H	9	8	1.1
CH_3	CH_3	22	10	2.2
CH_3	C_2H_5	21	2	10.5
CH_3	*n*-C_3H_7	21	1	21.0
CH_3	*n*-C_4H_9	18	2	9.0
CH_3	*i*-C_3H_7	18	—	—
C_2H_5	H	30	—	—
C_2H_5	C_2H_5	14	0.2	70
CH_3	C_2H_5	20	1.5	13
CH_3O	H	19	—	—
CH_3O	C_2H_5	63	—	—
F	H	12	0	—
Cl	H	20	4	5.0
Br	H	5	2	2.5
I	H	1	7	0.14

therein), caused exclusive attack by ethyl β-aminocrotonate at C-3 of 2-trifluoromethyl-*p*-benzoquinone (see **615**) since only ethyl 5-hydroxy-2-methyl-4-trifluoromethylindole-3-carboxylate (**618**; R′ = CF_3, R = H) is obtained (54–62% yield).[489] If both chlorine and the trifluoromethyl group are substituents in *p*-benzoquinone, the trifluoromethyl group controls the course of reaction. Both 2-chloro-3-trifluoromethyl-*p*-benzoquinone (**622**) and 2-chloro-5-trifluoromethyl-*p*-benzoquinone (**625**) react with ethyl β-aminocrotonate to give good yields of the respective indoles **623** and **626**. Acid hydrolysis of the esters **623** and **626**, which is accompanied by both decarboxylation and removal of the trifluoromethyl group, provides the chloro-5-hydroxy-2-methylindoles **624** and **627**, respectively[489] (Eqs. 202 and 203).

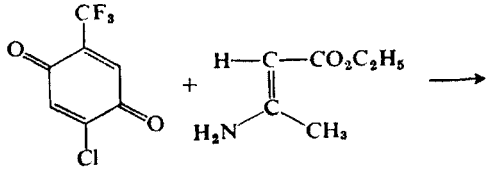


622

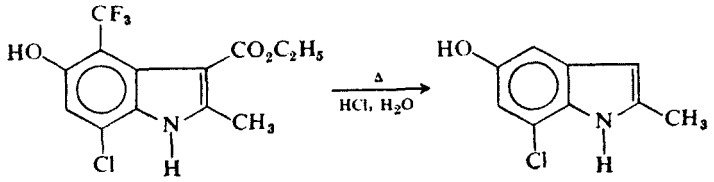


623 **624**

(202)



625

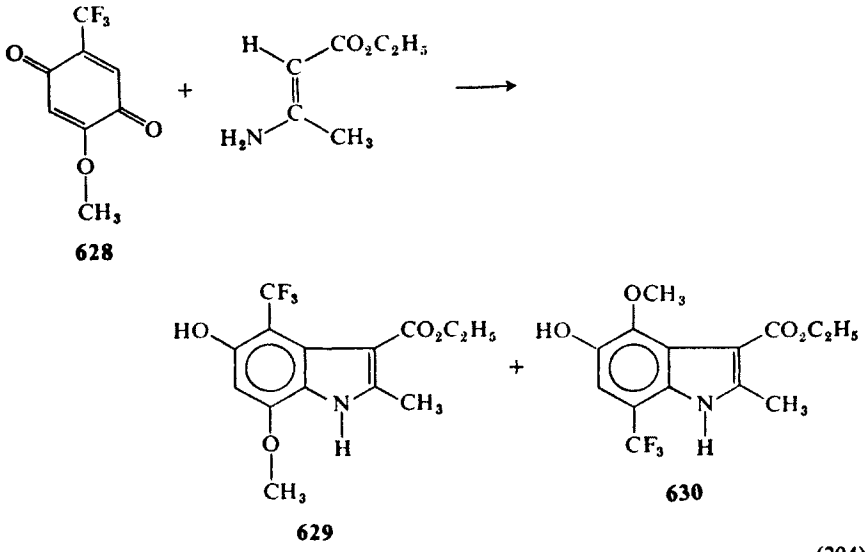


626 **627**

(203)

However, 2-methoxy-5-trifluoromethyl-*p*-benzoquinone (**628**) apparently provides *both* **629** and **630**, each in ~25% yield, although the orientation of

the substituents was not ascertained with certainty[489] since an unresolvable mixture was obtained on attempted removal of the trifluoromethyl group by hydrolytic cleavage (Eq. 204).

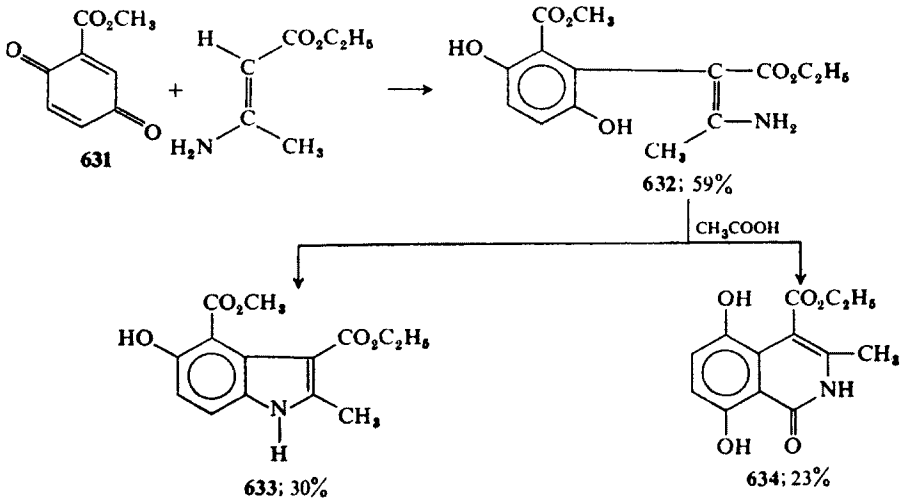


628

629 630

(204)

The electron-withdrawing carbomethoxy group produced the expected reaction between 2-carbomethoxy-*p*-benzoquinone (**631**) and ethyl



631

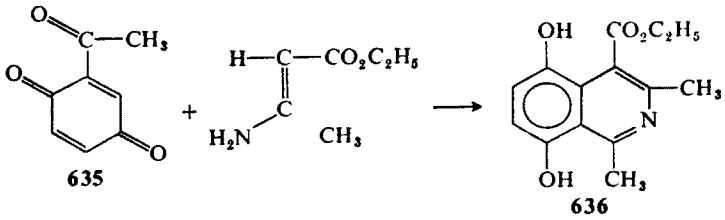
632; 59%

633; 30%

634; 23%

(205)

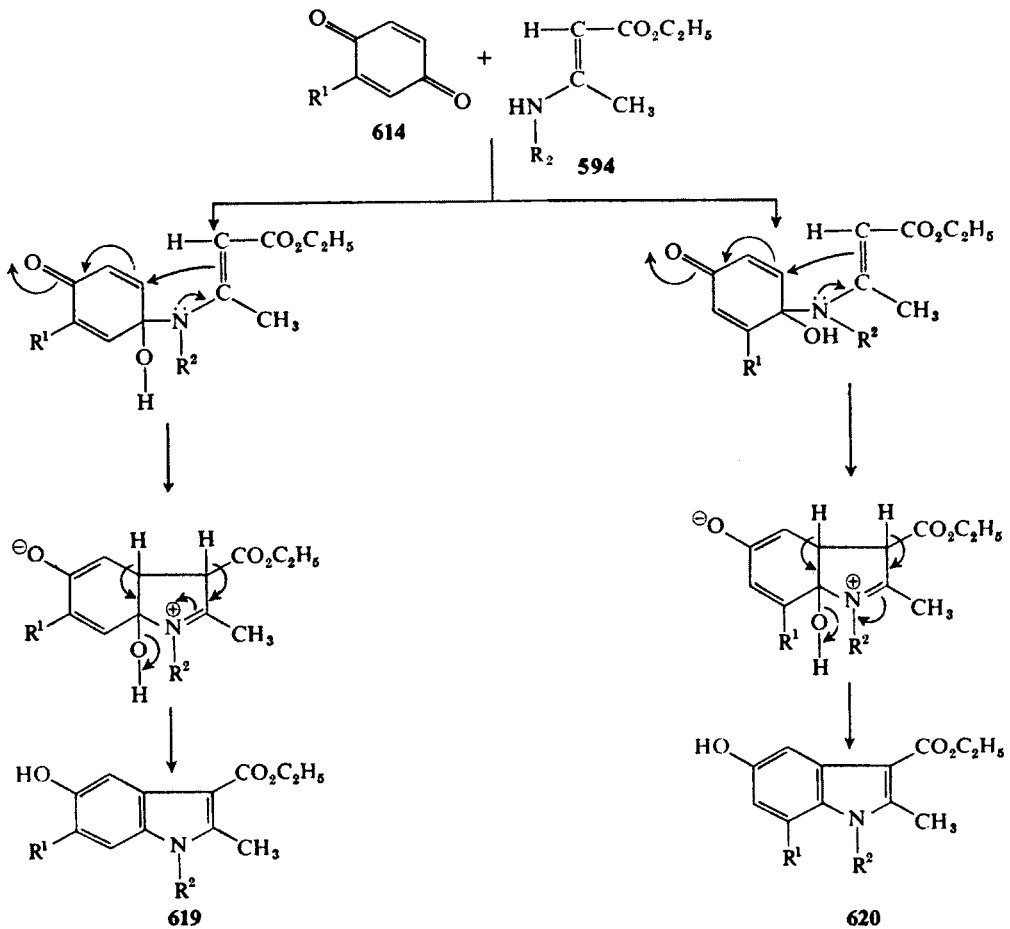
β-aminocrotonate[490] and gave the intermediate **632** which cyclized only after treatment with acetic acid in the presence of a small amount of **631**. Along with the expected **633** there was obtained ethyl 5,8-dihydroxy-3-methylisocarbostyril-4-carboxylate (**634**) which must have arisen from the alternative condensation of the carbomethoxy group of **632** with the amino moiety (Eq. 205). The reaction of 2-acetyl-*p*-benzoquinone (**635**) with ethyl β-aminocrotonate in hot chloroform[490] gave no indole but provided ethyl 5,8-dihydroxy-1,3-dimethylisoquinoline-4-carboxylate (**636**) (Eq. 206) instead.



635 **636**

(206)

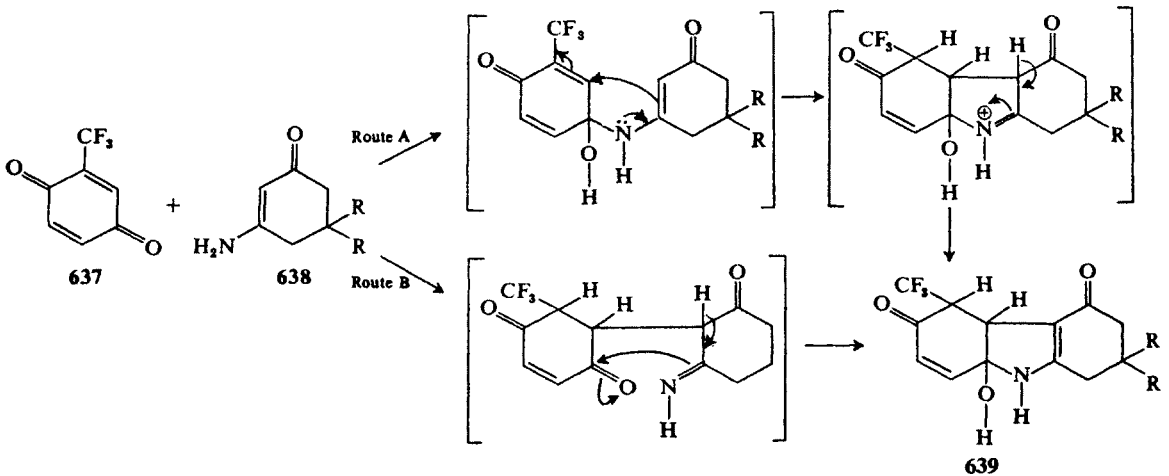
Two mechanisms have been advanced to explain the course of the Nenitzescu reaction. That proposed by Steck et al.[465] and described by Allen[488] is shown in Scheme 60. In this mechanism, the first step was considered to be an attack by the amino group of the ethyl β-aminocrotonate **594** on the carbonyl moiety of the *p*-benzoquinone **614**. Since it is known that the carbonyl group of quinones can add either bisulfite or hydroxyl ions directly and reversibly,[498, 499] this is not unreasonable as the first step. This mechanism would offer an explanation for the observation that as the bulk of the substituent R^2 on the nitrogen of the β-aminocrotonate **594** or of R^1 of **614** (Scheme 60) increases, the proportion of the 7-substituted indole **620** decreases.[477, 488] However, because β-amino crotonic acid esters possess the enamine rather than the imine structure[500] and since enamines are known to react as electrophilic species at the terminal carbon of the enamine structure,[493–495] and also because many reactions of quinones appear to occur by a Michael type addition to the olefinic double bond;[491, 495] Steck's scheme is unlikely. A recent report describes work which is believed to provide evidence that the mechanism of the Nenitzescu indole synthesis does not involve the condensation of the amino group of an enamine with the carbonyl moiety of a *p*-benzoquinone as its first step.[501] The reaction of 2-trifluoromethyl-*p*-benzoquinone (**637**) with 3-amino-5,5-dimethylcyclohex-2-enone (**638**, R = CH_3) for 15–45 min in acetic acid at 40–45° gave the compound **639**



Scheme 60

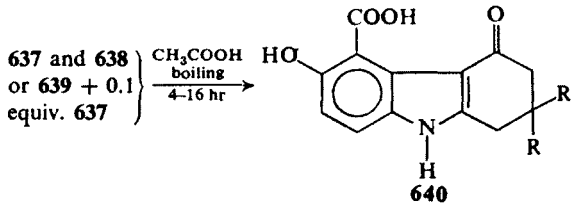
(R = CH_3) in ~40% yield (Scheme 61). When **637** and **638** (R = H) were heated 4 hr in boiling ethanol (conditions that usually provided a 5-hydroxyindole), only **639** (R = H) was obtained. It was suggested[501] that **639** (R = CH_3 or H) arose by initial nitrogen-carbon condensation (Route A). However, it is clear that **639** can be formed by initial carbon-carbon condensation (Route B) and may not occur via Route A. Hence, isolation of **639** does not provide evidence that in this case the initial step involves C—N bond formation.

The fact that **639** (R = CH_3) heated with a small amount of **637** in *boiling* acetic acid for 4–16 hr, or a mixture of **637** and **638** (R = CH_3) similarly treated, gave the indolic compound 5-carboxy-4-keto-6-hydroxy-2,2-dimethyl-1,2,3,4-tetrahydrocarbazole (**640**, R = CH_3) was evidence[501] that


CF3
O
O
637
+
O
H2N
R
R
638
Route A
Route B
CF3
O
O
R
R
N
O
H
H
CF3
H
H
H
O
O
R
R
N
O
H
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N
H
CF3
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H
O
R
R
N
O
H
H
639

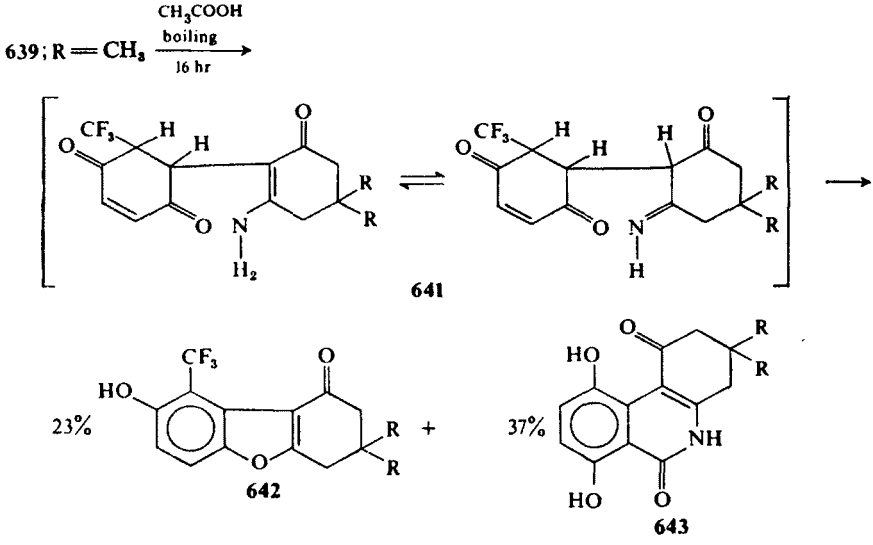
Scheme 61

639 (R = CH_3) was an intermediate in the reaction of **637** and **638** to form the carbazole **640** (R = CH_3). Similarly, when a mixture of **639** (R = H) and 0.1 equiv of **637** was heated in boiling acetic acid, **640** (R = H) was obtained (Eq. 207).



640 (207)

That the conversion of **639** to the tetrahydrocarbazole **640** did not arise by simple acid-catalyzed dehydration was shown[501] by the fact that **639** (R = CH_3) when heated without a small amount of **637**, in boiling acetic acid, gave only the two compounds **642** (R = CH_3) and **643** (R = CH_3) in 23 and 37% yield, respectively (Eq. 208). Compound **639** is a mixed oxygen-nitrogen hemiacetal which can easily revert to the species **641**, which, as

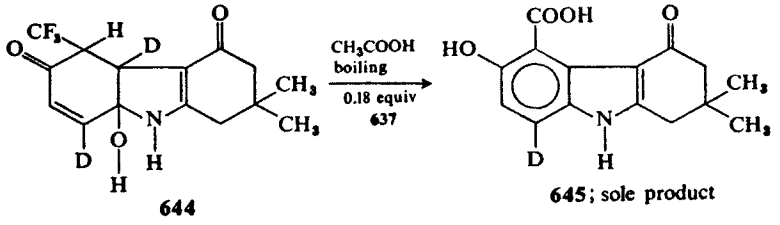


(208)

result of subsequent hydrolysis, would account for the formation of **642** and **643**.

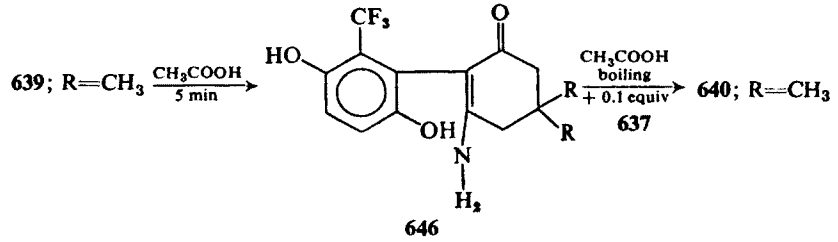
The attempt to dehydrogenate **639** (R = CH_3) with *1 equiv* of the quinone **637** to a quinonimine, which might by subsequent reduction yield the indole, was unsuccessful.[501] Furthermore, the possibility that **639** first dissociates to **637** and **638** and then recombines to form the indolic species **640** was ruled out

by finding only **645** and none of **640** (R = CH_3) when the dideutero compound **644** was heated in boiling acetic acid containing 0.18 equiv of **637**[501] (Eq. 209). Support for the conversion of **639** (R = CH_3) to **641** (R = CH_3)



(209)

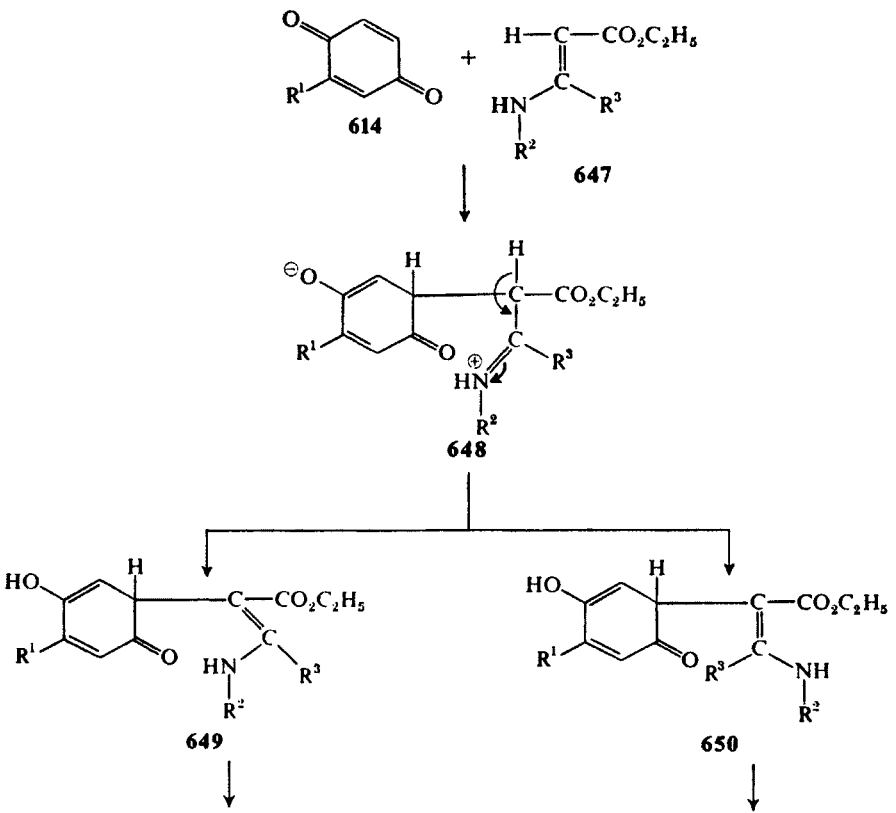
was obtained[501] when **639** (R = CH_3) was treated briefly (5 min) with acetic acid to provide an 85% yield of the hydroquinone **646** (R = CH_3) (Eq. 210).



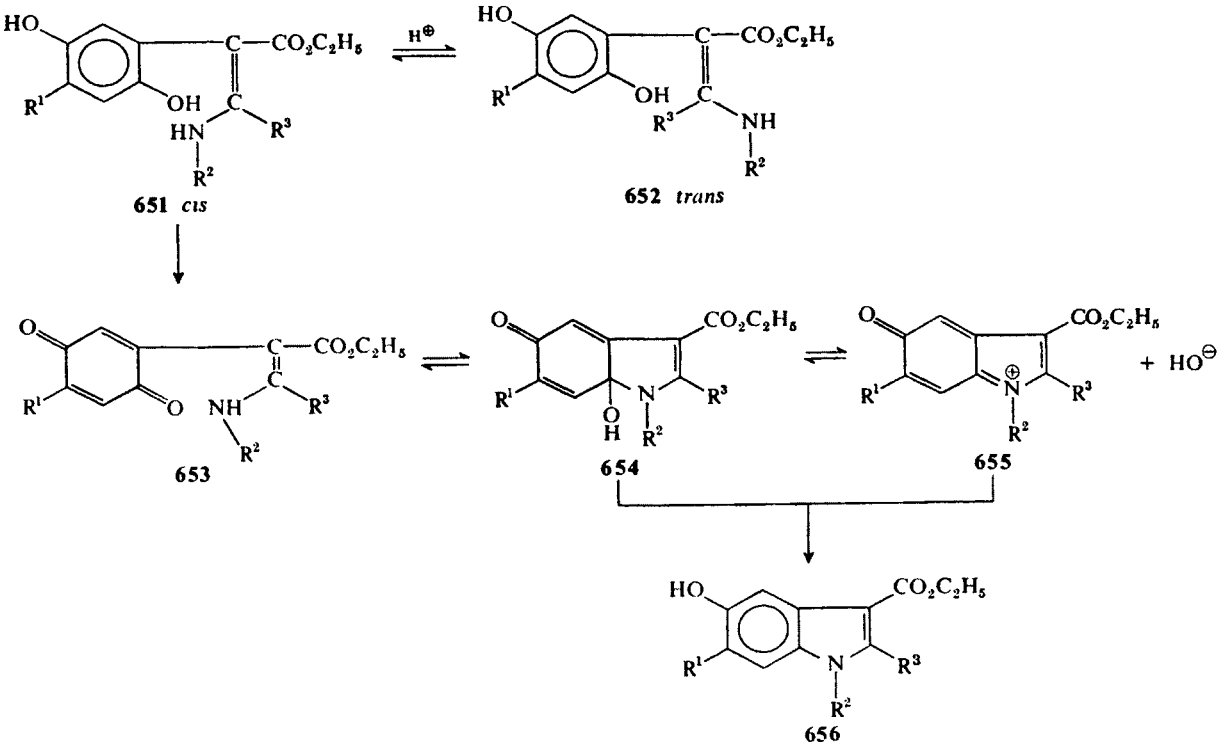
(210)

The second mechanism advanced to account for the Nenitzescu indole synthesis is one that appears to agree best with the available information. This was suggested first by Beer et al. in 1953[466] and also considered as a likely route by Domschke and Fürst.[468] It has recently been developed further independently by Allen et al.[478, 488] and by Raileanu and Nenitzescu[473] and also given additional support by Monti.[472] The sequence in Scheme 62 is that described by Allen et al.[488] but with some modification to accommodate later information.[501]

The reaction of the β-aminocrotonate **647** with the *p*-benzoquinone **614** agrees with the known reactions of enamines[493–495] and *p*-benzoquinones.[491] The electronic properties of the substituent R^1 in **614** apparently control the direction of attack by **647**. Electron-donor substituents (R^1) direct the attack primarily to C-5 of **614**, but to a smaller extent also to C-6, while strongly electron-withdrawing groups direct the nucleophilic species **647** to C-3.[491] The adduct **648** would tautomerize rapidly via **649** or **650** to the *cis* and *trans* isomers **651** and/or **652**. That the dienone **649** does not cyclize directly to the indole **656** via **657** (Eq. 211) is supported by the observation that ethyl α-(3-ethyl-2,5-dihydroxyphenyl)-β-ethylaminocrotonate, an anlog of **651**, did not form an indole when heated in refluxing acetone, but did so if heated

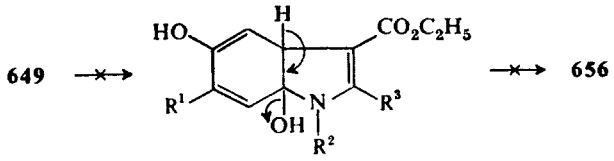


Scheme 62



Scheme 62 (*contd*)

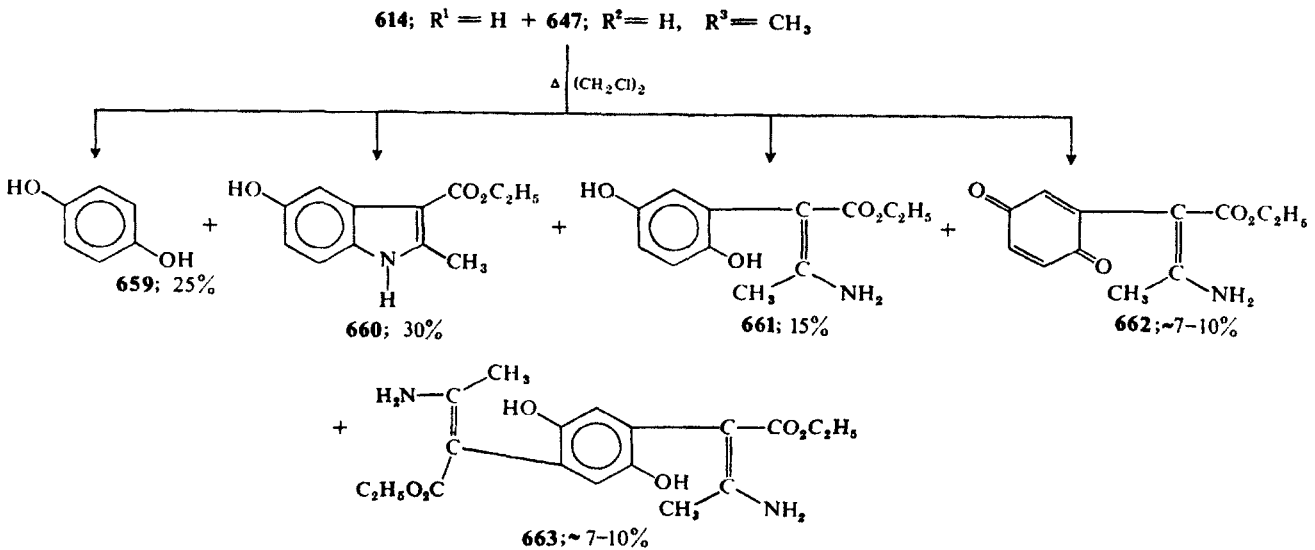
in refluxing acetone in the *presence of a small amount of o-toluquinone.*[488] This indicates that an oxidation must be involved at this stage, *before* cyclization and indole formation can occur.



(211)

It is clear that of the two geometric isomers **651** and **652**, it is that isomer with the amino group *cis* to the dihydroxyphenyl moiety that would cyclize to form the indole. However, since it is known that enamines protonate on the terminal carbon of the double bond[502] and thus can lead to an equilibrium mixture of *cis* and *trans* isomers, it is thus possible to convert the *trans* isomer **652** in part to the *cis* isomer **651** by the addition of acid[473, 478, 488–490] and thus proceed with the cyclization and indole formation. The preference of direction of tautomerization of the adduct **648** to form either the *cis* enamine **651** or the *trans* enamine **652** could be determined by steric[478, 488] and possibly electronic[473] factors. If the substituent R^2 on the nitrogen atom of **647** is small, e.g., hydrogen or methyl, and R^3 is also small, e.g., methyl, then both *cis* and *trans* isomeric enamines should be formed, with the *cis* isomer continuing reaction to form the indole. This has in fact been demonstrated. From the reaction of 2-methyl-*p*-benzoquinone (**614**, $R^1 = CH_3$) with the enamine **647** ($R^2 = H$, $R^3 = CH_3$) there was obtained, in addition to the expected indole isomers ethyl 2,6-dimethyl-5-hydroxyindole-3-carboxylate and ethyl 2,7-dimethyl-5-hydroxyindole-3-carboxylate, a 5% yield of the *trans* isomer **652** ($R^1 = R^3 = CH_3$, $R^2 = H$),[478, 488] which by treatment with acid and a small amount of **614** ($R' = CH_3$) was converted into ethyl 2,6-dimethyl-5-hydroxyindole-3-carboxylate. The reaction of 2-methyl-*p*-benzoquinone with **647** ($R^2 = i\text{-}C_3H_7$, $R^3 = CH_3$) gave, along with the expected ethyl 2,6-dimethyl-5-hydroxy-1-isopropylindole-3-carboxylate (18%), and 18% yield of the *trans* enamine ethyl α-(2,5-dihydroxy-3-methylphenyl)-β-isopropylaminocrotonate, which apparently could not be converted *in situ* by acid to the *cis* isomer since none of the expected ethyl 2,7-dimethyl-5-hydroxy-1-isopropylindole-3-carboxylate was obtained.[478, 488]

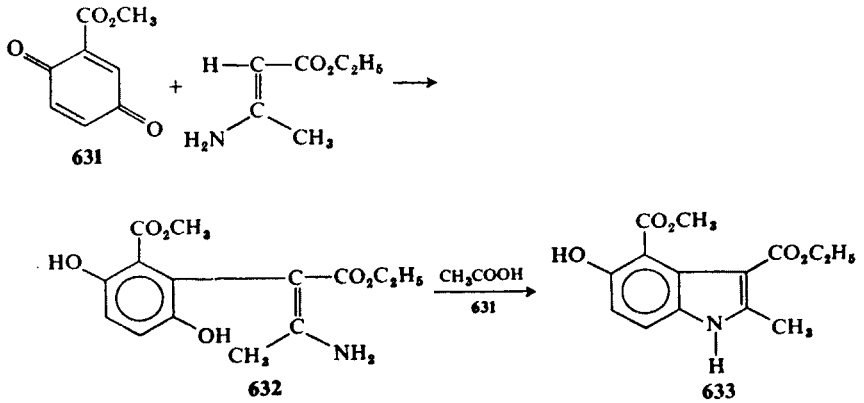
Monti[472] has found that the reaction of *p*-benzoquinone (**614**; $R^1 = H$) with ethyl β-aminocrotonate (**647**; $R^2 = H$, $R^3 = CH_3$) in dichloroethane gave a mixture of five isolable compounds, **659–663** inclusive, in the yields indicated in Scheme 63. The last three compounds were found to be the *trans* enamines. Thermal treatment of **661** did not convert it to the indole **660**, in agreement with the previous finding[488] that oxidation of compounds such


614; R¹ = H + 647; R² = H, R³ = CH₃
Δ (CH₂Cl)₂
659; 25%
660; 30%
661; 15%
662; ~7–10%
663; ~ 7–10%

Scheme 63

as **661** as well as acid-catalyzed isomerization was necessary before cyclization could occur. Presumably the hydroquinone **659** arose from the oxidation of **661** to **662** by *p*-benzoquinone **614** (R^1 = H). The bis adduct **663** could arise from addition of a second molecule of the aminocrotonate **647** (R^2 = H, R^3 = CH_3) to the quinone **662**.[472]

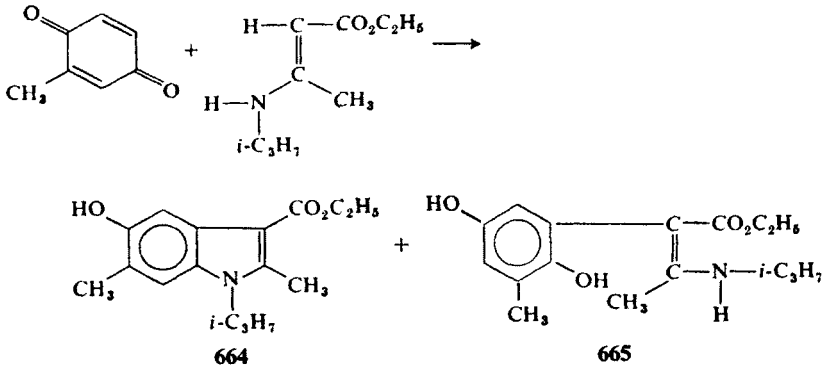
Not only does the steric effect of the substituent on the nitrogen of the β-aminocrotonate **647** control the preference for *cis* **651** or *trans* **652** enamine formation, but the substituent attached to the *p*-benzoquinone also plays a similar, apparently steric role which becomes noticeable if the enamine attacks the 2-substituted quinone at C-3 to form a vicinal trisubstituted aryl ring. This is illustrated in the reaction of 2-carbomethoxy-*p*-benzoquinone (**631**) with ethyl β-aminocrotonate which provides in 59% yield the *trans* adduct **632**.[490] This product requires treatment with acetic acid in the presence of a small amount of **631** to isomerize it to the *cis* enamine, which is now amenable to cyclization and indole formation **633** following preliminary oxidation to the quinone[490] (Eq. 212).



(212)

The compound 2-acetyl-*p*-benzoquinone (**635**), upon reaction with ethyl β-aminocrotonate, also gives the corresponding *trans* enamine analogous to **632**, but this for some reason did not isomerize to the *cis* isomer since no indole could be obtained from it.[490] Another example of this phenomenon is the reaction of 2-methyl-*p*-benzoquinone with **647** (R^2 = *i*-C_3H_7, R^3 = CH_3) which gave the expected ethyl 2,6-dimethyl-5-hydroxy-1-isopropylindole-3-carboxylate (**664**) as well as an 18% yield of the *trans* enamine **665** which could not be converted by the addition of acid and some 2-methyl-*p*-benzoquinone to the corresponding indole[478, 488] (Eq. 213).

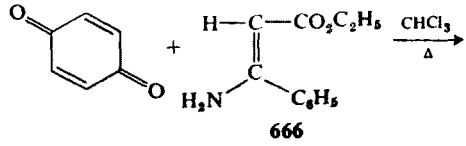
Raileanu and Nenitzescu[473] have found that the reaction of *p*-benzoquinone with ethyl β-aminoacrylates **646**, in which a phenyl substituent was



664 665

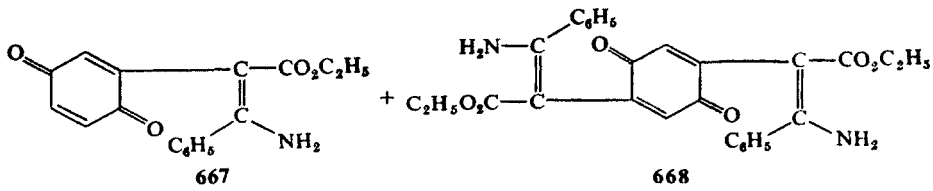
(213)

also in the β position, when heated in chloroform or benzene (usual solvents for the Nenitzescu reaction) did not give an indole. Instead they obtained the quinones **667** and **668**, the latter in only 3.5% yield (Eq. 214). The major



666

(214)

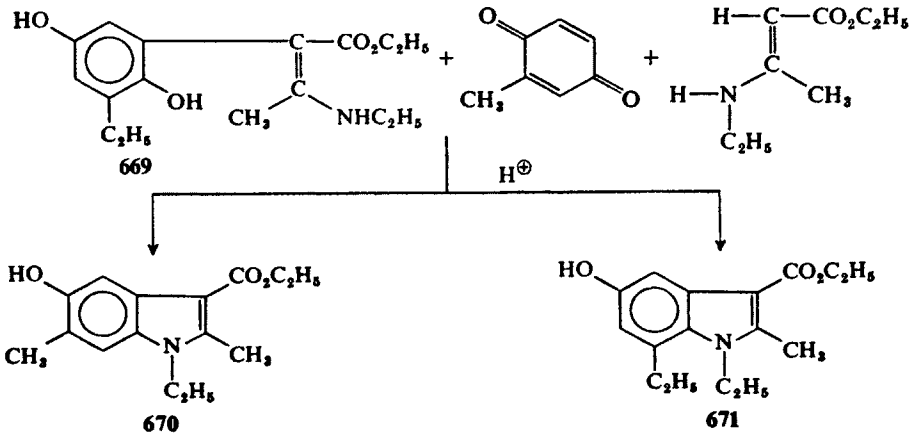


667 668

product **667**, treated in acetic acid with some *p*-benzoquinone, gave ethyl 5-hydroxy-2-phenylindole-3-carboxylate in 40% yield. It was considered that the *trans* enamine **667** was formed because of the phenomenon of "overlay control." Thus, in the tautomerization of the adduct **648**, the pi electron system of the phenyl ring preferred the position close to and parallel to the dienone structure, hence causing, in this case, apparently exclusive formation of the *trans* enamine **650** ($R^1 = R^2 = H$, $R^3 = C_6H_5$) which then must have been oxidized to the quinone **667** by the *p*-benzoquinone. It was found[473] that if *p*-benzoquinone was allowed to react with **666** in boiling acetic acid rather than in chloroform, a 43% yield of ethyl 5-hydroxy-2-phenylindole-3-carboxylate was obtained. The acetic acid apparently isomerized the *trans* enamine **652** ($R^1 = R^2 = H$, $R^3 = C_6H_5$) to the *cis* isomer which then

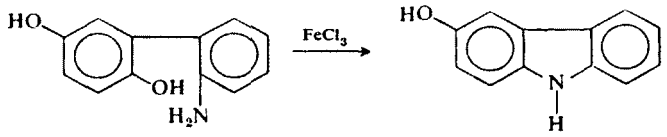
could form the indole. It should be noted in this connection that *p*-benzoquinone and ethyl *β*-benzylaminocinnamate or ethyl *β*-*n*-butylaminocinnamate (**647**; $R^3 = C_6H_5$, R^2 = benzyl or *n*-butyl) have reacted successfully in refluxing ethyl alcohol to provide the 5-hydroxy-2-phenyl-1-benzyl- (or *n*-butyl-) indole-3-carboxylate without the use of acetic acid.[485, 486]

It has been shown[478, 488] that the dihydroxyphenylenamines such as **669** failed to provide the indole even when treated with a catalytic amount of acid. However, if **669** was heated under Nenitzescu conditions with toluquinone and ethyl *β*-ethylaminocrotonate plus a catalytic amount of acid, not only was the expected ethyl 1-ethyl-2,6-dimethyl-5-hydroxyindole-3-carboxylate (**670**) obtained, but a 12–26% yield of ethyl 1,7-diethyl-2-methyl-5-hydroxyindole-3-carboxylate (**671**) was also found (Scheme 64). Because



Scheme 64

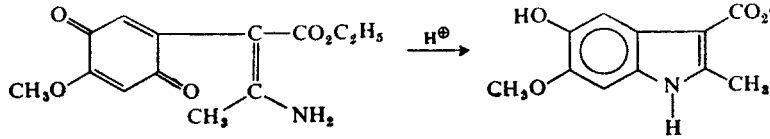
experiments showed that no exchange of the crotonate moiety occurred with species such as **669**,[478, 488] it is clear that **671** came from **669** because of the presence of the toluquinone. Accordingly, there seems to be no doubt that in the final stage of Beer's mechanism involving the conversion of the *cis* enamine **651** to the indole **656**, the enamine **651** must first be oxidized to the quinone **653** to permit cyclization to the species **654** or **655**, which in turn requires reduction to convert it to the indole **656**. The similarity of this oxidation step to the oxidation by catalytic amounts of ferric chloride required to cyclize *o*-aminophenylhydroquinone **672** to 3-hydroxycarbazole[503] has been pointed out[473] (Eq. 215). The postulation of the intermediate **654** receives support from the recent work[501] in which a similar structure **639** was isolated from the reaction of **637** with **638**. The conversion of **639** to **646** by treatment of **639** with acetic acid[501] is in agreement with the view that the conversion of **653** to **654** to **655** is reversible.



672 (215)

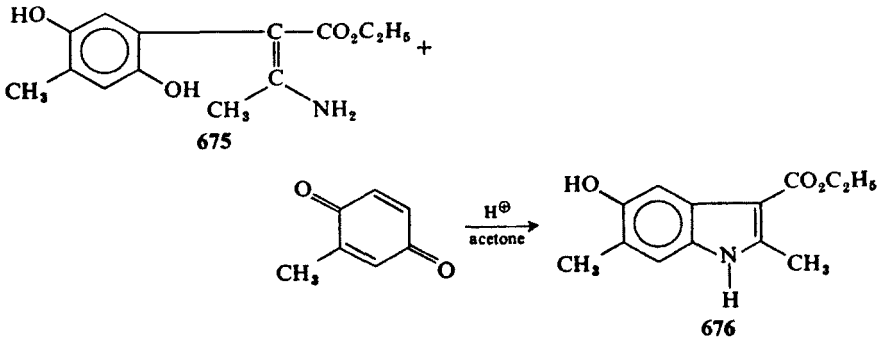
It is quite likely that the *original* quinone is the species which oxidizes the dihydroxyphenylenamine **651** or **652** to the quinone **653** (or the *trans* isomer) since Monti[472] has isolated a 25% yield of hydroquinone from the reaction of *p*-benzoquinone with ethyl β-aminocrotonate. However, a "more advanced intermediate quinone" may also provide this oxidation as well.[478, 488]

That a reduction is required at a stage in the mechanism after the quinone **653** has been formed has been shown by Allen et al.[478, 488] The quinone enamine **673**, even if it is in the presence of a catalytic amount of acid to isomerize it to the *cis* isomer and is heated in acetone, still requires the addition of sodium hydrosulfite in order to convert it to ethyl 2-methyl-6-methoxy-5-hydroxyindole-3-carboxylate (**674**, 22% yield) (Eq. 216). Some



673 674 (216)

evidence as to the identity of the species which provides the reduction of **654** or **655** in the Beer mechanism of the Nenitzescu indole synthesis has been provided by Allen et al.[478, 488] Compound **675**, in the presence of a catalytic amount of acid (as the hydrochloride of **675**) to isomerize it to the *cis* isomer, when heated in acetone with an equivalent amount of toluquinone, rapidly developed a red solution but gave no indole. The addition of sodium hydrosulfite gave a 52% yield of the indole **676**. But if **675** was heated in acetone containing a catalytic amount of acid and only 0.1 equiv of toluquinone, then the indole **676** was obtained in 55% yield (Eq. 217). This is in agreement with

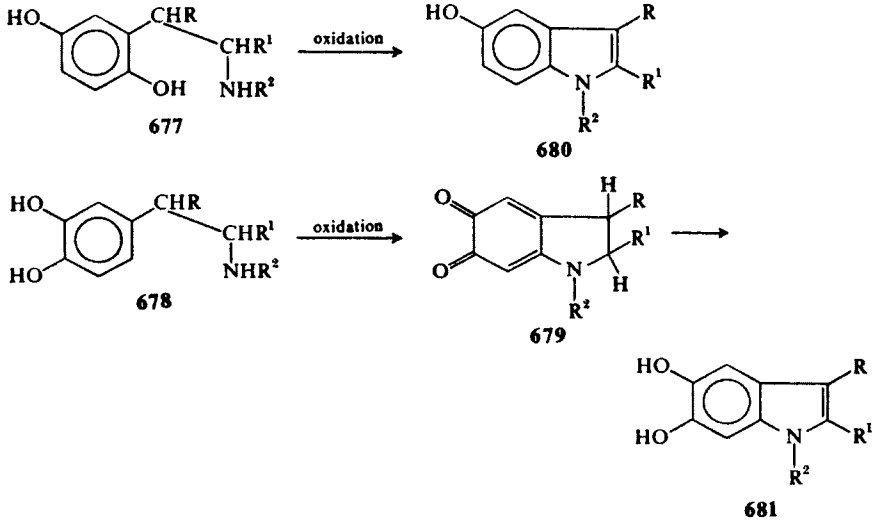


675 676 (217)

the view that certainly for the unsubstituted amino species it is the hydroquinone adduct **651** (or **652**) and not the toluhydroquinone that reduces the species **654** or **655**. The role of the toluquinone is to *initiate* the conversion of the hydroquinone adduct **651** to the quinone adduct **653**.[478, 488]

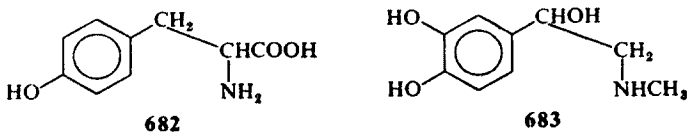
F. Indoles from the Oxidation of β-(Hydroxyphenyl)ethylamines

The oxidation of *β*-(*o*- or *p*-dihydroxyphenyl)ethylamines (e.g., **677** or **678**), usually followed in the case of the *β*-(3,4-dihydroxyphenyl)ethylamines **678** by treatment of the highly colored *o*-quinone intermediate **679** with a reducing agent, a base, or zinc acetate, provides a route for the synthesis of indoles **680** or **681** containing one or two hydroxyl groups in the benzene ring (Scheme 65). The development of this method of synthesizing indoles

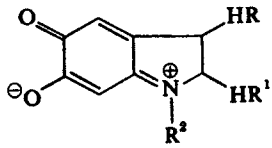


Scheme 65

stems from the interest in the oxidation of biologically important compounds such as tyrosine (*p*-hydroxyphenylalanine; **682**) and adrenaline (epinephrine, suprarenin, *N*-methyl-*β*-hydroxy-*β*-(3,4-dihydroxyphenyl)-ethylamine; **683**) to quinones and the fact that indoles derived from these



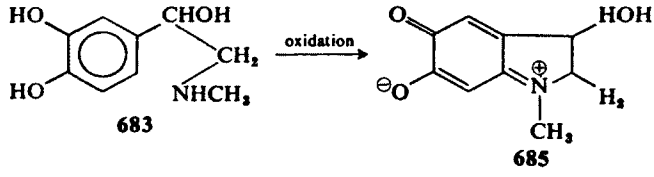
reactions are of interest as intermediates in the formation of the melanin pigments. The β-(3,4-dihydroxyphenyl)ethylamines **678** have been given the general term "catecholamines."[504] The oxidation products of these catecholamines are colored 2,3-dihydroindole-5,6-quinones **679** and given the generic name "aminochrome."[504, 505] Although **679** has been widely used to represent the structure of the aminochromes, their chemical and physical properties are more in accord with the zwitterion **684**.[506, 507] Accordingly, throughout



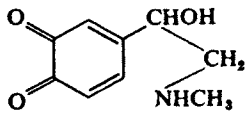
684

this discussion structure **684** will be used to represent the aminochromes. The review by Heacock[504] discusses the chemistry of these aminochromes with some emphasis on their biological significance.

The air oxidation of catecholamines to the aminochromes in a buffered (pH 6–8) solution is reported to be catalyzed either by ions of metals such as copper, manganese, or nickel, or by enzymes.[504] However, such oxidations have not been useful as general methods of producing aminochromes, except in the case of the red solid first isolated and correctly identified by Green and Richter[508] from the air oxidation of adrenalin **683** in aqueous solution containing catechol oxidase, and named by them as adrenochrome **685**. It is interesting that this red solid had been isolated 2 years previously from the oxidation of adrenaline **683**, but erroneously considered to be the adrenaline quinone **686**.[509]



683 **685**

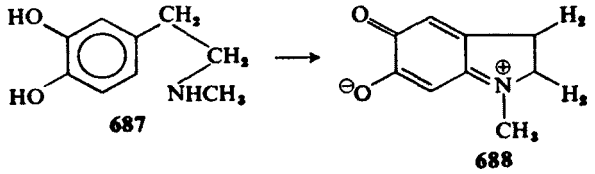


686

Of much greater importance for the purposes of this discussion is the chemical oxidation of the β-(*o*- or *p*-dihydroxyphenyl)-ethylamines. A comprehensive list of the chemical oxidants that have been employed on the catecholamines with varying degrees of success has been presented in the

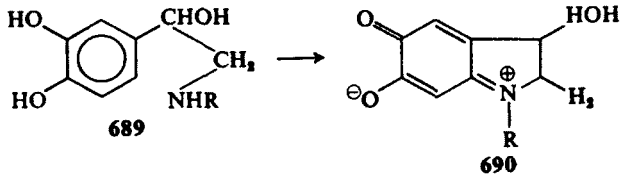
review by Heacock.[504] These are silver oxide,[505, 507, 510–522] potassium ferricyanide with sodium bicarbonate,[508, 514, 523–531] lead dioxide,[523, 532] manganese dioxide,[533–535] mercuric salts,[536, 537] ceric sulfate,[537] Fenton's reagent (ferrous sulfate and hydrogen peroxide),[538] potassium permanganate,[539] sodium nitrite,[540] iodine in the presence of calcium carbonate to keep acidity low,[508, 537, 541–543] bromine,[505, 507, 508, 541] and iodic acid or potassium iodate.[505, 517, 523, 525, 537, 541, 544–548]

Of these oxidants, silver oxide, potassium ferricyanide, and potassium iodate have been most popular and have been used not only on the catechol amines but also on other β-dihydroxyphenylethylamines. If aqueous solutions of the aminochromes are desired, potassium ferricyanide is a satisfactory oxidant to use for the preparation. The very high water solubility of the aminochromes and their tendency to decompose when their aqueous solutions are concentrated[504] prohibits their isolation from aqueous solution. The use of silver oxide in methanol containing some formic acid, first introduced by Veer,[510] has enabled isolation of several aminochromes in the solid state.[505, 507, 511, 517–519, 537, 549–553] By this method, the following crystalline aminochromes have been obtained. Adrenochrome (**685**) has been obtained from adrenaline (**683**),[505, 507, 511, 517] DL-adrenchrome-β-^{14}C from the correspondingly labeled DL-adrenaline,[554] epinochrome (**688**) from epinine (**687**)[505] (Eq. 218), *N*-isopropylnoradrenochrome (**690**, R = *i*-C_3H_7)



(218)

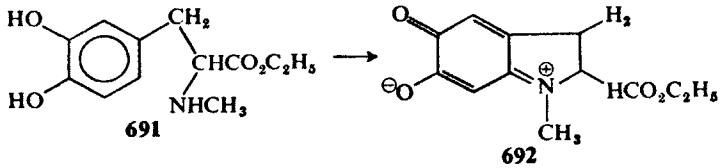
from *N*-isopropylnoradrenaline (**689**, R = *i*-C_3H_7)[512, 555] (Eq. 219), *N*-ethylnoradrenochrome (**690**, R = C_2H_5) from *N*-ethylnoradrenaline (**689**;



(219)

R = C_2H_5),[555] noradrenochrome (**690**, R = H) from noradrenaline (**689**; R = H),[556] and 2-carbethoxyepinochrome (**692**) from α-carbethoxyepinine (**691**) (methyl dopa ester)[505] (Eq. 220). The procedure was improved later by subjecting the catecholamines to two successive oxidations with excess silver oxide in dilute methanol containing formic acid.[505] Large quantities of

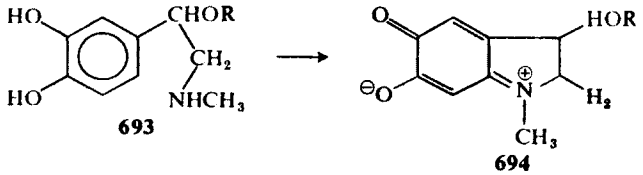
adrenaline (~50 g) have been satisfactorily converted to adrenochrome at no sacrifice in yield.[518]



(220)

The reported instability of aminochromes, both in solution and in the solid state,[508, 510] has been found to be due to the presence of occluded silver (colloidal or ionic).[511] Its elimination by passage of the solution of the reaction mixture through an anion exchange resin,[511] a filter bed of sodium sulfate,[505] or by centrifugation of the solution[549] has provided stable aminochromes.

Other solvents have been used successfully in the silver oxide oxidation of catecholamines. In ethanol, silver oxide has converted adrenaline (**683**) to adrenochrome (**685**), but the latter was found to be unstable.[557] Silver oxide oxidation of adrenaline in methanol containing 12% of a 1:1 mixture of water and ethyl formate is stated to give adrenochrome in 74% yield.[522] The reaction of silver oxide on noradrenaline (**689**; R = H) in dry acetonitrile is reported to provide solid noradrenochrome (**690**; R = H),[556] an aminochrome found to be less stable than is adrenochrome (**690**; R = CH_3).[558] The adrenaline ethers **693** (R = CH_3 or C_2H_5), when subjected to silver oxide oxidation in acetonitrile, provided the red solid adrenochrome ethers **694** (R = CH_3 or C_2H_5) whereas similar oxidation in methanol gave red solutions from which the crystalline ethers **694** could not be obtained[555] (Eq. 221). The methyl, ethyl, and isopropyl adrenaline ethers have also been



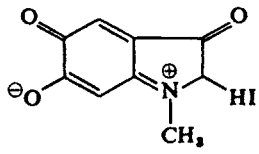
(221)

oxidized to the corresponding adrenochrome *O*-alkyl ethers and isolated as their semicarbazones.[516] Oxidation of catechol amines in aqueous solution by a suspension of silver oxide has also been used to prepare solutions of aminochromes.[507, 513, 559]

The oxidation of catecholamines with excess potassium iodate or iodic acid in aqueous solution, with no attempt to control the acidity, provides compounds that have been considered to be 2-iodoaminochromes (**684**, R′ = I).[505, 523, 541, 546, 560] However, a report appeared in 1963[560a] which clearly showed that these 2-iodoaminochromes are in fact the isomeric

7-iodoaminochromes, providing eventually the corresponding 7-iodoindoles. Hence, compounds reported to be 2-haloaminochromes and indicated in the following paragraphs as such, should no doubt be the 7-haloaminochromes. Because this has not been proven in all cases, although it is quite likely so, these compounds will be represented as 2(7?)-haloaminochrome.

Six equivalents of iodine are required to form the 2(7?)-iodoaminochromes.[541] These 2(7?)-iodoaminochromes are much less soluble in water than are the unhalogenated aminochromes and hence precipitate from the aqueous reaction mixture during oxidation of the catecholamines. By this method the following 2(7?)-iodoaminochromes have been obtained obtained as solids, "some of which have not been properly characterized."[504] 2(7?)-Iodoadrenochrome (**684**, R = OH, R^1 = I, R^2 = CH_3) has been obtained from adrenaline **683**.[505, 541, 546] The compound obtained by the oxidation of adrenaline with iodic acid in 85% methanol and considered to be 2(7?)-iodooxoadrenochrome (**695**)[544] has been shown to be 2(7?)-iodoadrenochrome.[561] 2(7?)-Iodo-1-isopropylnoradrenochrome (**684**, R = OH, R^1 = I,



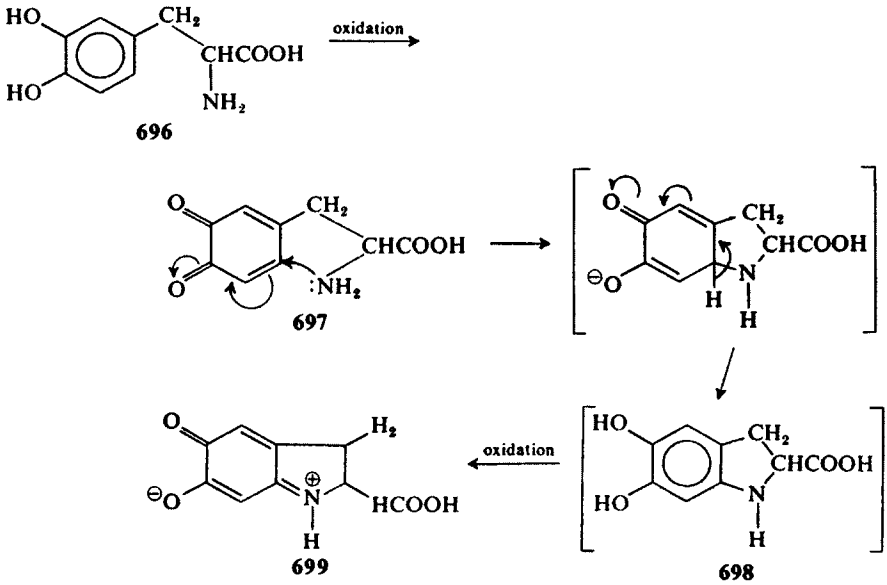
695

R^2 = i-C_3H_7) has been obtained from *N*-isopropylnoradrenaline (**678**, R = OH, R^1 = H, R^2 = i-C_3H_7).[523] 2(7?)-iodo-2-methylnoradrenochrome (**684**, R = OH, R^1 = I, R^2 = H, and C_2—H replaced by C_2—CH_3) from β-(3,4-dihydroxyphenyl)-β-hydroxy-isopropylamine (**678**, R = OH, R^1 = CH_3, R^2 = i-C_3H_7),[523] and 2(7?)-iodoepinochrome (**684**, R = H, R^1 = I, R^2 = CH_3) from epinine (**678**, R = R^1 = H, R^2 = CH_3).[505, 561] The compound derived from the reaction of epinine with potassium iodate and originally thought to be 3-iodoepinochrome (**684**; R = I, R^1 = H, R^2 = CH_3)[525] is in reality 2(7?)-iodoepinochrome.[561] 3(7?)-Iodo-2-carbethoxynorepinochrome (**684**, R = I, R^1 = $CO_2C_2H_5$, R^2 = H) has also been obtained from the potassium iodate oxidation of the ethyl ester of 3,4-dihydroxyphenylalanine (**678**, R = R^2 = H, R^1 = $CO_2C_2H_5$).[525]

If the amount of potassium iodate or iodic acid is limited, it is possible to stop the reaction at the stage where the catecholamine has been oxidized to the unhalogenated aminochrome.[544] This modification has permitted the oxidation of *N*-ethylnoradrenaline (**678**, R = OH, R^1 = H, R^2 = C_2H_5) by iodic acid in 90% methanol (containing glacial acetic acid) to *N*-ethylnoradrenochrome (**684**, R = OH, R^1 = H, R^2 = C_2H_5), isolable as dark red-violet crystals.[555]

Oxidation of adrenaline (**683**) with iodine usually stops at the adrenochrome stage **685**, but if the acidity of the solution is increased, the 2(7?)-iodoadrenochrome is obtained as well.[537, 541, 547] Bromine in acetate buffer oxidizes adrenaline to adrenochrome but also reacts further to provide 2(7?)-bromoadrenochrome.[505, 507, 508, 541]

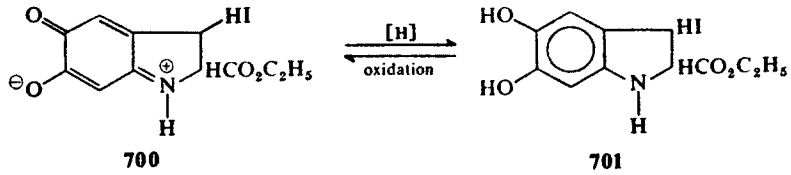
The mechanism of formation of aminochromes by oxidation of catecholamines has been considered by several investigators.[508, 513, 520, 523, 525, 527, 562–564] The postulate first advanced by Raper[513, 562, 563] to account for the formation of melanin from "dopa" (3,4-dihydroxyphenylalanine) by enzyme-catalyzed oxidation is shown in Scheme 66. Dopa is first oxidized to the quinone **697**



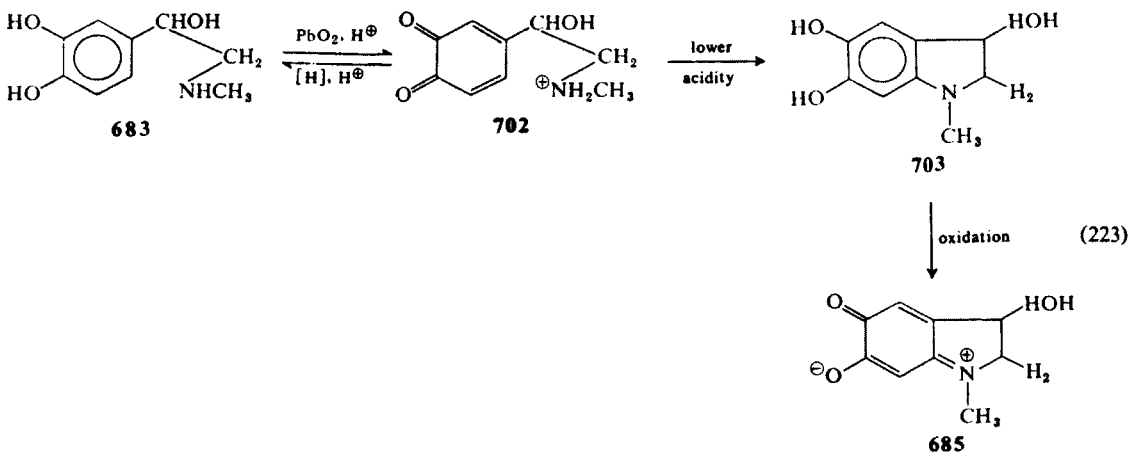
Scheme 66

which then cyclizes to "leucodopachrome" **698** and this colorless product is oxidized to "dopachrome" **699**.

The possibility that the aminochrome **699** can be reduced back to the colorless leuco compound **698** is supported by the discovery that ethyl 2,3-dihydro-3(7?)-iodoindole-5,6-quinone-2-carboxylate (**700**) can be reduced to the leuco compound **701** which in turn can be oxidized to **700**[525] (Eq. 222).



(222)


HO
CHOH
CH2
NHCH3
HO
683
PbO2, H⊕
[H], H⊕
O
CHOH
CH2
⊕NH2CH3
O
702
lower
acidity
HO
HOH
HO
N
H2
CH3
703
oxidation
O
HOH
⊖O
⊕N
H2
CH3
685

(223)

Subsequent work has provided general support for this mechanism. Although to date the intermediate quinone of the type **697** has not been isolated, evidence indicates that it is formed, but under the conditions of low acidity which lead to cyclization, it has only a transitory existence.[504, 565] A study of the oxidation potential of adrenaline (**683**) supports the view that the adrenaline quinone (cf. **697**) is formed as an intermediate but has a very short lifetime.[566]

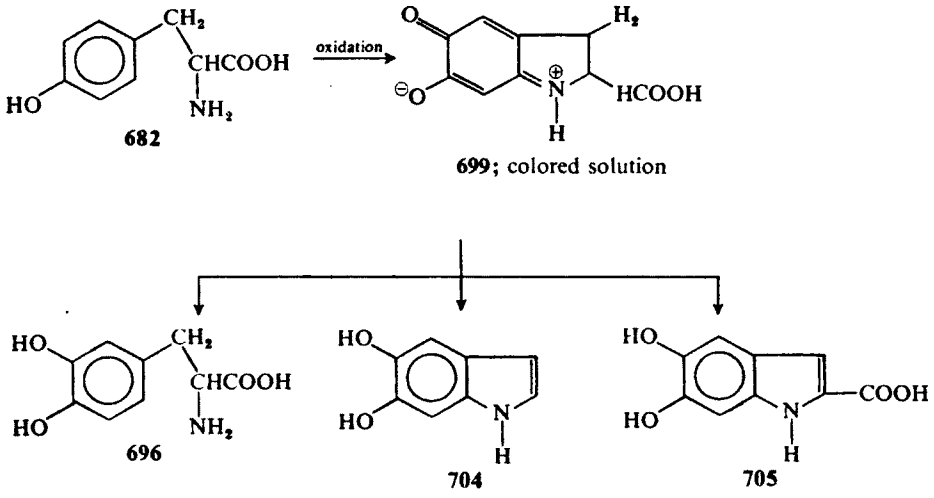
The oxidation of adrenaline (**683**) with lead dioxide in highly acidic media provides a yellow-orange solution, the color of which is considered to be due to the "adrenaline quinone" **702** which can be reduced back to adrenaline (**683**)[523, 532, 567, 568] (Eq. 223). Other catecholamines oxidized under similar highly acidic conditions also give yellow solutions which are thought to contain the corresponding *o*-quinones analogous to **697** or **702**.[523] In such strongly acidic media the amino group exists as the salt, and accordingly cannot undergo a Michael-type nucleophilic addition to the α,β-unsaturated ketonic moiety (e.g., **697** → **698**). When the acidity is reduced by addition of a buffer, the amino group is freed and will then add rapidly to the quinone to produce first the "leucochrome" (e.g., **698** or **703**) which is readily oxidized to the aminochrome (e.g., **699** or **685**). When the acidic orange-yellow solution obtained by lead oxide oxidation of adrenaline (**683**) was freed from excess oxidant and then treated with sodium acetate or sodium bicarbonate, the color changed immediately and irreversibly to the deep red characteristic of adrenochrome (**685**). Half of the original adrenaline (**683**) was recovered while the other half became adrenochrome (**685**), thus suggesting that the leuco compound **703**, first formed when the solution was buffered, was rapidly oxidized to adrenochrome by a portion of the adrenaline quinone **702** which in turn was reduced back to adrenaline.[523] Addition of oxidizing agent to this solution intensified the red color of adrenochrome, no doubt by oxidation of the reformed adrenaline.[523]

The generally better yield of products obtained from catechol amines substituted on the nitrogen atom by an alkyl group, while poor yields are obtained in many cases wherein primary catechol amines are used, is believed to be related to the greater basicity of the secondary amines which would facilitate the cyclization step **697** → **698**[525] (Scheme 66).

The conversion of the aminochromes to 5,6-dihydroxyindoles has been achieved by a variety of methods which involve either a spontaneous or thermally assisted change, action of reducing agents, catalysis by base, or catalysis by metal or metal ion.

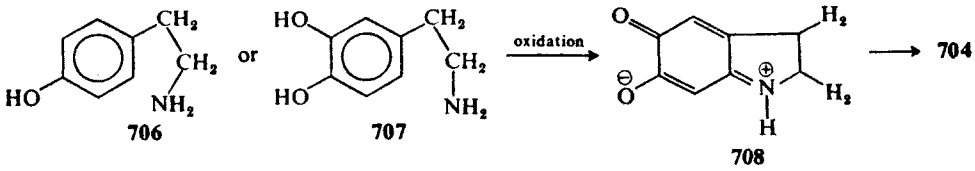
The spontaneous or thermal conversion was first observed and defined by Raper[562] who found that the tyrosinase-catalyzed air oxidation of tyrosine (**682**) gave a red solution which, when kept under vacuum for a few days, lost its color and produced not only some 3,4-dihydroxyphenylalanine (**696**), as had been found previously,[569] but also 5,6-dihydroxyindole (**704**) as the

main indolic product along with some 5,6-dihydroxyindole-2-carboxylic acid (**705**) (Scheme 67). The conversion of **699** to **704** and **705** could be



Scheme 67

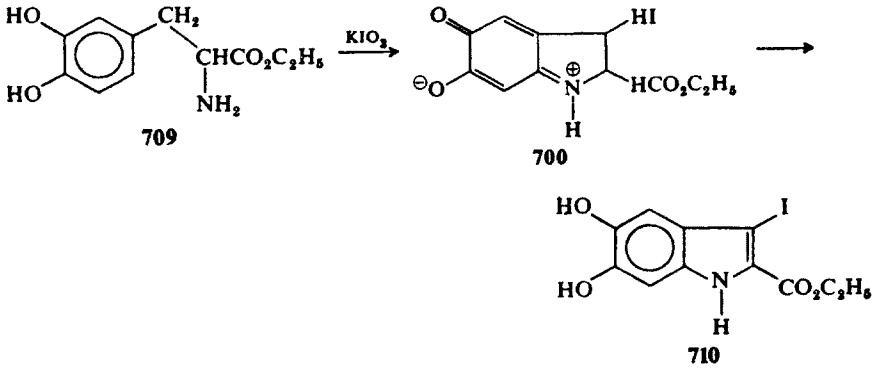
accelerated by heating the aminochrome in an inert atmosphere.[569] Several examples of this spontaneous or thermal conversion have been reported. It has been observed in the formation of 5,6-dihydroxyindole (**704**) from norepinochrome (**708**) which in turn was obtained from the enzyme-catalyzed air oxidation of either tyramine (**706**) or β-(3,4-dihydroxyphenyl)ethylamine (**707**)[513] (Eq. 224). Epinochrome (**688**), kept for several months in a sealed



(224)

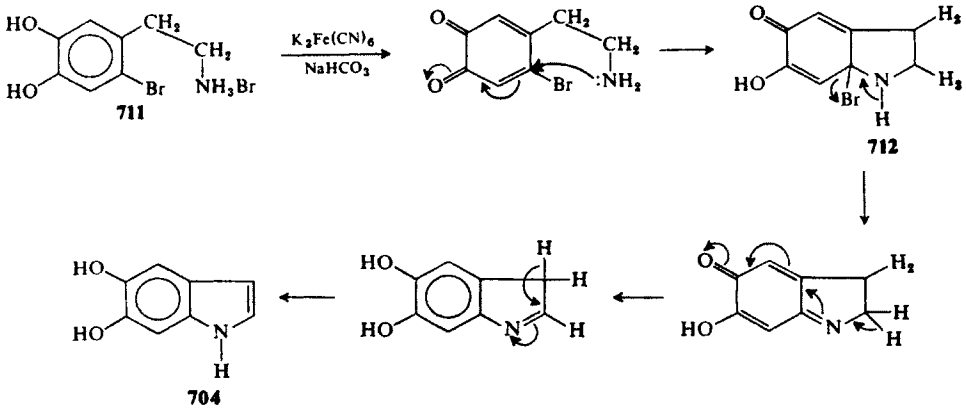
tube, gave 5,6-dihydroxy-1-methylindole.[570] On storage, the aminochrome ethyl 2,3-dihydro-3(7?)-iodoindole-5,6-quinone-2-carboxylate (**700**), obtained by oxidation of the ethyl ester **709** of 3,4-dihydroxyphenylalanine **696** with potassium iodate, slowly changed to ethyl 3(7?)-iodo-5,6-dihydroxyindole-2-carboxylate (**710**)[525] (Eq. 225). Treatment of an aqueous solution of

β-(2-bromo-4,5-dihydroxyphenyl)ethylamine hydrobromide (**711**) with potassium ferricyanide and sodium bicarbonate gave a solution which, after removal



(225)

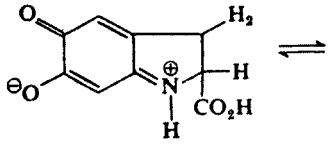
of a voluminous blue-black precipitate and extraction of the filtrate with ethyl acetate, provided 5,6-dihydroxyindole (**704**) though in only 8% yield.[514] The route for the formation of **704** might well follow that given in Scheme 68,



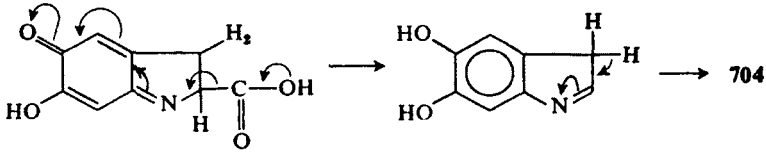
Scheme 68

involving formation of the *p*-bromoquinone **712**. This should lose hydrogen bromide readily, and subsequent proton rearrangements would form the product **704**. A similar scheme would explain the spontaneous conversion of the aminochrome **699** to the indole **704**[562] and account for the facile loss of carbon dioxide under these mild conditions (Eq. 226). It is doubtful that decarboxylation would occur *after* the indole nucleus has been formed since removal of carbon dioxide from indole-2-carboxylic acids requires conditions

more vigorous than were employed in the conversion of **699** to **704**. Another example illustrating the spontaneous conversion is found[514] in the oxidation by potassium ferricyanide of an aqueous solution of β-(3,4-dihydroxyphenyl)-*N*-(3,4-dihydroxybenzyl)ethylamine (**713**) to an aminochrome which rapidly

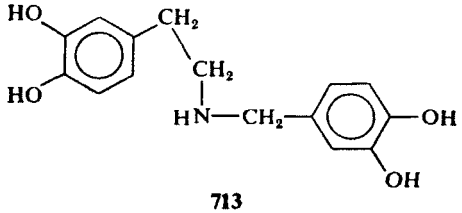


699



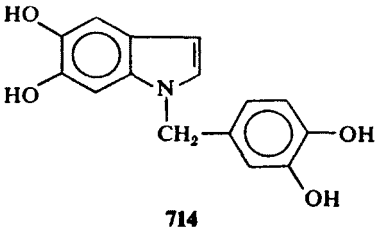
(226)

changed during the course of the reaction to the indolic product **714** (Eq. 227).



713

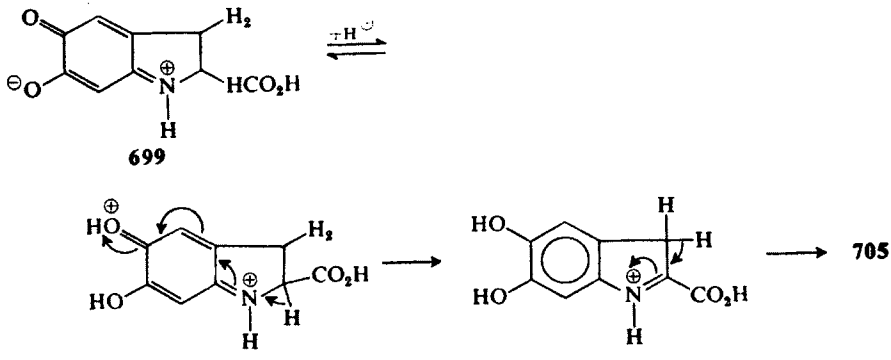
(227)



714

Raper[513, 562] found that the conversion of the aminochrome **699** to the indolic products **704** and **705** was markedly accelerated by the presence of sulfur dioxide in the aqueous solution, but under these conditions the chief product was 5,6-dihydroxyindole-2-carboxylic acid (**705**), and only a trace of 5,6-dihydroxyindole (**704**) was observed (Eq. 228). The aminochrome obtained from the enzymatic oxidation of *N*-methyltyrosine, treated in aqueous solution with sulfur dioxide, gave 5,6-dihydroxy-1-methylindole-2-carboxylic acid isolated as the dimethyl ether.[513] Similarly, an aqueous

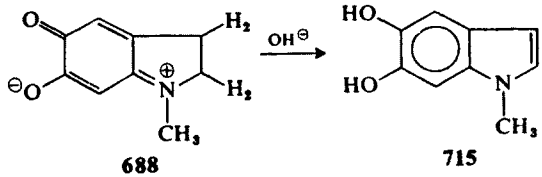
solution of epinochrome (**688**) containing sulfur dioxide gave 5,6-dihydroxy-1-methylindole, also isolated as its dimethyl ether.[513] It is known that reducing agents do promote the conversion of aminochromes to indoles, and accordingly it has been considered that this is the property of sulfur dioxide that causes the conversion of aminochromes to indoles.[562, 571] However, this is by no means certain and has been questioned.[562] It may well be that it is the sulfurous *acid* that is responsible for the observed enhanced rate of conversion. Indeed, the presence of the acid would account for the preferential retention of the carboxylic acid group as well as the accelerated rate of rearrangement by maintaining the protons on both the carboxyl group and the ring nitrogen. Furthermore, protonation of the oxygen moieties by the sulfurous acid would promote prototropic rearrangement, conceivably as shown in Eq. (228).



699 **705**

(228)

The stability of aminochromes is markedly dependent upon the pH of the solution.[511, 572] In the presence of strong base, epinochrome (**688**), obtained from the silver oxide oxidation of epinine (**687**), is rapidly converted into 5,6-dihydroxy-1-methylindole (**715**)[521] (Eq. 229). Treatment of an aqueous

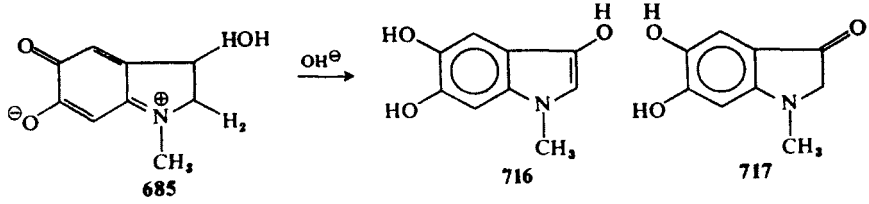


688 **715**

(229)

solution of adrenochrome (**685**) with alkali is reported to produce a material giving a strong green fluorescence and thought to be 2,3,5,6-tetrahydroxy-1-methyl-2,3-dihydroindole[573] but is undoubtedly the monohydrate of 3,5,6-trihydroxy-1-methylindole (adrenolutin; **716**)[511] (Eq. 230). The correct

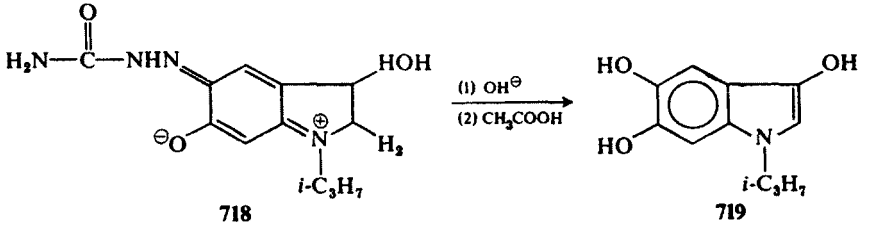
structure of the substance **716** is quite likely that shown by **717** since indoxyls have been found to exist mainly in the keto form as in **717**, both in the solid state and in solution in nonpolar solvents.[574] Mason and Wright[564] found that



685 **716** **717**

(230)

base catalyzes both the decarboxylation and the rearrangement of the aminochrome **699** to the 5,6-dihydroxyindole **704**. The aminochrome **700** also is changed rapidly by base to ethyl 5,6-dihydroxy-3(7?)-iodoindole-2-carboxylate (**710**),[525] and the monosemicarbazone of *N*-isopropylnoradrenochrome (**718**), treated first with alkali and then with acetic acid, provides the indoxyl 3,5,6-trihydroxy-1-isopropylindole (**719**)[523] (Eq. 231). This catalytic

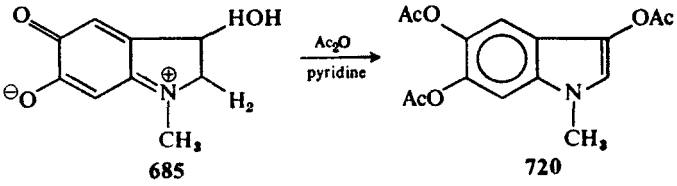


718 **719**

(231)

effect of base appears to be general in its ability to convert aminochromes to indoles.[517]

The base pyridine is also quite effective in this regard since a mixture of acetic anhydride and pyridine has changed adrenochrome (**685**) to 3,5,6-triacetoxy-1-methylindole (**720**) (Eq. 232). Under similar conditions, several

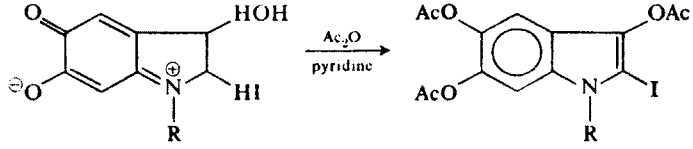


685 **720**

(232)

2(7?)-iodoepinochromes (**721a–c**), obtained from the potassium iodate oxidation of the appropriate catecholamines, have been converted, generally in good yield, to the acetylated 2(7?)-iodo-3,5,6-trihydroxyindole (**722a–c**)[523] (Eq. 233). The iodine atom is removed by subsequent treatment of **722a–c**

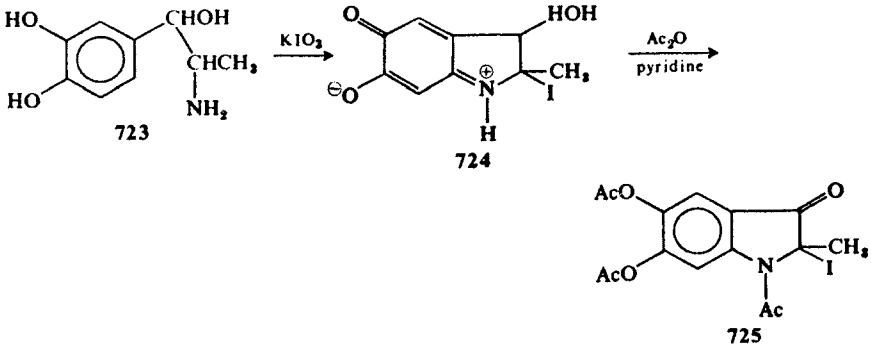
with zinc dust and acetic acid.[523] By analogy, the reaction of potassium iodate with 2-methylnoradrenaline (**723**) is believed to give 2(7?)-iodo-2-methylnoradrenochrome (**724**) which upon treatment with acetic anhydride



(233)

721a; R = CH_3 **722a**; R = CH_3
721b; R = *i*-C_3H_7 **722b**; R = *i*-C_3H_7
721c; R = H **722c**; R = CH_3CO

in pyridine is considered to provide 5,6-diacetoxy-1-acetyl-2,3-dihydro-2(7?)-iodo-3-keto-2-methylindole **725**[523] (Eq. 234). However, no proof of the structure of **724** or **725** was given.[523] The acetic anhydride–pyridine mixture has

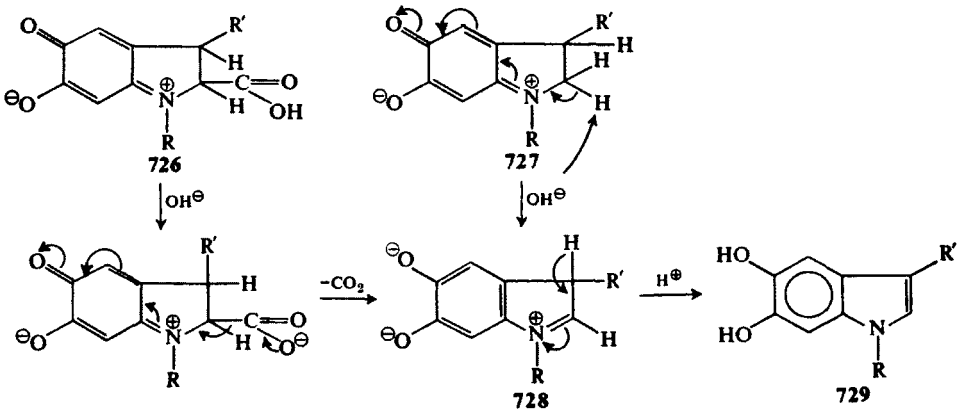


(234)

also been effective in converting what was originally thought to be 3-iodoepinochrome[525] to 5,6-diacetoxy-3(7?)-iodo-1-methylindole.[525] However, since the iodoepinochrome has been shown to be the 2(7?)-iodoepinochrome,[561] the compound obtained by treatment of the iodoepinochrome with acetic anhydride and pyridine is no doubt 5,6-diacetoxy-2(7?)-iodo-1-methylindole.

The mechanism for the base-catalyzed rearrangement of aminochromes to 5,6-dihydroxyindoles has not been established. However, the fact the decarboxylation of 2-carboxyaminochromes occurs along with the rearrangement and is apparently very easily accomplished, and that 3-hydroxyaminochromes retain the oxygen at position 3 in the indole structure formed, can be accommodated by a route such as that shown in Scheme 69 for the conversion of 2-carboxyaminochromes **726** (R = H or alkyl, R′ = H) or 3-hydroxyaminochromes **727** (R = H or alkyl, R′ = OH) to an intermediate

728 (R = H or alkyl, R′ = H or OH) which loses a proton to form the stable indole structure **729**. This implies that compound **726** or **727** (R = H), in the presence of base would lose the proton attached to the nitrogen atom



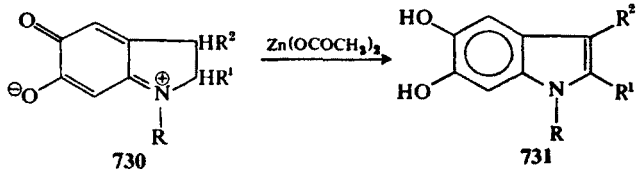
Scheme 69

and hence the positive charge on the nitrogen. Consequently aminochromes such as **726** or **727** with R = H would rearrange more slowly than their *N*-alkylated homologs.

It had been noted[575] that an aqueous solution of adrenochrome (**685**) was converted rapidly by zinc acetate into the green fluorescent compound 3,5,6-trihydroxy-1-methylindole (adrenolutin; **716**). This same product **716** was obtained by the catalytic action of hydroxide on adrenochrome.[575] On the basis of this observation, the catalytic action of zinc acetate was investigated further and found to be generally applicable.[524] Apart from ionic aluminum, which was definitely not as satisfactory, only zinc ions were able to convert aminochromes to the indoles.[524, 575] The combination of initial oxidation of catecholamines in aqueous solution with potassium ferricyanide in the presence of sodium bicarbonate, followed by the addition of zinc acetate, provides a very useful route whereby 5,6-dihydroxyindoles can be readily obtained, frequently in good yield.[523–425] Catecholamines with an alkyl substituent on the nitrogen (secondary amines) generally gave better yields of indoles than are obtained from analogous primary amines. This difference is thought to be related to the relative basicities of primary and secondary amines and hence their tendency to undergo Michael addition to the quinone moiety during the cyclization stage.[525] The aminochromes **730a–h** have been rearranged to 5,6-dihydroxyindoles **731a–h** by the use of zinc acetate (Table VI).

The substitution of zinc sulfate for zinc acetate was considered to be an improvement in the method when employed to prepare 5,6-dihydroxyindoles

TABLE VI

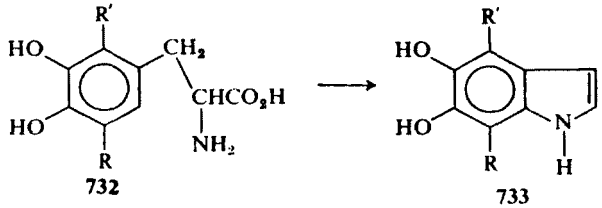


730 731

	R	R^1	R^2	R	R^1	R^2	Ref.
a	CH_3	H	H	CH_3	H	H	524
b	H	CO_2H	H	H	H	H	524
c	CH_3	I[a]	H	CH_3	I[a]	H	524, 525
d	CH_3	CO_2H	H	CH_3	H	H	525
e	H	H	H	H	H	H	525
f	H	CH_3	H	H	CH_3	H	525
g	H	$CO_2C_2H_5$	I[a]	H	$CO_2C_2H_5$	I[a]	525
h	CH_3	H	OH	CH_3	H	OH	575

[a] Probably the 7-iodoisomer, see pp. 439–440 and Ref. 560a.

containing a methyl group in the benzene ring.[527] Oxidation with aqueous potassium ferricyanide buffered by sodium bicarbonate, followed by treatment of the aminochrome with zinc sulfate, permitted the conversion of 3,4-dihydroxy-2-methylphenylalanine (**732**; R = H, R′ = CH_3) and 3,4-dihydroxy-5-methylphenylalanine (**732**; R = CH_3, R′ = H) to 5,6-dihydroxy-4-methylindole (**733**; R = H, R′ = CH_3) (40% yield) and 5,6-dihydroxy-7-methylindole (**733**; R = CH_3, R′ = H) (12% yield), respectively[527] (Eq. 235).

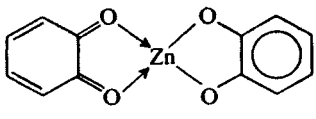


732 733 (235)

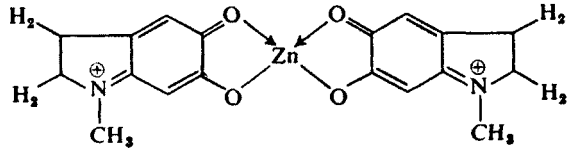
It is interesting that in the zinc ion-catalyzed rearrangement of aminochromes which possess a carboxyl group at C-2, for example, **730b** and **d**, carbon dioxide is invariably lost during formation of the indole (**731b** and **d**).

The mechanism by which zinc ion catalyzes the conversion of aminochromes to 5,6-dihydroxyindoles is not yet understood, but has been considered by Bu'Lock and Harley-Mason.[524, 525] They found that when catechol was oxidized in the presence of zinc acetate, a dark green complex was obtained which was composed of two molecules of catechol and one atom

of zinc. This they formulated as **734** with one ring benzenoid and the other *o*-quinonoid. On this basis they suggested that a similar complex might occur involving two molecules of the aminochrome and one atom of zinc which might be represented by Structure **735**. Spontaneous decomposition of this

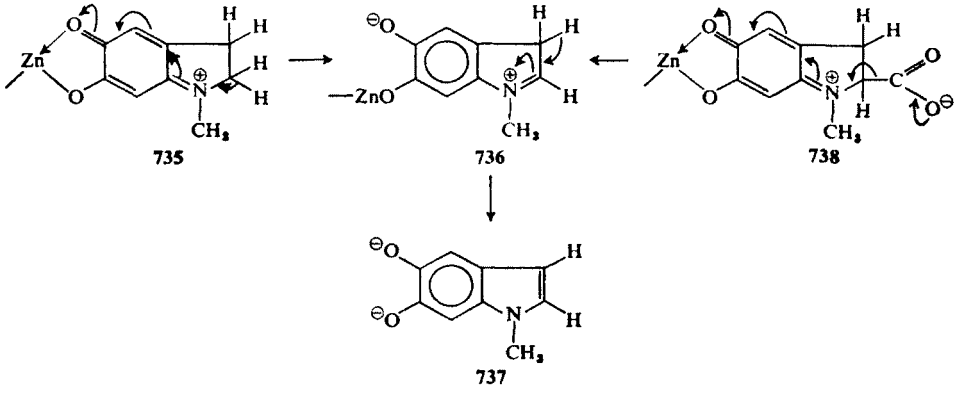


734



735

complex with accompanying loss of protons from the C-2 and C-3 positions would then result in isomerization to the indole.[525] It is clear that if such an association was indeed formed, there should be a twofold effect. The positive charge on the nitrogen of *N*-alkylated aminochromes would thus be intensified and enhance the rate of loss of a proton from C-2. The coordination of the zinc ion with the quinonoid oxygen atom would facilitate the movement of electrons from the nitrogen through the *p*-quinone system to the oxygen and facilitate the conversion **735** → **736** → **737** shown in Scheme 70. The



Scheme 70

observation that a carboxyl group at C-2 is always lost under these conditions can be accommodated by such a scheme, possibly by formation of the zinc salt of the carboxylic acid group followed by loss of carbon dioxide and a proton in the change **738** → **736** → **737**. The invariable retention of the C-3 hydroxyl group when adrenochrome (**685**) is converted to the indoxyl 3,5,6-trihydroxy-1-methylindole by zinc acetate[575] is in agreement with such a scheme.

Palladium on charcoal has also been found to catalyze the conversion of aminochromes to 5,6-dihydroxyindoles. Epinochrome (**688**), shaken at room temperature for only a few minutes with palladium-charcoal catalyst,

either in water or in anhydrous methanol under an atmosphere of hydrogen or of nitrogen, gave 5,6-dihydroxy-1-methylindole (**715**) in greater than 80% yield.[570] No evidence for hydrogen uptake was noted.[570] Adrenochrome (**685**) under similar conditions failed to rearrange.[570] However, Harley-Mason[507] has reported that an aqueous solution of adrenochrome, shaken at room temperature for 20 min with palladium-charcoal and hydrogen, *did* absorb one atom of hydrogen for one mole of adrenochrome. The adrenochrome was converted to two products, roughly in equal proportions, one of which was 5,6-dihydroxy-1-methylindole (**715**; 33% yield) and the other was a water-soluble substance considered to be isomeric with the adrenochrome but which could be converted by the addition of sodium hydroxide to the aqueous solution (after removal of **715**) into 3,5,6-trihydroxy-1-methylindole (32% yield). Some doubt exists regarding the observation that the reduction of adrenochrome requires only one atom of hydrogen. Polarographic studies[576] had shown previously that the reduction of adrenochrome involved a *two*-electron change. This has been corroborated,[577] and thus two atoms of hydrogen rather than one appear to be required for the reduction of each mole of adrenochrome.

A number of chemical reducing agents have been used to convert aminochromes to 5,6-dihydroxyindoles. Most of the reports have dealt with the application of these reducing agents to adrenochrome itself,[425, 506, 507, 517, 529, 571, 573, 578, 579] although a few have applied this technique to reduce 2(7?)-iodoadrenochrome[425, 517, 561] or 2(7?)-bromoadrenochrome[507] to 5,6-dihydroxy-2(7?)-iodo-1-methylindole and 2(7?)-bromo-5,6-dihydroxy-1-methylindole, respectively, *N*-isopropyl- and *N*-ethylnoradrenochrome as well as their 2(7?)-iodo derivatives[517] to the corresponding *N*-alkylated-5,6-dihydroxyindoles, and dopachrome methyl ester[531] to methyl 5,6-dihydroxyindole-2-carboxylate (cyclodopa methyl ester).

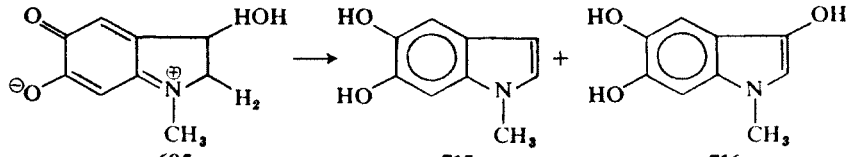
A paper chromatographic study has been made of the products obtained from the reduction of adrenochrome by fifteen reducing agents.[571, 578] These are sulfur dioxide, sodium hydrosulfite (sodium dithionite), sodium hydrogen sulfite, sodium sulfite, sodium glyoxal, hydrogen sulfite, sodium formaldehyde sulfoxylate, sodium borohydride, zinc and 2% acetic acid, ascorbic acid, cysteine, glutathione, thioglycollic acid, thiourea dioxide, dihydroxymaleic acid, and dihydroxyfurmaric acid. Results were interpreted on the basis of the R_F values of spots, developed by the use of Ehrlich's reagent. The first six reagents gave yellow strongly fluorescent spots in the region R_F 0.86–0.92 (in the system employed), considered to be due to an adrenochrome-bisulfite addition product rather than a true reduction product.[578] Such a bisulfite complex can be converted to adrenochrome by alkali,[580, 581] with the further conversion of the adrenochrome to 3,5,6-trihydroxy-1-methylindole under

the catalytic influence of the alkali.[511, 523, 525] Sodium dithionite also gave a blue-violet spot in the R_F zone 0.41–0.45, characteristic of 5,6-dihydroxy-1-methylindole. If the sodium dithionite is fresh, reduction of the adrenochrome apparently occurs to give a substantial amount of the 5,6-dihydroxy-1-methylindole while the proportion of the bisulfite addition product is decreased,[507] although it is stated that some of the bisulfite addition product always occurs.[517, 571] The remainder of the fifteen reducing agents gave as their primary reduction product the 5,6-dihydroxy-1-methylindole. Ascorbic acid gave not only this dihydroxyindole but two other substances which show color reactions characteristic of indoles and catechols.[578] This reducing agent has become quite useful, since the potassium ferricyanide oxidation of adrenaline to adrenochrome followed by reduction of this adrenochrome with ascorbic acid has been shown to provide 5,6-dihydroxy-1-methylindole in 60% yield based on adrenaline.[529] Sodium borohydride or zinc with 2% acetic acid are stated to give much better yields (up to 70%) of 5,6-dihydroxy-1-methylindole.[517] Although hydrogen sulfide also gave a good yield of this dihydroxyindole, the product was contaminated with sulfur.[517] Treatment of adrenochrome with zinc and acetic anhydride gave 5,6-diacetoxy-1-methylindole.[425]

The reaction of 2(7?)-iodoaminochromes with the reducing agents sodium dithionite,[425, 561] ascorbic acid,[517, 561] sodium borohydride, zinc plus 2% acetic acid, and BAL (2,3-dimercapto-1-propanol)[561] gave the corresponding 5,6-dihydroxy-2(7?)-iodoindole. However, these were usually accompanied to a greater or lesser extent by the 5,6-dihydroxyindole, apparently due to the simultaneous or subsequent loss of the halogen.[561] That sodium dithionite does remove the halogen from a 2(7?)-iodoindole has been demonstrated by the conversion of 5,6-dihydroxy-2(7?)-iodo-1-methylindole [obtained from zinc acetate-catalyzed isomerization of 2(7?)-iodoepinochrome (**730**; R = CH_3, R^1 = I, R^2 = H)] to 5,6-dihydroxy-1-methylindole[524] and by the reaction of either 2(7?)-iodoadrenochrome (**730**, R = CH_3, R^1 = I, R^2 = OH) or *N*-isopropyl-2(7?)-iodonoradrenochrome (**730**, R = *i*-C_3H_7, R^1 = I, R^2 = OH), first with zinc acetate and then with sodium dithionite to produce 3,5,6-trihydroxy-1-methylindole and 3,5,6-trihydroxy-1-isopropylindole, respectively, though in poor yield.[523] Zinc and acetic acid[523] or magnesium and acetic acid[425] have been used to remove the iodine atom from 5,6-dihydroxy-2(7?)-iodoindoles.

The mechanism of the reductive rearrangement of aminochromes to 5,6-dihydroxyindoles has been considered by Harley-Mason.[507] He had observed that adrenochrome (**685**) shaken with palladium-charcoal and hydrogen absorbed one atom of hydrogen for one mole of adrenochrome and thus gave both 5,6-dihydroxy-1-methylindole (**715**) and 3,5,6-trihydroxy-1-methylindole (**716**) in *nearly equal amounts* (Eq. 236). Closely similar results were

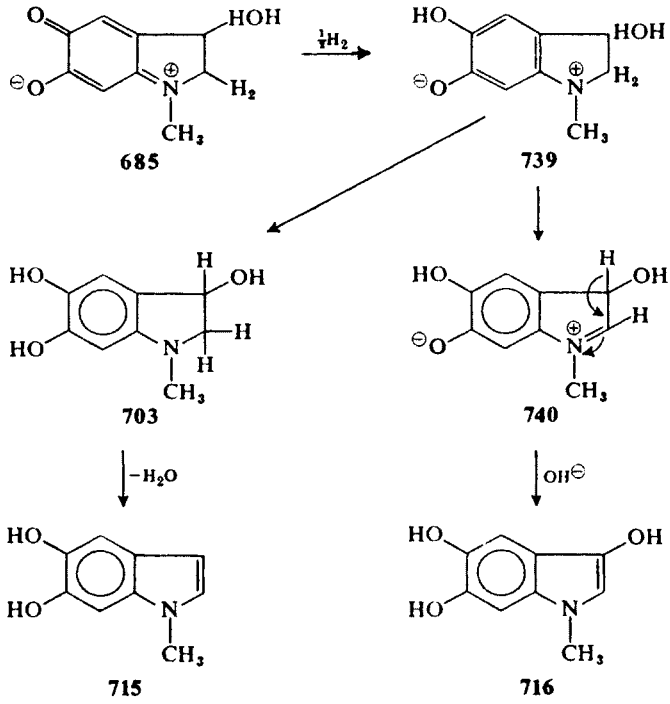
obtained when adrenochrome was treated with sodium dithionite. Harley-Mason[507] considered that the first step is the production of a semiquinone **739**, the result of the addition of one hydrogen atom. A disproportionation



	685	715	716
Pd-C;		33%	32%
$Na_2S_2O_4$;		32%	28%

(236)

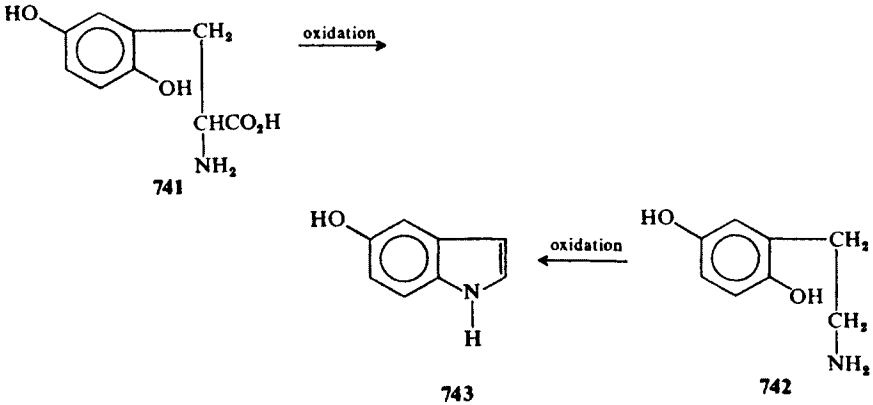
of the semiquinone **739** then gives in equimolar proportion the two substances 3,5,6-trihydroxy-1-methyl-2,3-dihydroindole (**703**) and a zwitterion **740** which is isomeric with the adrenochrome (**685**). Compound **703** is unstable and rapidly loses water to form the stable product **715** which can be extracted with ether. The highly water-soluble species **740**, left after removal of the indole **715**, requires the addition of a base to catalyze the final rearrangement to 3,5,6-trihydroxy-1-methylindole (**716**) (Scheme 71). Support for this



Scheme 71

scheme was believed[507] to lie in the observation by Green and Richter[508] that reduction of adrenochrome gave an optically active solution, a result confirmed by Harley-Mason[507] who found also that the rotation did not change when the reduced solution stood at room temperature for a 24-hr period. It was therefore thought that **703** could not be responsible for the optical activity because of the unstable nature of **703**. Hence, a species such as **740** was invoked to account for this on the basis of the belief that *all* of the adrenochrome had been converted to **739** and that **739** subsequently disproportionated.[507] Both of the reducing systems, sodium dithionite and palladium-charcoal with hydrogen, were thought to follow the same scheme of reduction because of the similarity of results in the observed proportion of the two products **715** and **716** obtained.[507] However, since the total yield of these two products is only ~60%, one cannot define a mechanism on the basis of such results. Furthermore, the observation that there is a *two*-electron addition in the reduction of adrenochrome[576, 577] requires a re-examination of the scheme proposed for the path of reduction of adrenochrome.[507] The possibility exists that only a part of the adrenochrome has been reduced by either palladium-charcoal or sodium dithionite for some reason, maybe because of a competitive reaction such as bisulfite complex formation in the latter case, and this could account for the observed optical activity. The action of base in forming 3,5,6-trihydroxy-1-methylindole is a known reaction both directly with adrenochrome itself or the bisulfite addition complex of adrenochrome.

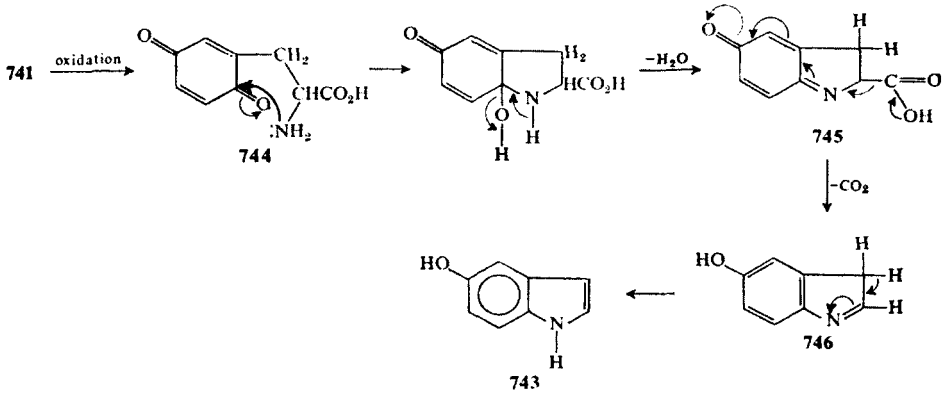
β-(Dihydroxyphenyl)ethylamines other than the catecholamines have also provided a source of hydroxyindoles. The potassium ferricyanide oxidation of either 2,5-dihydroxyphenylalanine (**741**) or β-(2,5-dihydroxyphenyl)-ethylamine (**742**) produces 5-hydroxyindole (**743**) in high yield[582] (Eq. 237). A likely route for this conversion has been proposed[526, 582] involving oxidation



741 743 742

(237)

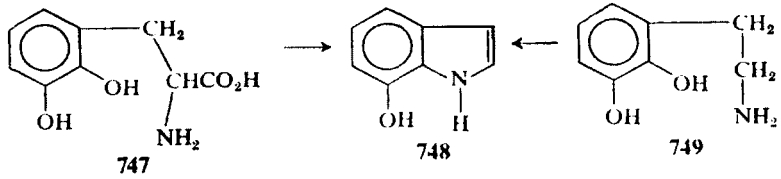
of the dihydroxyphenyl moiety to the *p*-quinone **744** which spontaneously cyclizes by a 1,2-addition of the amino group to the quinone to form the *p*-quinonimine **745**. Subsequent decarboxylation, no doubt to the indolenine **746**, followed by proton rearrangement then produces the 5-hydroxyindole **743** (Scheme 72). Although neither the quinone **744** nor the quinonimine **745**



Scheme 72

has been isolated, the initial formation of highly colored material which then loses color appears to support the suggested scheme.[582] If the carboxyl group is first esterified, the product obtained by this process is the 5-hydroxyindole-2-carboxylic acid ester.[582]

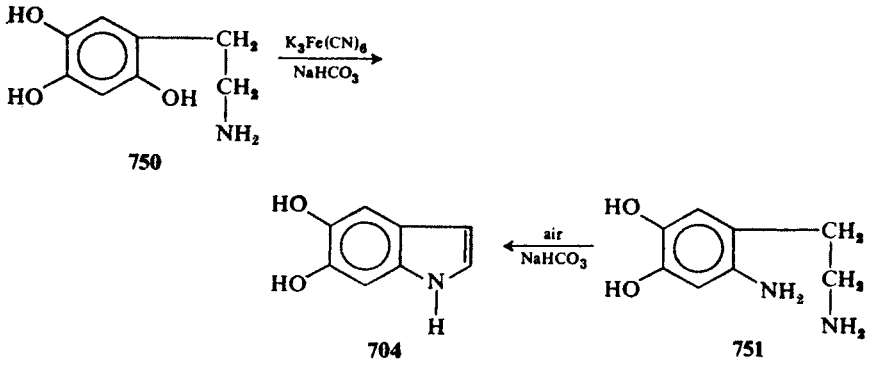
Ferricyanide oxidation of 2,3-dihydroxyphenylalanine (**747**) gives a 20% yield of 7-hydroxyindole (**748**), but only if ethyl acetate is added to the mixture to be oxidized in order to extract the 7-hydroxyindole as soon as it is formed and thus prevent its further oxidation.[582] The carboxyl group of **747** appears to provide a stabilizing effect during this conversion since β-(2,3-dihydroxyphenyl)ethylamine (**749**) treated similarly gave only traces of **748**[582] (Eq. 238).



(238)

Oxidation of β-(2,4,5-trihydroxyphenyl)ethylamine (**750**) with potassium ferricyanide under the usual conditions ($NaHCO_3$) readily gave 5,6-dihydroxyindole in good yield.[514] The same product **704** was obtained in 30–50% yield by merely shaking a solution of β-(2-amino-4,5-dihydroxyphenyl)ethylamine

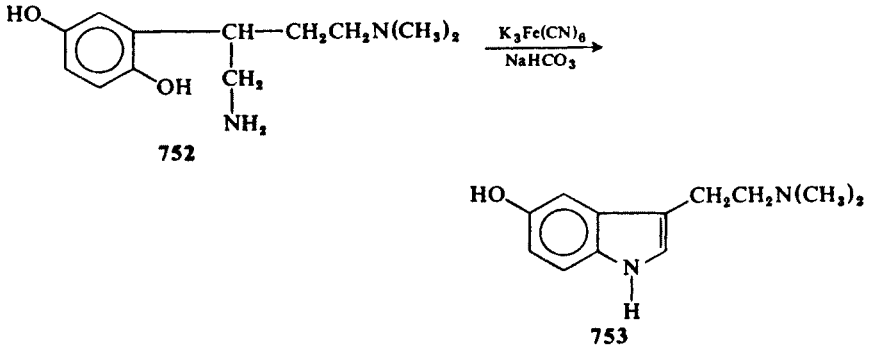
(751) containing sodium bicarbonate in the presence of air (Eq. 239). This air oxidation of 751 is extremely easy and is preferred to the oxidation by potassium ferricyanide, since use of the latter oxidizing agent causes formation of the sparingly soluble amine ferricyanide.[514]



(239)

A 20–25% yield of 5-aminoindole can be obtained by shaking an aqueous mixture of sodium acetate, silver oxide, and β-(5-amino-2-hydroxyphenyl)-ethylamine.[515] Other oxidizing agents are found to be much less satisfactory in this case.

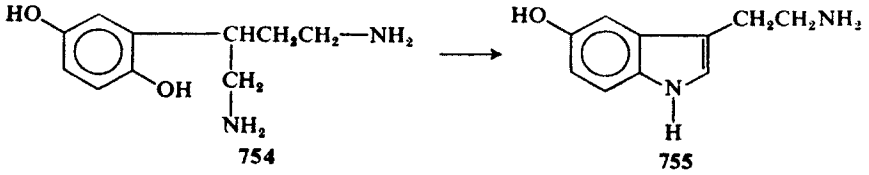
The sodium bicarbonate buffered potassium ferricyanide oxidation of 2-(2,5-dihydroxyphenyl)-4-dimethylaminobutylamine (752) gives the indole bufotenine (753) in 45% yield (Eq. 240). Similar treatment of 2-(2,4,5-



(240)

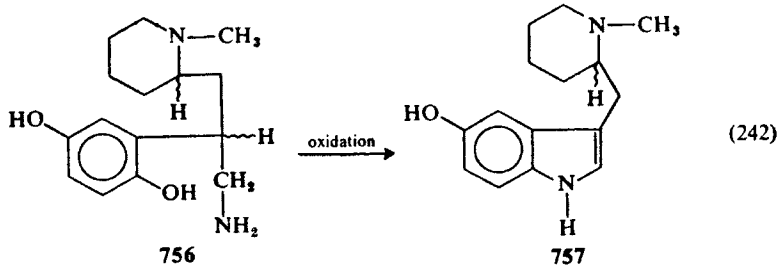
trihydroxyphenyl)-4-dimethylaminobutylamine produces 6-hydroxybufotenine in low yield. This product has been isolated only as its picrate.[515] The same oxidation conditions have converted 2-(2,5-dihydroxyphenyl)-4-aminobutylamine (754) to serotonin (enteramine, thrombocytin; 755) in

25% over-all yield from the precursor 2,5-dimethoxybenzaldehyde[515] (Eq. 241). This is stated to be the best available method for the preparation of serotonin.



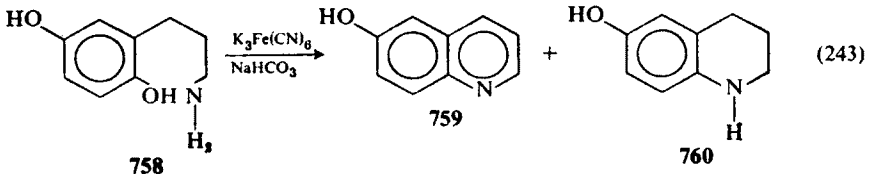
(241)

Moore and Capaldi[583] have used the buffered ferricyanide oxidation to convert **756** to **757** in 35% yield (Eq. 242). They have also shown that while



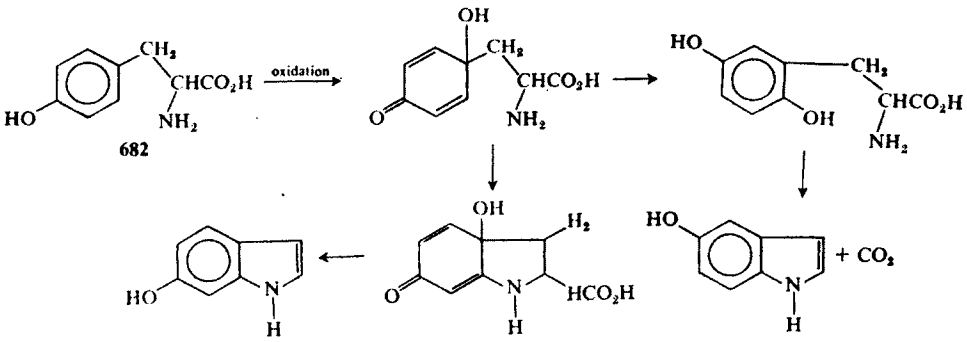
(242)

oxidation of 2-(2,5-dihydroxyphenyl)-4-aminobutylamine (**754**) is reported to give only the indole, serotonin (**755**), with no detectable trace of the alternative quinoline product,[515] the latter type of product will form if the alternative formation of the indole is not possible. Thus, γ-(2,5-dihydroxyphenyl)propylamine (**758**), when oxidized with 1 equiv of ferricyanide, gives a mixture of 6-hydroxyquinoline (**759**) and 6-hydroxy-1,2,3,4-tetrahydroquinoline (**760**) in 43% yield (Eq. 243). If 2 equiv of oxidant are used, only **759** is obtained.[583]



(243)

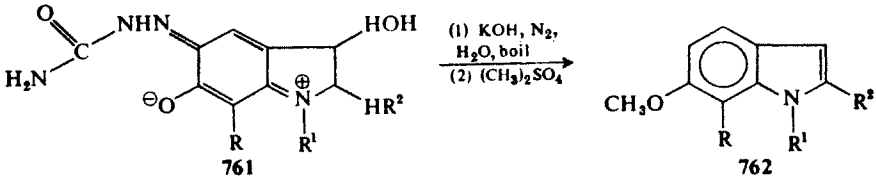
Harley-Mason's work on the oxidation of 3,4-dihydroxyphenylalanines and 2,5-dihydroxyphenylalanines has led to the suggestion of a possible route to the biogenesis of hydroxyindoles from tyrosine (**682**)[526, 584] This is shown in Scheme 73.



682

Scheme 73

Based on the report that benzoquinone monosemicarbazone heated with alkali is converted nearly quantitatively to phenol,[585] Heacock and Hutzinger[586] have found that the alkaline degradation of a number of aminochrome semicarbazones **761** gave the corresponding 6-hydroxyindoles **762** (as their methyl ethers following reaction with methyl sulfate) in satisfactory yield (Eq. 244).

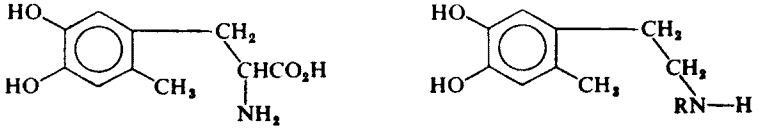


761 762

a; $R = R^2 = H$; $R^1 = CH_3$
b; $R = R^1 = CH_3$; $R^2 = H$
c; $R = R^2 = H$; $R^1 = i\text{-}C_3H_7$
d; $R = R^1 = H$; $R^2 = CH_3$
e; $R = H$; $R^1 = R^2 = CH_3$

(244)

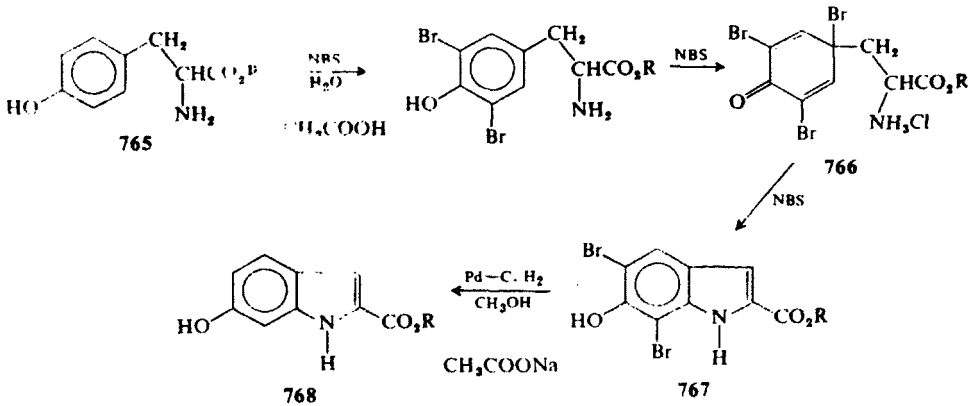
It has been assumed, based on the nature of the products isolated, that catecholamines when oxidized cyclize in only one direction which will produce the 2,3-dihydroindole-5,6-quinone. Cromartie and Harley-Mason have produced additional evidence to support this view.[527] Neither the compound (2-methyl-4,5-dihydroxyphenyl)alanine (**763**), nor β-(2-methyl-4,5-dihydroxyphenyl)ethylamine (**764**; R = H) nor its *N*-benzyl derivative **764**



763 764

(R = benzyl) could be induced to cyclize when oxidized as usual with either silver oxide or potassium ferricyanide.

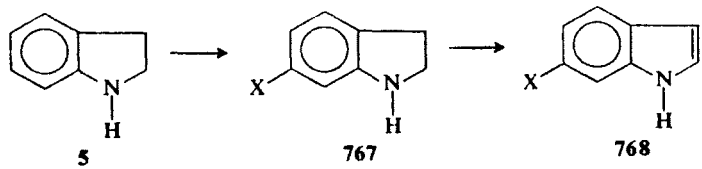
A novel nonenzymatic conversion of methyl or ethyl tyrosinate (**765**; R = CH_3 or C_2H_5) to methyl or ethyl 6-hydroxyindole-2-carboxylate (**768**) has recently been reported[587] involving bromination and oxidation of **765** by *N*-bromosuccinimide (NBS). The isolable bromodienone **766** is apparently stabilized by the ionized amino group which is unable to undergo a Michael addition to the dienone. The cyclization product **767** has been isolated and reductively debrominated to the indole **768** (Scheme 74).



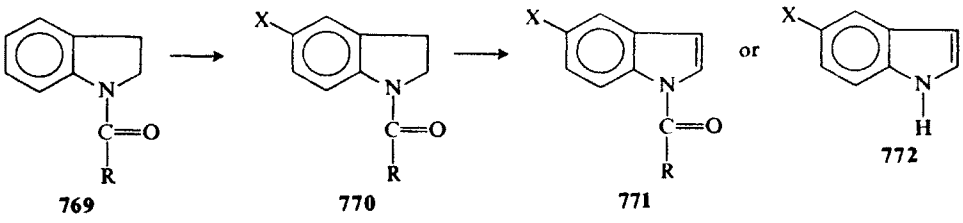
Scheme 74

G. Indolines as Sources of Indoles

The introduction of substituents into the indole nucleus by direct reaction is limited to a relatively few useful reactions. Usually substituents in the aryl ring and/or the pyrrole ring are incorporated before the indole nucleus is formed by using suitably substituted precursors. However, recent work[588-591] has shown that substituents can be introduced quite readily into the aryl ring or on the nitrogen atom if the indole is first obtained as, or converted to, the 2,3-dihydro derivative (indoline). These indolines, e.g., **5** and **769**, can be considered as *o*-alkylated arylamines, which now can undergo electrophilic substitution reactions. Subsequent dehydrogenation of the resulting substituted



(245)



769 770 771 772

(246)

indolines **767** and **770** provides the correspondingly substituted indoles **768**, **771**, and **772** (Eqs. 245 and 246). A recent review by Preobrazhenskaya[592] gives an excellent summary of the methods of indoline formation, of electrophilic substitution of indolines, and of their conversion to indoles, covering the literature to 1967.

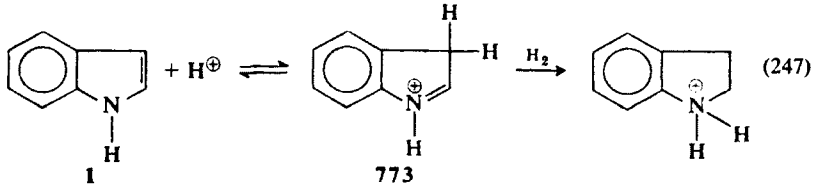
1. *Preparation of Indolines*

Indolines have been prepared by a number of different methods. The indole nucleus itself can be selectively reduced to the 2,3-dihydroindole. Catalytic hydrogenation with Raney nickel in alcohol solution is reported to convert indole to indoline in 71% yield.[593] This has been applied successfully to convert substituted indoles to indolines,[594, 595] indole-3-alkanoic acids[591, 596] or indole-3,4-diacetic acid[597] or their esters[598] to the corresponding 2,3-dihydro derivatives, and 7-azaindoles to 7-azaindolines.[404, 599] Conditions are generally quite clearly defined since an increase in hydrogenation temperature causes "overreduction,"[591] leading to octahydroindoles[600–602] and to cleavage of the pyrrole ring.[599, 603] Under these more severe conditions *N*-alkylated octahydroindoles are obtained from indoles, unsubstituted on the nitrogen atom and hydrogenated in alcohol solution.[601, 602]

Copper chromite[452] is reported to be much more selective than is Raney nickel in preferential reduction of the pyrrole ring of indoles.[600, 604] By its use 2,3-dimethylindole has been converted exclusively to the *trans*-2,3-dimethylindoline isomer.[605] It has been pointed out, however, that the equilibrium indole $\rightleftharpoons$ indoline becomes much less favorable for 2,3-disubstituted indolines.[604] Palladium hydroxide on barium sulfate in an acetic acid–aqueous hydrochloric acid mixture at 60° reduces indole to indoline (90%) in 1.5 hr, but longer reduction time (14 hr) results in an 80% yield of octahydroindole.[606] Hydrogenation of indole in acetic acid, using platinum as catalyst, produces octahydroindole,[607] while platinum oxide is reported to catalyze the reduction of the esters of indole-3-alkanoic acids to the indoline-3-alkanoic acids in the presence of hydrochloric acid.[608] High yields (85–100%) of the indolines have been obtained by platinum oxide-catalyzed hydrogenation of

indoles and 1,2,3,4-tetrahydrocarbazoles dissolved in a mixture of aqueous fluoboric acid and alcohol.[609]

Chemical reduction of indoles with either tin or zinc dust and hydrochloric acid has given useful yields of the corresponding indolines.[610–613] Under these conditions, indole rapidly polymerizes to dimers and trimers.[614] However, little or no polymerization of indole is obtained if the reduction is carried out with zinc dust in 85% phosphoric acid under nitrogen.[615] Under these conditions 2,3-dimethylindole is reduced in 28% yield to a 2:1 mixture of *cis*- and *trans*-2,3-dimethylindoline, distinguishable by their nmr spectra.[616] Reduction of 2,3-dimethylindole with tin and hydrochloric acid is reported to produce the *cis* and *trans* isomers in the ratio of 3:2.[605] The reduction in acid media is considered to involve the protonation of the indole **1** at C-3 as the first step, as clearly demonstrated by Hinman and Whipple,[214] followed by reduction of the protonated indolenine **773**[609, 615, 617] (Eq. 247). The



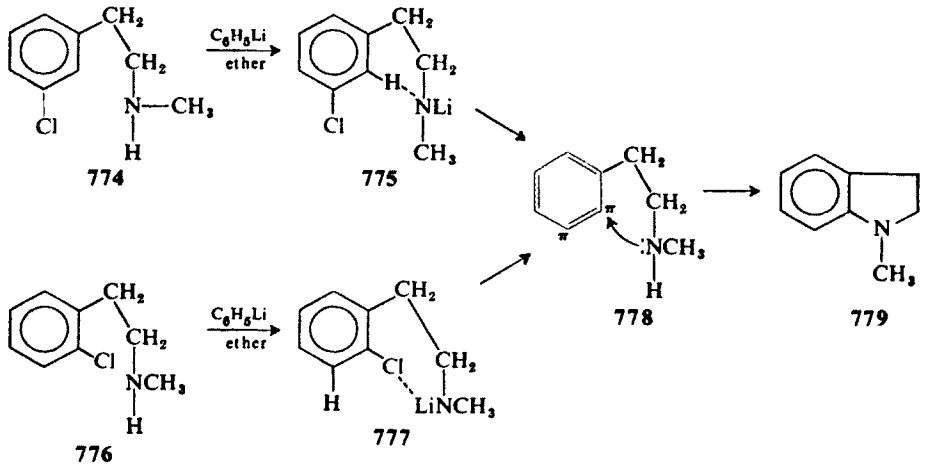
(247)

introduction of alkyl groups into the pyrrole ring appears to facilitate reduction under acidic conditions[592] since *N,N'*-dimethyltryptamine is easily reduced to the indoline by zinc and hydrochloric acid[618] and 3-(nitroisobutyl)-indole is readily converted to the 3-(nitroisobutyl)indoline when hydrogenated in alcohol and hydrochloric acid with platinum oxide.[619] Under these conditions the 2,3-double bond of the indole is more readily reduced than is the nitro group.[619]

Lithium aluminum hydride has been found to reduce indoles to indolines but only if the pyrrole ring nitrogen is substituted.[17]

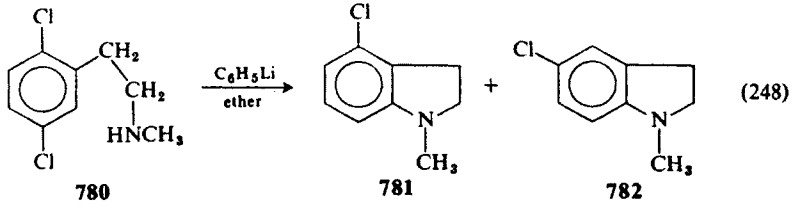
Of greater interest for the purposes of this discussion is the preparation of indolines from precursors that are not indolic in structure.

The reaction of β-(*o*- or *m*-chlorophenyl)ethylamines with phenyllithium, lithium diethylamide, sodamide, or sodium hydride in ether provides indolines in yields ranging from 20 to 88%.[620–625] The course of the reaction given in Scheme 75 is considered to involve first the conversion of the β-chlorophenylethylmethylamine **774** or **776** to the lithium salt **775** or **777** which then by either intramolecular or intermolecular proton abstraction from **775** and **777**, respectively, is converted to the aryne **778**. The latter undergoes rapid intramolecular nucleophilic attack by the secondary amino group to form the 1-methylindoline (**779**).[620–622] Evidence for intermolecular removal of proton from **775** as well as from **777** was obtained when the



Scheme 75

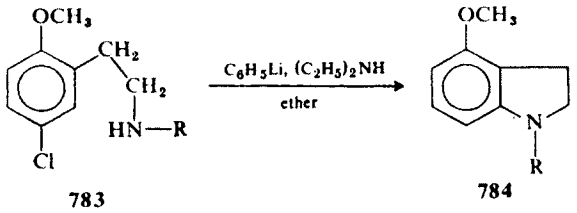
addition of lithium diethylamide to an ether solution of **774** and phenyllithium was found to increase the rate of reaction as well as increase the yield of the indoline **779** to as high as 88%.[621] Rate increase and an improvement in the yield (to 72%) of the indoline **779** was also found when lithium diethylamide was added to a solution of **776** and phenyllithium in ether. The rate of reaction of **774** was found to be about 10–15 times that of **776**.[622] The fact that the conversion of either **774** or **776** to the aryne was first order with or without the addition of the base lithium diethylamide to the equimolar mixture of phenyllithium and **774** or **776**, and that the addition of lithium diethylamide more than doubled the rate, was considered evidence for complex formation (e.g., **775** and **777**) and that the added diethylamide also formed such a complex with **775** or **777**.



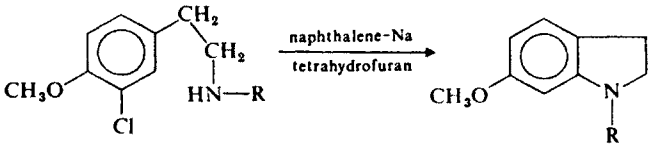
(248)

The reaction of β-(2,5-dichlorophenyl)ethylmethylamine (**780**) with phenyllithium in ether[624] gave two products, 4-chloro-1-methylindoline (**781**) and 5-chloro-1-methylindoline (**782**) (Eq. 248), the former in greater proportion as might be expected from the relative rates of reaction found for **774** and **776**.[622]

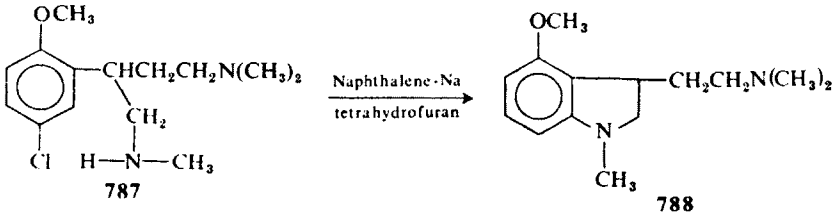
This reaction has been extended more recently to the cyclization of β-(5-chloro-2-methoxyphenyl)ethylamine (**783**, R = H, CH_3, $C_6H_5CH_2$) to the 4-methoxyindoline (**784**; R = H, CH_3, $C_6H_5CH_2$)[625] (Eq. 249). The ready



783 **784** (249)



785 **786** (250)

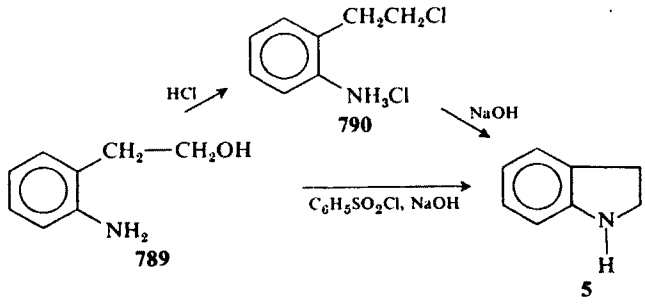


787 **788** (251)

availability of precursors of the β-phenylethylamines indicates that this method of cyclization could be very useful. The reagent naphthalene-sodium in tetrahydrofuran was found to be effective but gave lower yields of the indoline than did a mixture of phenyllithium and diethylamine in ether.[625] By use of naphthalene-sodium in tetrahydrofuran, β-(3-chloro-4-methoxyphenyl)ethylamine (**785**; R = H, CH_3 or C_2H_5) and 4-dimethylamino-2-(5-chloro-2-methoxyphenyl)-*N*-methylbutylamine (**787**) were converted in useful yields to the corresponding indolines **786** and **788**[625] (Eqs. 250 and 251).

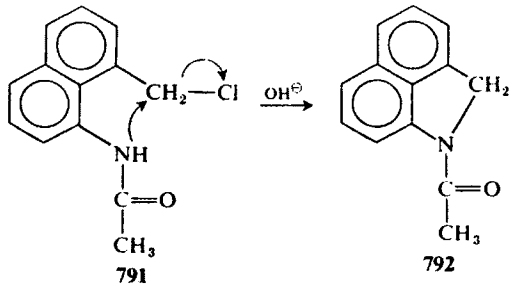
Indolines have also been formed by cyclization of β-(*o*-aminophenyl)ethyl chloride or -ethyl alcohol. It has been shown that β-(*o*-aminophenyl)ethanol (**789**) forms the chloride **790** when boiled with concentrated hydrochloric acid. Treatment of the latter with sodium hydroxide provides the indoline **5**.[626] The reaction of **789** with benzenesulfonyl chloride in aqueous sodium

hydroxide also forms the indoline **5** along with a trace of 1-benzenesulfonylindoline[626] (Eq. 252). Alkaline conditions also have converted β-(*o*-acetaminophenyl)ethyl chloride to 1-acetylindoline.[626] This reaction has been



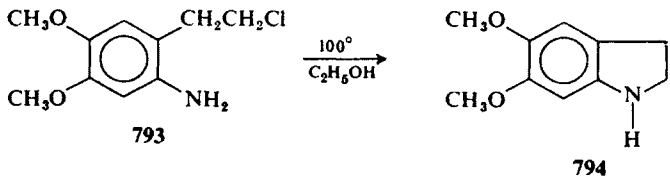
(252)

used to cyclize 1-acetamino-8-chloromethylnaphthalene (**791**) to 1-acetylbenz[*c*,*d*]indoline (**792**)[627] (Eq. 253). Aqueous conditions tend to remove the



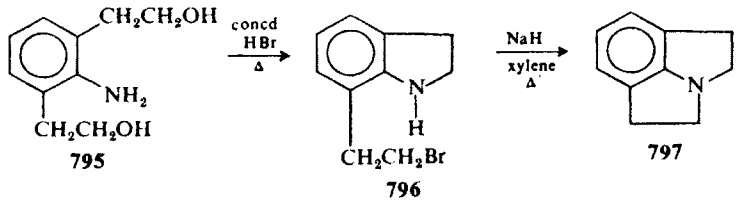
(253)

halogen, but a yield of 60% of **792** is obtained if **791** is treated with 2 *N* sodium hydroxide in acetone, while **792** can be formed in **87**% yield if dry, powdered sodium hydroxide is used in the acetone medium.[627] Base is not essential for such conversions since β-(2-amino-4,5-dimethoxyphenyl)ethyl chloride (**793**), when heated at 100° in ethanol or benzene in a sealed tube,[628] forms 5,6-dimethoxyindoline (**794**) (Eq. 254), Anet et al.[629] have found that



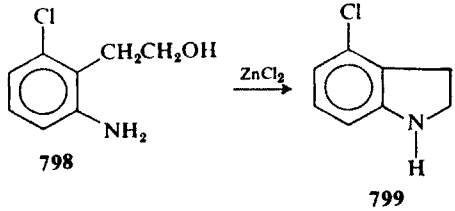
(254)

2,6-bis(β-hydroxyethyl)aniline (**795**), heated in boiling concentrated hydrobromic acid, forms 7-(β-bromoethyl)indoline (**796**). However, the conversion of **796** to 1,2,4,5-tetrahydropyrrolo[3,2,1-*h*,*i*]indole (**797**) does require the use



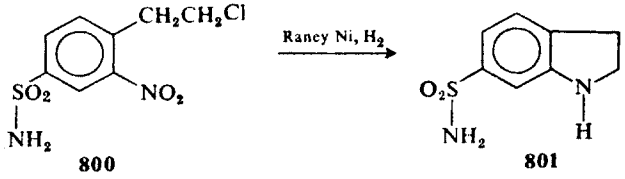
(255)

of sodamide in boiling xylene (Eq. 255). Also, β-(2-amino-6-chlorophenyl)-ethyl alcohol (**798**) cyclizes to 4-chloroindoline (**799**) when treated with zinc chloride[624] (Eq. 256).



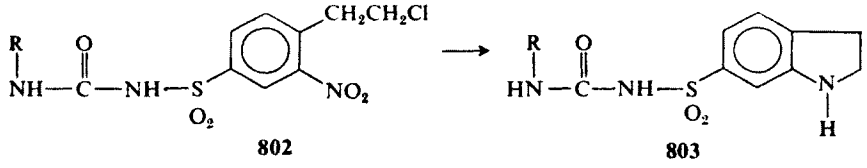
(256)

The reduction of 4-β-chloroethyl-3-nitrobenzenesulfonamide (**800**) with hydrogen and Raney nickel can be carried out in ethyl acetate or aqueous alkali to provide indoline-6-sulfonamide (**801**)[630] (Eq. 257). Similarly, by a



(257)

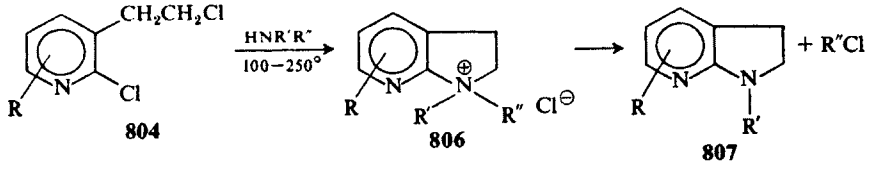
one-step hydrogenation cyclization over Raney nickel in the presence of ammonia or sodium hydroxide, 1-[3-nitro-4-(β-chloroethyl)phenylsulfonyl]-3-butylurea (**802**; R = butyl) or -3-cyclohexylurea (**802**, R = cyclohexyl) have been converted into the corresponding indoline **803**[831] (Eq. 258).



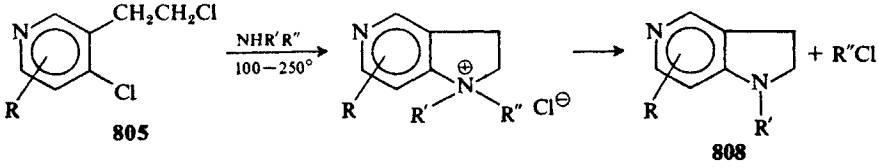
(258)

A useful reaction by which many substituted 5- and 7-azaindolines (**807** and **808**) have been prepared is the high temperature reaction of 2- and 4-chloro-3-(β-chloroethyl)pyridine (**804** and **805**) with a primary or secondary

amine.[592, 632–637] The first step is considered to be replacement of the 2- or 4-chloro substituent by the amino group —NR′R″ which then reacts with the β-chloroethyl group to give first the salt **806** and subsequently the indoline[592] (Eqs. 259 and 260).

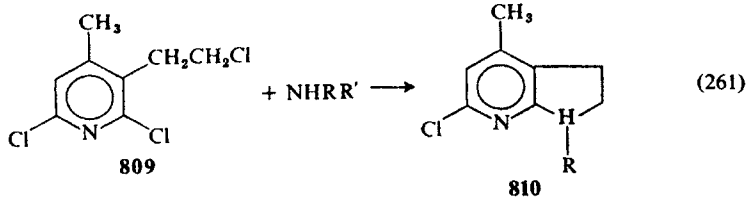


(259)



(260)

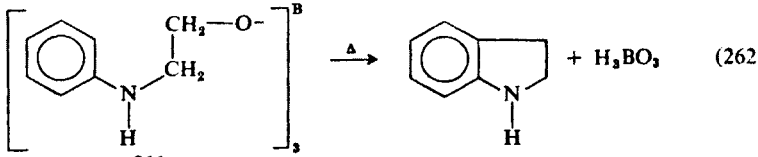
The reaction of 2,6-dichloro-3-(2-chloroethyl)-4-methylpyridine (trichlorocollidine; **809**) reacts with secondary amines to produce 1-substituted 6-chloro-4-methyl-7-azaindole **810** (Eq. 261). The facility of the reaction



(261)

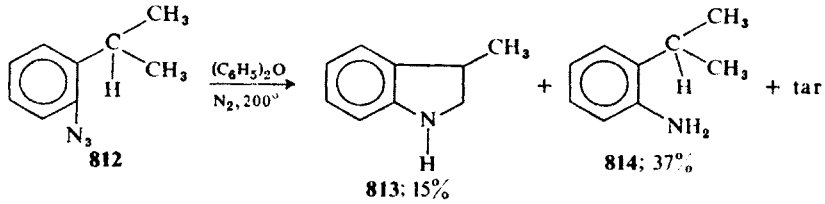
depends upon the nature of the substituents R and R′ of the amine. Dimethylamine begins to react at 80°, diethylamine at 120°, while methylaniline requires temperatures above 140°.[632] Monoalkylated anilines provide only the 1-phenyl-7-azaindolines.[638] Yields vary from 5–91% but fall as the chain length of the alkyl group of the amine is increased.[632, 636] Primary aromatic amines not only produce the 1-aryl-7-azaindolines from **809** but also displace the 6-chloro substituent to form 6-anilino-4-methyl-1-phenyl-7-azaindoline as well.[635] Ammonia, however, does not displace the 6-chloro substituent of **810**.[635] The compound 2-chloro-3(2-hydroxyethyl)-4-methylpyridine also will react with secondary amines to form the azaindoline, but requires temperatures (~300°) which are higher than those needed to cyclize the 3-chloroethyl analogs.[634]

An interesting and potentially useful reaction has been reported[638] by which indoline was obtained, along with boric acid, from the distillation under reduced pressure of the boric acid ester of *N*-(β-hydroxyethyl)aniline **811** (Eq. 262).

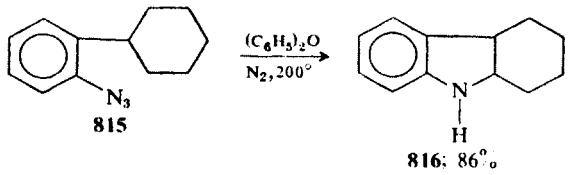


811 (262)

The thermal decomposition of suitably substituted arylazides has also provided a route to indolines[639] although the yields are strongly dependent upon the structure of the aryl azide. A solution of *o*-azidocumene (**812**) in diphenyl ether, heated at 200° under nitrogen, gave a mixture of 3-methylindoline (**813**) and *o*-aminocumene (**814**) in yields of 15 and 37%, respectively, along with much tar (Eq. 263). A similar reaction with *o*-azidocyclohexyl-



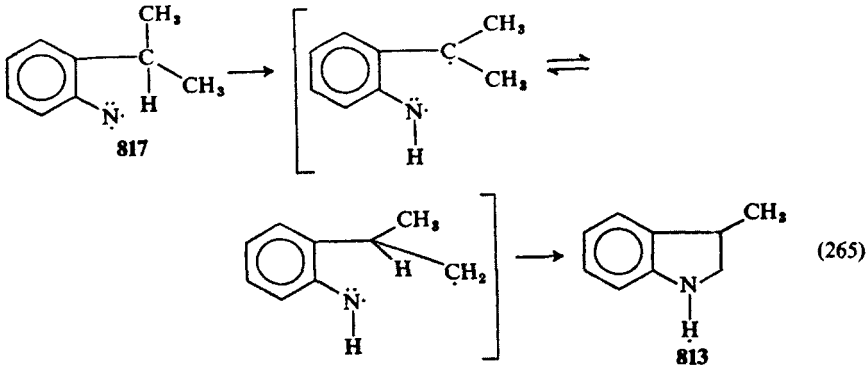
812 **813**; 15% **814**; 37% (263)



815 **816**; 86% (264)

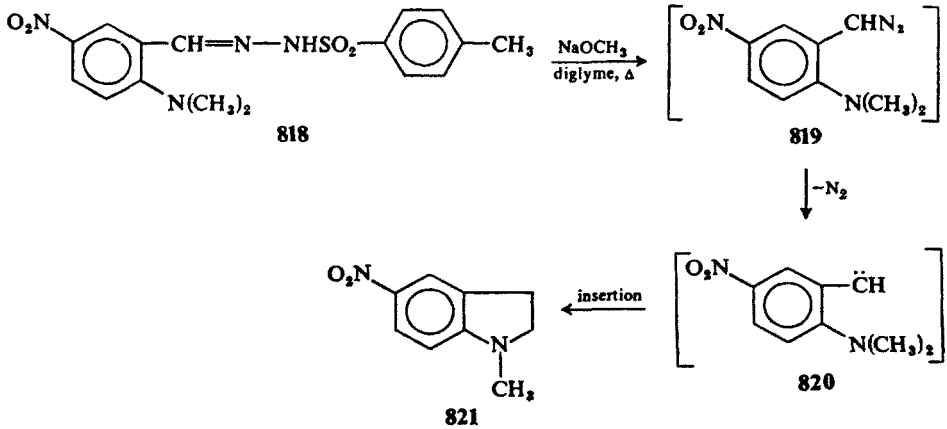
benzene **815** gave a smooth reaction providing a 1:1 mixture of the *cis* and *trans* isomers of 1,2,3,4,4*a*,9*a*-hexahydrocarbazole (**816**) in high yield as the only isolable product (Eq. 264). Generally the corresponding amine (e.g., **814**) is also formed in up to 30% yield. Comparison of yields and nature of the products supports the view[639] that the reaction occurs by means of the azene **817** which is in the triplet rather than singlet state and which forms the indoline according to the route shown in Eq. (265), involving first, hydrogen abstraction and then cyclization.

Recently a facile synthesis of the indoline system has been described[640] involving an intramolecular cyclization by an arylcarbene. The hydrazone **818**, heated with sodium methoxide in boiling diethyleneglycol dimethyl ether



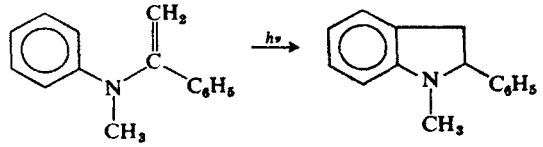
(265)

(diglyme), is thought to form the diazomethyl compound **819** which, under the thermal conditions employed, loses nitrogen to form the carbene **820** which in turn cyclizes to the indoline **821**. If the dimethylamino group of **818** is replaced by the diethylamino or piperidino moieties, the corresponding indolines are also readily obtained in yields of ca. 40% (Scheme 76).

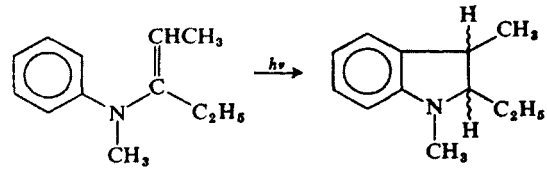


Scheme 76

Chapman and Eian[641] have described a photochemical synthesis of indolines from *N*-arylenamines. The enamines, obtained by the reaction of *N*-alkylanilines with ketones, are irradiated in ether solution at room temperature to provide the indoline. Thus, irradiation of α-(*N*-methylanilino)styrene (**822**) (from *N*-methylaniline and acetophenone) gives 1-methyl-2-phenylindoline (**823**) in 60% yield (Eq. 266). A mixture of the *cis* and *trans* isomers of **824** produces the two isomers of **825** (43%) when similarly irradiated (Eq. 267). Irradiation of *N*-arylenamines obtained from cyclic ketones, **826**, gives chiefly the *trans* tricyclic products **827** except in the case of **826a** where only



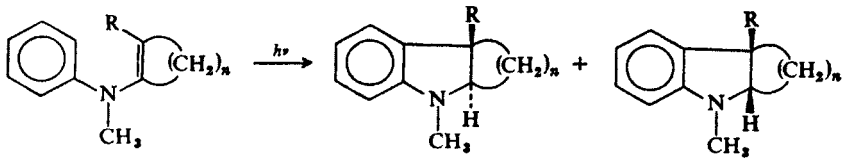
822 823 (266)



824 825 (267)

the *cis* isomer **828a** was obtained. Yields of products, measured by gas liquid chromatography (isolated yields in parentheses) are generally good (Table VII). This appears to be a useful method to obtain structures with angular

TABLE VII

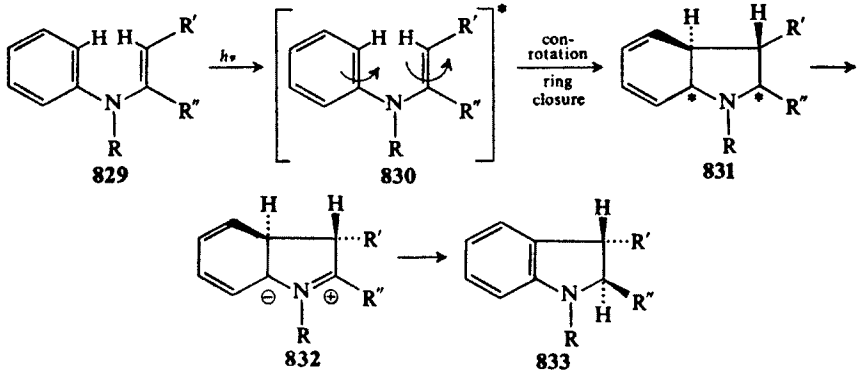


826 827 828

			% Yield	% Yield
a	R = H	$n = 3$	—	52(35)
b	R = H	$n = 4$	71(55)	3
c	R = H	$n = 5$	68(47)	2
d	$R = CH_3$	$n = 4$	77(75)	—

substituents at C-3. The mechanism of the reaction has not yet been clarified but the cyclization as given in Scheme 77 is considered[641] to occur by way of a conrotatory process characteristic of photochemical reactions of divinylamines.[642, 643] Irradiation of **829** produces an excited species **830** which by conrotatory ring closure to **831** and subsequent electron demotion forms the dipolar species **832**. The intermediate species **832** then undergoes a thermal, suprafacial [1,4] sigmatropic shift of a hydrogen atom[642, 644] to form the *trans*-2,3-disubstituted indoline **833**.

A novel and useful route to 2-methyl- and 2,3-dimethylindolines has become available[605, 645] by the acid-catalyzed rearrangement of *N*-allylanilines (**834**; R″ = H) or *N*-crotylanilines (**834**; R″ = CH_3) (Eq. 268).

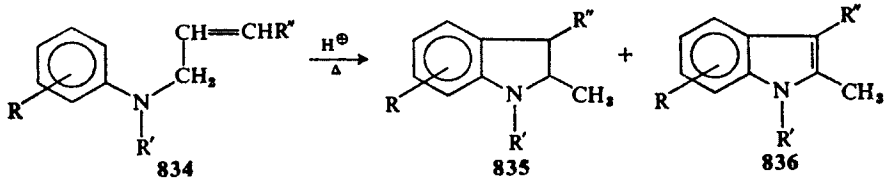


Scheme 77

The reaction is exothermic once it has begun and is advantageously carried out in an inert high boiling solvent such as 2-methylnaphthalene. Both the indoline **835** and the indole **836** are usually obtained, with the former the predominant product in nearly all cases. Not only polyphosphoric acid[645] but also concentrated hydrochloric acid[605] promotes this reaction. Under the conditions employed, the *N*-allylaniline **834** and acid are present in the proportion of 3:1. The rearrangement of *N*-crotylaniline (**834**; R = R′ = H, R″ = CH_3) is reported to proceed so smoothly that merely refluxing a mixture of excess aniline with crotyl chloride or bromide suffices. The range of substituted allylanilines explored[605, 645] is shown in Table VIII.

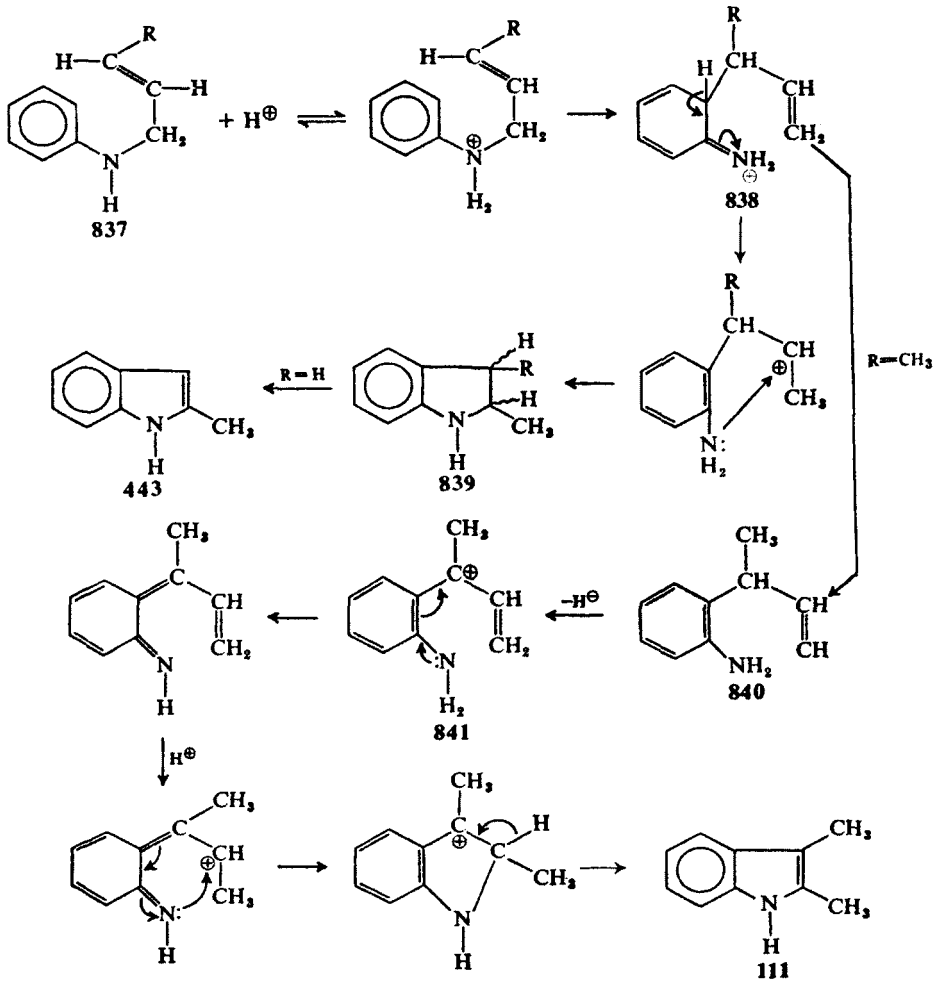
The reaction is considered to proceed[605, 645] in a manner similar to an acid-catalyzed Claisen rearrangement[212, 213] according to Scheme 78, thus

TABLE VIII



(268)

R	R′	R″	R	R′	R″
2-CH_3	H	H	7-CH_3	H	H
4-CH_3	H	H	5-CH_3	H	H
2-CH_3	H	CH_3	7-CH_3	H	CH_3
H	CH_3	H	H	CH_3	H
4-F	H	H	5-F	H	H
4-Cl	H	H	5-Cl	H	H (only **836**)

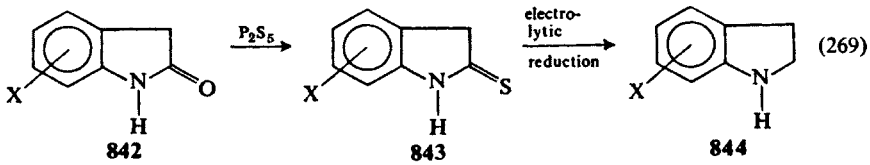


Scheme 78

accounting for the fact that the substituent R of the allyl group is always located at C-3 of the indoline or the indole. The fact that *o*-allylaniline heated with hydrochloric acid gives 2-methylindoline (**839**; R = H)[605] supports the concept of rearrangement of the *N*-allyl group to the *ortho* position, **837** → **838**. Since 2-methylindoline (**839**; R = H) is slowly converted to 2-methylindole (**443**) when heated under these acidic conditions, the formation of 2-methylindole is believed to occur by this route. However, the *cis–trans* mixture of 2,3-dimethylindoline (**839**; R = CH_3) obtained by this procedure does not oxidize to 2,3-dimethylindole (**111**) under these conditions. Hence

it is considered[605] that an oxidation by loss of an hydride ion **840** → **841** must occur *before* cyclization has taken place. The carbonium ion **841** so formed then suffers electronic rearrangement and eventual cyclization to **111** as shown in Scheme 78.

The reduction of isatin (**9**), oxindole (**6**), or indoxyl (**7**) and some of their derivatives has also provided indolines.[592] Electrolytic reduction of isatin and indoxyl has produced indoline in small yield.[646] However, prior conversion of an oxindole **842** to the thiooxindole **843**, which is then electrolytically reduced to the indoline (**844**, X = H, 4-CH_3O, 6-CH_3O), has been found



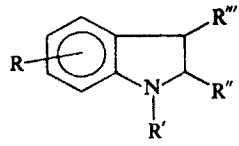
(269)

to be a more convenient process[647, 648] (Eq. 269). The high pressure nickel-catalyzed reduction of 1-acetylindoxyl is reported[649] to provide 1-acetylindoline in 90% yield. Lithium aluminum hydride reduction of oxindoles, obtained by the Stollé reaction,[650] has given a mixture of indoles and indolines with the former predominating.[17, 624, 651] Oxindole itself could not be reduced but 1-methyloxindole did reduce in this manner.[17]

2. *Substitution Reactions of Indolines*

The *N*,*N*-disubstituted *o*-toluidines undergo electrophilic substitution *para* to the alkyl substituent, a result that appears to stem from the fact that the alkyl and disubstituted amino groups cannot lie in the plane of the benzene ring. On the other hand, the hetero ring of indoline holds the alkyl and substituted amino groups on adjacent carbons of the benzene ring more closely in the plane of the aryl ring, and hence these substituents can exert their well-known relative directive effect on electrophilic substitution.[592] Accordingly, nitration of indolines having the nitrogen either unsubstituted or alkylated occurs at C-6 due to protonation of the amino moiety in the strongly acidic medium (i.e., **5** → **767**). If the nitrogen is acylated and thus protected against such protonation, nitration occurs chiefly at C-5 *para* to the amino moiety as expected (i.e., **769** → **770**). If position 5 is blocked, then C-7 (*ortho* to the amino unit) is attacked. Direct bromination of indolines, unacetylated on the nitrogen, produces 5-bromoindolines. As expected, the nitro substituent has been reduced to the amine, which in turn by diazotization has permitted the preparation of a variety of aryl ring-substituted indolines. These principles have been employed to provide substituted

indolines, a number of examples of which are shown in Table IX and using the general structure **845**.



845

3. *Dehydrogenation of Indolines to Indoles*

The various methods of dehydrogenating indolines to indoles have been described adequately in detail by Preobrazhenskaya.[592] Accordingly, mention will be made here only of those systems commonly employed. The most popular oxidizing agent is chloranil, usually in a boiling solvent such as xylene since heat accelerates the rate of dehydrogenation.[17, 77, 588, 589, 633, 636, 652–655, 659, 667] Chloranil[633, 636] or dichlorodicyano-*p*-benzoquinone[592] in xylene satisfactorily converts azaindolines to azaindoles. The high redox potential of these two reagents is sufficient to overcome the increased resistance to dehydrogenation caused by the electron-withdrawing properties of the nitrogen atom in the aryl ring of the azaindolines. A nitro group attached to the benzene ring of an indoline also increases the resistance to dehydrogenation to the indole. In fact, none of the several dehydrogenating methods used was able to convert 5,7-dinitroindoline to the dinitroindole.[657] Azaindolines have been converted to the azaindoles smoothly and in high yield by treatment with sodium in liquid ammonia.[669] The 6-chloro-7-azaindoline gave better conversion to the indole if lithium and liquid ammonia were used.[635] The first step of the dehydrohalogenation of these azaindolines with metal in liquid ammonia appears to be replacement of the hydrogen atom on the nitrogen by metal since *N*-alkylated or *N*-arylated azaindolines remain unchanged.[669] *N*-Benzyl- or *N*-acylazaindolines are dehydrogenated by prior cleavage of the benzyl or acyl groups from the nitrogen atom.[669]

Palladium black or palladium (5 or 10%) on charcoal, usually in boiling solvents such as xylene, *p*-cymene, or mesitylene, has been used in most instances along with an hydrogen acceptor such as cinnamic or maleic acid (or anhydride).[588, 590, 596, 625, 629, 657, 660, 661, 668, 670] In some cases this has been found to give better results than those obtained with chloranil.[661] Raney nickel in water, along with an hydrogen acceptor such as maleic acid, has also been found satisfactory.[596, 625] However, groups such as the nitro substituent are reduced as well and halogen substituents are reductively removed. Raney nickel has been used in a variety of solvents including

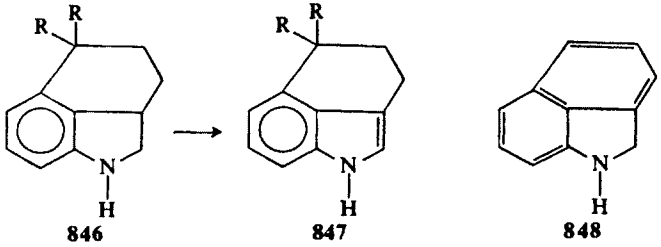
TABLE IX

R	R′	R″	R‴	Ref.	R	R′	R″	R‴	Ref.
6-NO_2	CH_3	H	H	588	5-Br	CH_3CO	H	H	658, 661
6-NH_2	CH_3	H	H	588	5-F	CH_3CO	H	H	659
6-NO_2	H	H	H	590, 652, 656, 659	5-F	H	H	H	659
6-NH_2	H	H	H	591, 652	5-Br	CH_3CO	H	CH_2CO_2H	591
6-NO_2	H	CH_3	H	652, 663	5-I	CH_3CO	H	H	77
6-NH_2	H	CH_3	H	652	5-OH	CH_3CO	H	H	660
6-NO_2	CH_3	CH_3	H	665	5-OCH_3	CH_3CO	H	H	660
6-NO_2	PhCO	H	H	590	5-CN	CH_3CO	H	H	661
6-NH_2	PhCO	H	H	590	5-CHO	CH_3	H	H	667
6-NO_2	H	H	CH_3	663	5-CH_3CO	CH_3CO	CH_3	H	654
6-NO_2	H	—$(CH_2)_4$—		664	5-CH_3CO	H	H	H	654
6-NO_2	1,7$(CH_2)_3$	CH_3	CH_3	666	5-$ClCH_2CO$	CH_3CO	CH_3	H	654
6-NO_2	CH_3CO	H	H	652, 659, 660	5-C_2H_5	H	H	H	654
6-NH_2	CH_3CO	H	H	659	7-NH_2	CH_3CO	H	H	658, 660, 661
6-F	CH_3CO	H	H	659	7-I	CH_3CO	H	H	658
6-F	H	H	H	659	7-Br	H	H	H	658
6-OH	CH_3CO	H	H	660	7-CN	CH_3CO	H	H	661

6-OCH_3	CH_3CO	H	H	660	7-OH	CH_3CO	H	H	660
6-CN	H	H	H	661	7-CH_3O	CH_3CO	H	H	660
5-NO_2	CH_3CO	H	H	652, 658, 659, 660	5-Br, 6-NO_2	CH_3	H	H	652, 653
5-NH_2	CH_3CO	H	H	660	5,7-diNO_2	CH_3CO	H	H	652, 657
5-NO_2	H	H	H	590, 657, 658					
5-NO_2	CHO	H	H	661	5,7-diNO_2	H	H	H	657
5-NO_2	CH_3CO	H	CH_2CO_2H	591	5-Br, 7-NO_2	CH_3CO	H	H	658, 661
5-NH_2	H	H	CH_2CO_2H	591	5-NO_2, 7-Br	H	H	H	658
5-NH_2	H	H	$(CH_2)_2CO_2H$	591	5-NH_2, 7-Br	H	H	H	658
5-NH_2	H	H	H	591	5,6-diNH_2	CH_3CO	H	H	662
5-CNS	CH_3	H	H	589	5-NO_2, 6-$NHCOCH_3$	CH_3CO	H	H	662
5-PhCOS	CH_3	H	H	589	5-$NHCOCH_3$ 6-NO_2	CH_3CO	H	H	662
5-ClO_2S	CH_3CO	H	H	655, 668	5-Br, 7-NO_2	CH_3CO	H	CH_2CO_2H	591
5-HO_3S	H	H	H	655					
5-Br	CH_3	H	H	652, 653					
5-Br	H	H	H	661					

cyclohexane, benzene, toluene, and xylene, the aromatic solvents under these conditions acting as hydrogen acceptors.[671]

The versatile reagent manganese dioxide[672] converts indolines of the type **846** to the corresponding indole **847** in good yield, with no tendency to form the naphthalene structure **848**, which apparently occurs quite readily with several dehydrogenating systems[673] (Eq. 270). Merely shaking the indoline

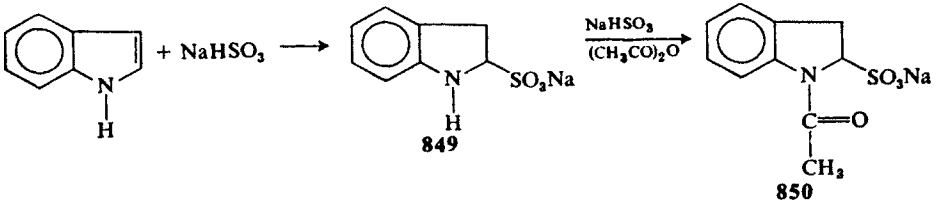


(270)

846 with manganese dioxide in methylene chloride at room temperature suffices.

4. *Substituted Indoles from the Adduct of Sodium Bisulfite and Indole*

Indole reacts with sodium bisulfite at pH 4 to produce indoline-2-sulfonate (**849**) in high yield (Eq. 271). This adduct was first made by Hesse[674] and used later to purify indoles.[675] Since **849** now has properties of an aromatic



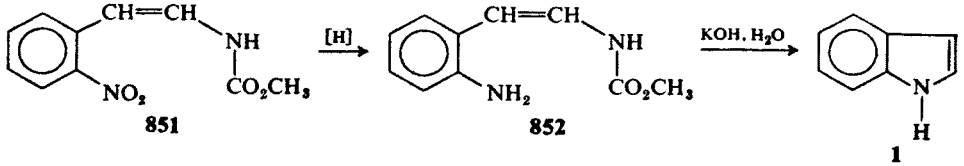
(271)

amine, it has been subjected to electrophilic substitutions. Treatment of the products with alkali regenerates the indole, now substituted in the aromatic ring. The adduct is first acetylated, using a mixture of acetic anhydride and sodium bisulfite, to protect the nitrogen. The 1-acetylindoline-2-sulfonate **850** has been treated with bromine to give, after basification, 5-bromoindole in 71% yield.[676, 677] Similarly, iodine chloride with potassium iodide reacted with **850** to give 5-iodoindole[676, 677] while nitration of **850** gave in 65% yield a mixture of 5-nitro- and 7-nitroindole, the former as the chief product, which could be separated by chromatography.[676] In each case, treatment of

the halogenated or nitrated 1-acetylindoline-2-sulfonate with aqueous alkali removed both the acyl and bisulfite groups.

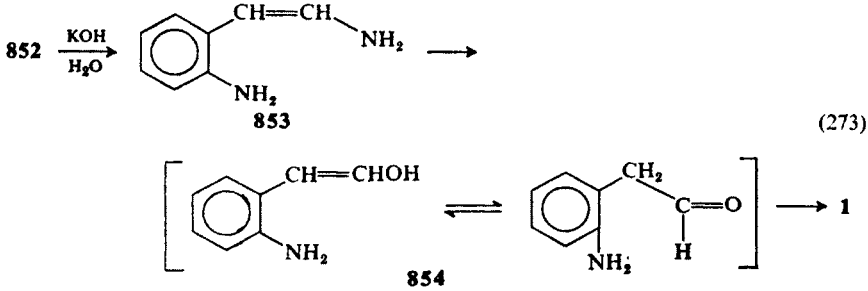
H. Indoles from the Reduction of 2,β-Dinitrostyrenes

Weermann[678, 679] had found that the reduction of methyl *o*-nitrostyrylcarbamate (**851**), followed by alkaline hydrolysis of the resulting amine **852**, provided a new route for the synthesis of indole (Eq. 272). The course of the



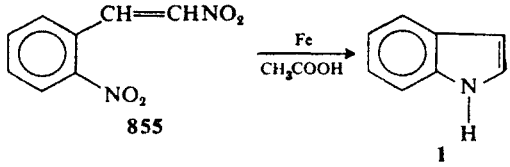
851 **852** **1** (272)

reactions was considered[678] to follow the route **852** → **853** → **854** → **1** shown in Eq. (273), although neither the diamine **853** nor the *o*-aminophenylacetaldehyde **854** was isolated. In an attempt to produce the diamine **853** by reduction of 2,β-dinitrostyrene **855** with iron powder or zinc dust and acetic acid,



(273)

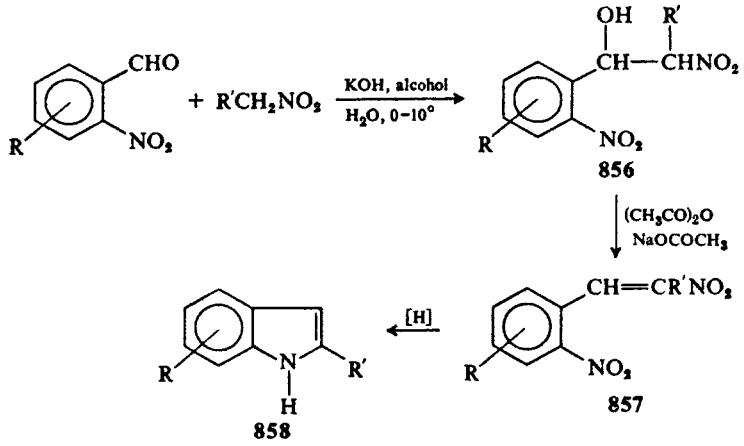
van der Lee[680] obtained indole (9–11% yield) rather than the expected diamine. Shortly before van der Lee's report appeared, Nenitzescu had described[681] the formation of indole in as much as 30% yield from his attempts at partial reduction of 2,β-dinitrostyrene (**855**) to *o*-nitrophenylacetaldoxime (Eq. 274).



(274)

Since that time, many reports have appeared illustrating the utility of 2,β-dinitrostyrenes as intermediates for the synthesis of indoles. The facile

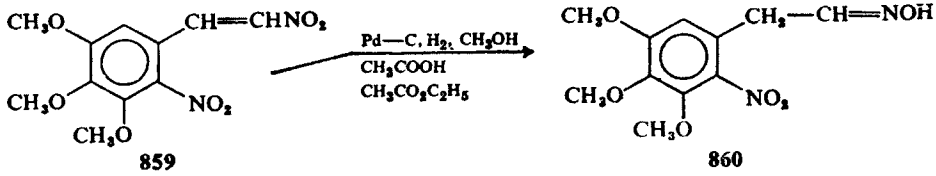
condensation of *o*-nitrobenzaldehyde with nitromethane or nitroethane, or the nitration of β-nitrostyrenes themselves, provides the required substituted 2,β-dinitrostyrene quite readily in many cases (Scheme 79).



Scheme 79

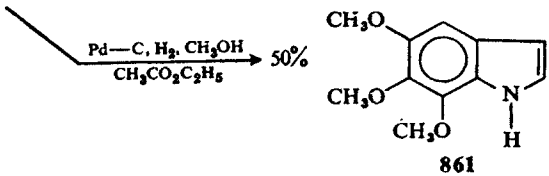
The condensation of the nitroalkane with benzaldehyde or a substituted benzaldehyde is base-catalyzed and has been accomplished most conveniently by either heating a solution of the aldehyde, nitroalkane, ammonium acetate, and acetic acid under reflux[455, 595, 682–684] or by low temperature (0–15°) treatment of the aldehyde and nitroalkane with a mixture of water, methyl or ethyl alcohol, and a base such as sodium hydroxide[444, 685–689] or potassium hydroxide.[412, 420, 444, 691–698] If the condensation is carried out at low temperatures (0–10°) under the latter conditions, it is possible to obtain the intermediate alcohol **856**,[444, 685, 693, 695, 699, 700] but this may be contaminated by some of the 2,β-dinitrostyrene **857**.[685] Since it is the dinitrostyrene that is usually desired, the dehydration of the alcohol precursor **856** is often accomplished by acidification with concentrated hydrochloric acid.[685–689] However, dehydration of **856** to **857** is frequently not complete under these circumstances,[686] hence the preferred practice is to heat the product obtained from acidification of the alcohol **856** with a mixture of acetic anhydride and sodium acetate[412, 444, 685, 686, 690, 691, 694–697, 700] in order to ensure complete dehydration. Acetylation of the alcohol **856** at room temperature in the presence of perchloric acid and subsequent treatment of the acetate with hot acetic anhydride–sodium acetate is reported to give better results than the direct reaction of the alcohol **856** with the hot acetic anhydride–sodium acetate mixture.[693] The condensation of the nitroalkane with the 2-nitrobenzaldehyde in a refluxing solution of ammonium acetate and acetic acid provides the dinitrostyrene **857** directly.[455, 595, 682–684]

The reduction of the 2,β-dinitrostyrene **857**, presumably to the diamine (cf. **853**), accompanied by the spontaneous cyclization of the product to the indole **858**, has been accomplished in most instances by treatment of an ethanol–acetic acid solution of the dinitrostyrene with iron powder,[412, 420, 455, 514, 682-684, 691, 695, 696, 699] a mixture empioyed by Weerman,[678, 679] or with iron filings.[681, 687, 689] Satisfactory results have been obtained by low-pressure hydrogenation of the dinitrostyrene with the catalyst palladium on carbon, using as solvent a mixture of ethanol and acetic acid,[444, 686, 688, 690] alcohol and ethyl acetate,[444, 495] or ethyl acetate.[697] Raney nickel has also been used successfully at 100° with a hydrogen pressure of 100 psi.[699] The presence of acetic acid in the palladium on carbon-catalyzed hydrogenation has been found detrimental in the reduction of 3,4,5-trimethoxy-2,β-dinitrostyrene (**859**)[444] since under these conditions the only isolable product was 2-nitro-3,4,5-trimethoxyphenylacetaldoxime (**860**) obtained in a very low yield (Eq. 275). Reduction with iron powder and acetic acid failed to provide any isolable indole.[444] However, low-pressure catalytic (Pd-C) hydrogenation of **859** in methanol–ethyl acetate solution gave 5,6,7-trimethoxyindole **861** in 50% yield[444] (Eq. 275). The resistance experienced



859 **860**

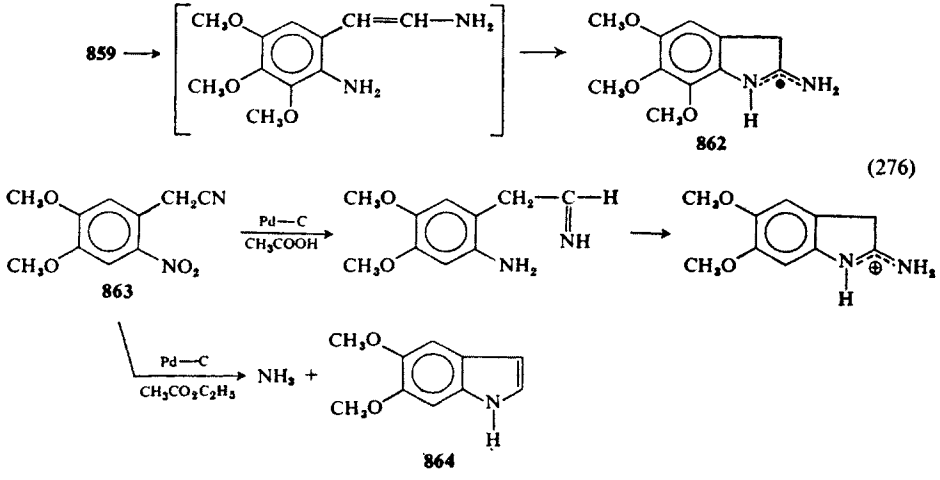
(275)



861

in the reductive conversion of the dinitrostyrene **859** to the indole **861** in the presence of acetic acid is considered[444] to be due to the formation of a protonated amidinium ion **862** which is resonance stabilized (Eq. 276). The concept of the resonance-stabilized amidinium ion had been advanced[701] to explain the failure of 2-nitro-4,5-dimethoxyphenylacetonitrile (**863**) to form an indole when catalytically hydrogenated with palladium-carbon in acetic acid, whereas similar reduction of **863** under neutral conditions in ethyl acetate did provide 5,6-dimethoxyindole (**864**) (Eq. 277).

Palladium-carbon catalyzed hydrogenation of 5-chloro-2,β-dinitrostyrene has caused simultaneous elimination of the halogen atom to produce the

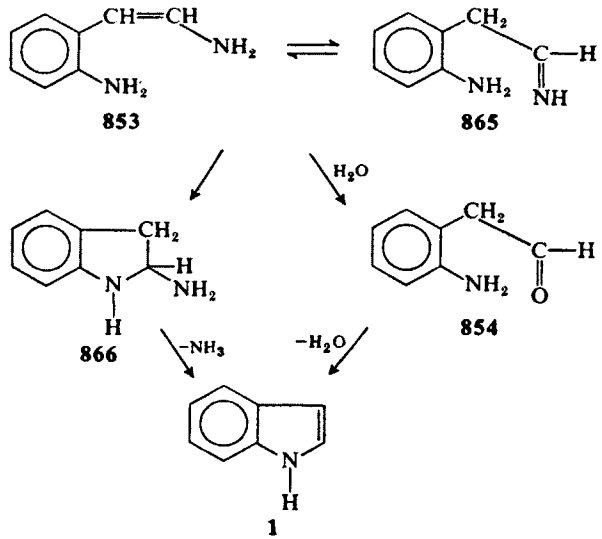


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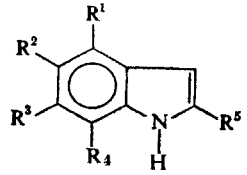
(277)

unsubstituted indole.[141] However, fluorine substituents in the aryl ring of 2,β-dinitrostyrenes apparently survive such catalytic reduction.[690, 697]

No study has been made of the detailed mechanism by which reduction of 2,β-dinitrostyrenes produces indoles. Burton and Duffield[694] have indicated that the diamine **853** shown in Scheme 80 might be formed. Such a diamine has been postulated as an intermediate in the Robinson mechanism advanced to account for the Fischer indole synthesis[9, 160] and is not unreasonable as an



Scheme 80



R^1	R^2	R^3	R^4	R^5	Ref.
Cl					689
		Cl			692
	F				690
		F			697
	OH	OCH_3		CH_3	455
	OCH_3	OH		CH_3	455
		OH	OCH_3	CH_3	455
		OCH_3	OH	CH_3	455
	OH	OCH_3			682
	OCH_3	OH			682
	OCH_3	OCH_3			514, 686
		OCH_3	OCH_3		595
		OCH_3			687
	OCH_3	OCH_3	OCH_3		444, 595, 699
OCH_3			OCH_3		696
	OCH_3				687
			OCH_3		688
	OH	OH			682, 693
	$OCOCH_3$	$OCOCH_3$			691, 693
	OH	$OCOCH_3$			693
	$OCOCH_3$	OH			693
OH					412
$OCOCH_3$					412
	OH				412
	$OCOCH_3$				412
	$PhCH_2O$			Alkoxy[b]	695
	$PHCH_2O$				695
	$PhCH_2O$	$PhCH_2O$			420, 682
	C_2H_5O	OCH_3			684
	$OCOCH_3$	$OCOCH_3$		D	698
	└OCH_2O┘				683
OCH_3	└OCH_2O┘				683
	└OCH_2O ┘		OCH_3		683
OCH_3	└ OCH_2O┘		OCH_3		683
└ OCH_2O┘		OCH_3	OCH_3		683
OCH_3	OCH_3	└OCH_2O┘			683

[a] Blank spaces indicate hydrogen.

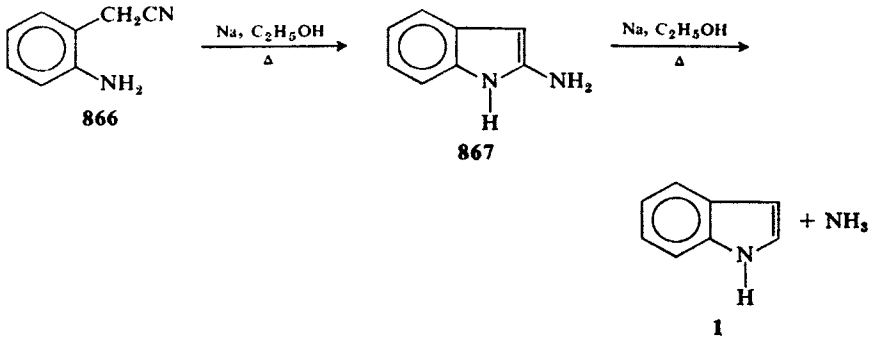
[b] OCH_3, C_2H_5O, C_3H_7O, $C_6H_{13}O$, $C_7H_{15}O$.

intermediate in the reduction of 2,β-dinitrostyrene. Tautomerization of the diamine **853** to the *o*-aminophenylacetaldimine **865** would provide a species that could either cyclize to the 2-aminoindoline **866** which would readily lose ammonia to form indole, or alternatively could first hydrolyze to form *o*-aminophenylacetaldehyde **854** which is known to cyclize and form indole by loss of water. In view of the findings of Bajwa and Brown concerning the reaction of isobutyraldehyde with *N'*-methyl-2,6-dimethylphenylhydrazine,[232, 233] the route **865** → **866** → **1** is indeed quite reasonable. However, the alternate route **865** → **854** → **1** cannot be excluded.

A number of indoles prepared by reduction of 2,β-dinitrostyrenes are listed in Table X.

I. Indoles from the Reduction of *o*-Nitrobenzyl Cyanides

The use of *o*-nitrobenzyl cyanides as precursors for the preparation of indoles was first introduced by Pschorr and Hoppe[702] who treated *o*-aminobenzyl cyanide (**866**) with sodium and alcohol and obtained a substance which they considered to be 2-aminoindole (**867**) on the basis of its elemental analysis and of its reaction with ethyl chloroformate to give the indole urethan. Further reaction of **867** with sodium and alcohol produced indole and ammonia[702] (Eq. 278). Several years later, following his discovery that



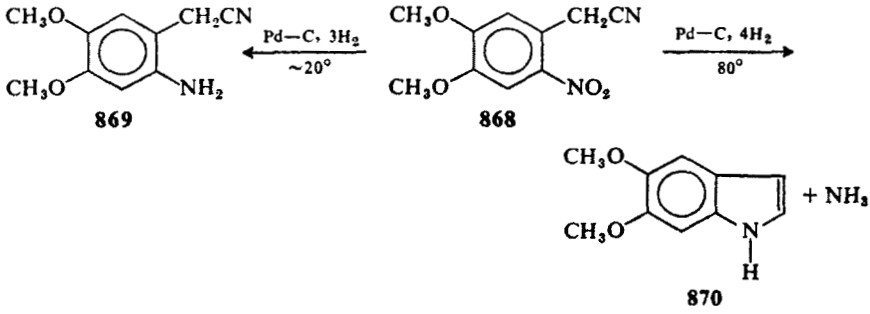
866 **867** **1**

(278

aldehydes can be prepared by the reaction of the cyano group of nitriles with a mixture of anhydrous stannous chloride and hydrogen chloride in ether and subsequent decomposition of the resulting complex product with aqueous alkali, Stephen[703] applied this reduction system to *o*-nitrobenzyl cyanide and obtained indole.

During the past two decades, a renewed interest has developed in the reduction of *o*-nitrobenzyl cyanides as a route to the formation of

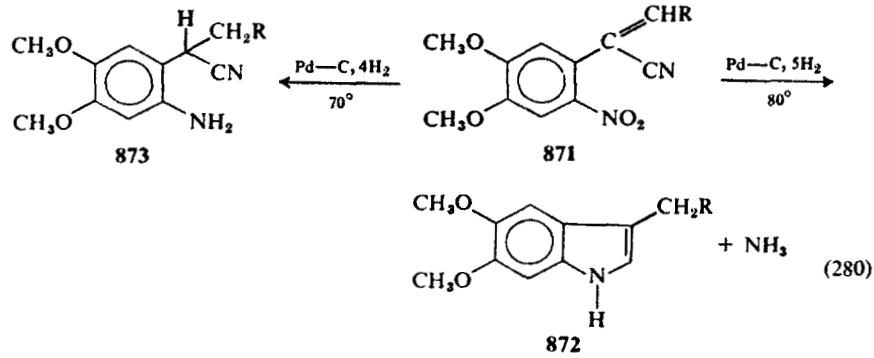
indoles.[380, 701, 704–708] Walker has shown[701] that the palladium-carbon catalyzed hydrogenation of 2-nitro-4,5-dimethoxyphenylacetonitrile (**868**) in ethyl acetate solution at room temperature absorbed 3 moles of hydrogen to produce the aminonitrile **869**, whereas at 80°, 4 moles of hydrogen were absorbed to give the product 5,6-dimethoxyindole (**870**) along with ammonia (Eq. 279). Similarly, nitriles such as **868** substituted in the α-position, e.g.,



869 **868** **870**

(279)

871, could also be reduced to the corresponding 3-substituted indoles.[701, 704] Thus α-(2′-nitro-4′,5′-dimethoxyphenyl)-β-(3′,4′-dimethoxyphenyl)acrylonitrile (**871**; R = 3,4-dimethoxyphenyl), when hydrogenated until 5 moles of hydrogen were absorbed,[701] gave ammonia and 3-(3′,4′-dimethoxybenzyl)-5,6-dimethoxyindole (**872**; R = 3,4-dimethoxyphenyl) in 58% yield (Eq. 280).

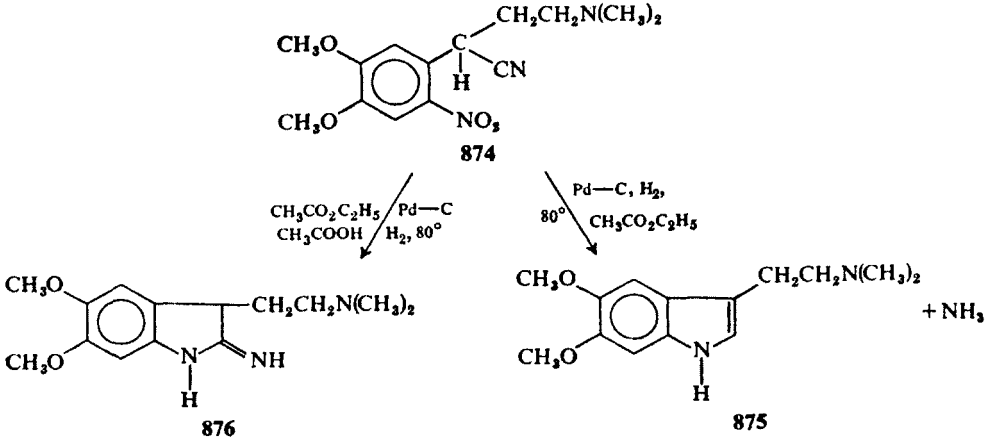


873 **871** **872**

(280)

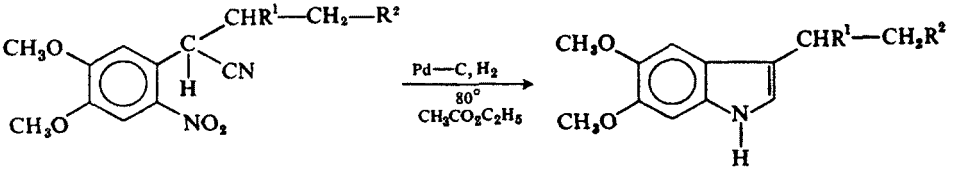
The fifth mole of hydrogen was absorbed very slowly. If the reduction was interrupted after 4 moles of hydrogen were taken up, the product obtained was α-(2′-amino-4′,5′-dimethoxyphenyl)-β-(3′,4′-dimethoxyphenyl)-propionitrile (**873**; R = 3,4-dimethoxyphenyl). These findings support the view that the aminonitrile **869**, **873** is an intermediate in the palladium-carbon reductive cyclization of *o*-nitrophenylacetonitriles to the indoles.[701] The Raney nickel-catalyzed hydrogenation of 2-nitro-4,5-dimethoxyphenylacetonitrile (**868**),

which first provided 2-amino-4,5-dimethoxyphenylacetonitrile (**869**) and upon further catalytic hydrogenation produced 5,6-dimethoxyindole (**870**) in very good yield,[705] is further evidence in support of this view. The palladium-carbon catalyzed hydrogenation of α-(2′-nitro-4′,5′-dimethoxyphenyl)-γ-dimethylaminobutyronitrile (**874**), carried out in ethyl acetate at 80°, produced 3-(β-dimethylaminoethyl)-5,6-dimethoxyindole (**875**). However, when acetic acid was added to the solution, hydrogenation failed to produce the indole **875** but gave a product whose dihydrochloride gave spectral and analytical data suggestive of a compound such as **876**[701] (Scheme 81). In subsequent work[704] it was shown that palladium-carbon catalyzed



Scheme 81

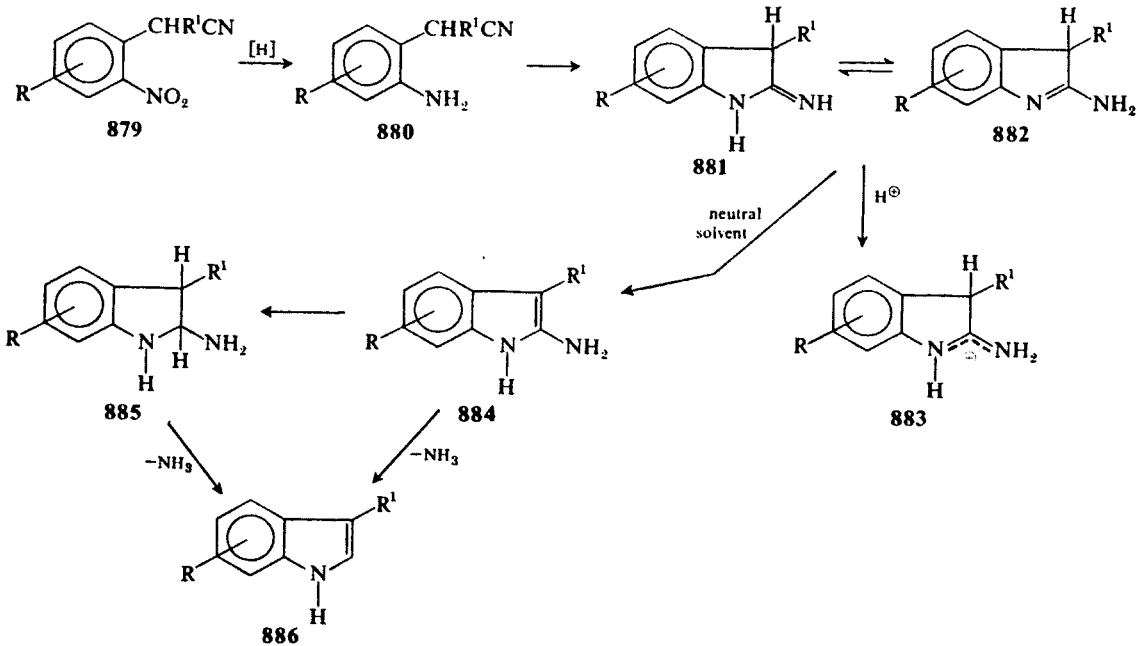
reductive cyclization of methyl γ-cyano-γ-(2-nitro-4,5-dimethoxyphenyl)-butyrate (**877a**) and the β-methyl homolog **877b** provided the corresponding indoles **878a** and **878b**, thus showing that cyclization of the amino group occurred preferentially with the cyano moiety to form the five-membered pyrrole ring rather than with the carboalkoxy group to form a seven-membered lactam (Eq. 281).



877a; $R^1 = H$; $R^2 = CO_2CH_3$ — **878a**; $R^1 = H$; $R^2 = CO_2CH_3$

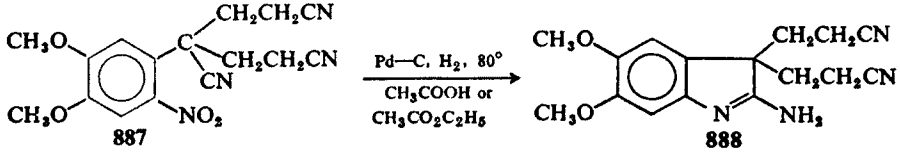
877b; $R^1 = CH_3$; $R^2 = CO_2C_2H_5$ — **878b**; $R^1 = CH_3$; $R^2 = CO_2C_2H_5$

(281)


CHR¹CN
[H]
R
NO₂
879
NH₂
880
H
R¹
N
NH
881
882
neutral
solvent
H⊕
885
884
883
−NH₃
886

Scheme 82

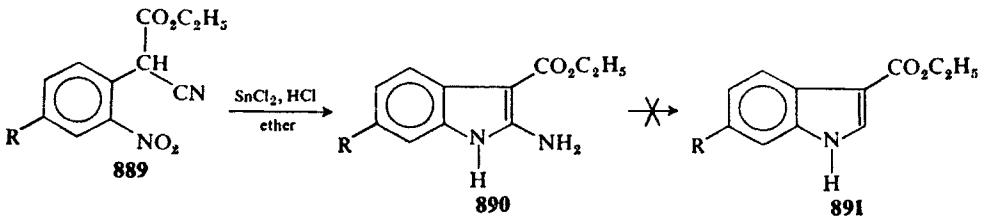
Walker has suggested[701] that the first step of the palladium-carbon catalyzed reductive cyclization of *o*-nitrobenzyl cyanides is rapid conversion of the nitro group to the amine **879** → **880**, which is then followed by addition of the amine to the cyano moiety to form an internal amidine **881** (Scheme 82). This might readiiy be converted to the tautomeric form **882**. Kebrle and Hoffmann[709] have stated that compounds usually considered as 2-aminoindoles, e.g., **884**, might exist instead either as the tautomeric isomer **881**, a 2-iminoindoline, or the isomer **882**, a 2-aminoindolenine. However, their pK_a, uv, and ir spectral studies clearly supported the 2-aminoindolenine structure **882**. Indeed it has been found[701] that the catalytic reduction of **887** produces only the indolenine **888**, although in this case there is no hydrogen atom at C-3 that could permit isomerization to a 2-aminoindole (Eq. 282).



(282)

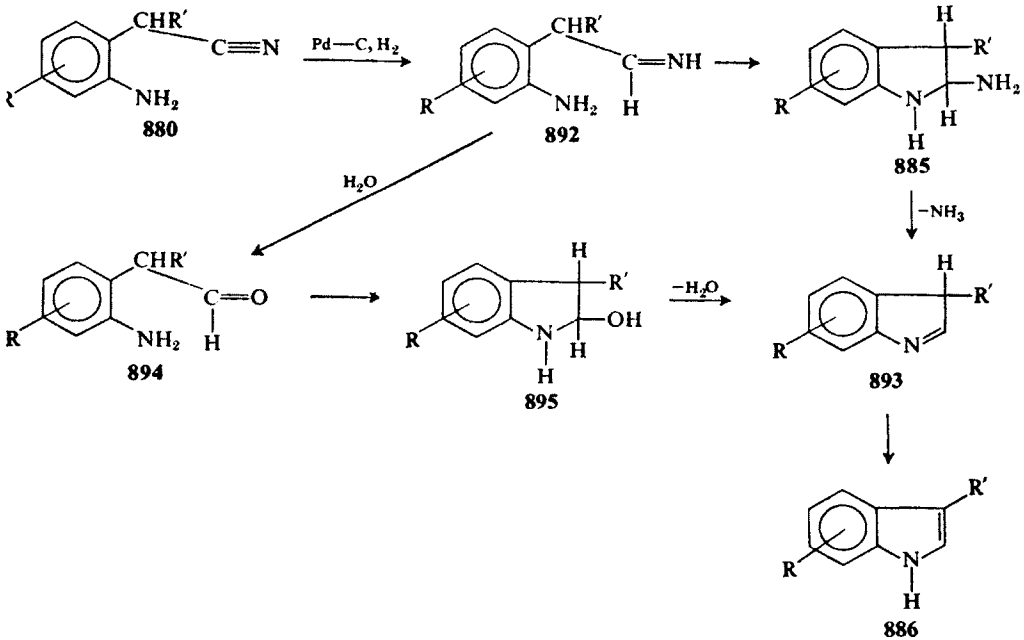
According to Walker's view,[701] the amidine **881**, formed in the second step of the reductive cyclization of **879**, under acidic conditions would form a protonated species **883** which resists further reduction due either to resonance stabilization of the amidinium ion **883** or because the protonated species is not absorbed on the catalyst surface. This could explain the failure of the *o*-nitrobenzyl cyanide **874** to provide an indole when hydrogenated in ethyl acetate–acetic acid solvent. However, in neutral solution the amidine **881**, because it possesses a hydrogen atom at C-3, could tautomerize to the 2-aminoindole **884**, which then under forcing reductive conditions loses the amino group to provide the indole **886**.[701] The alternative route to **886**, involving reduction of **884** to the 2-aminoindoline **885**, which then would lose ammonia to form the indole **886**, is thought to be less likely in view of the known resistance of the pyrrole ring double bond of indoles to hydrogenation in the presence of palladium-carbon catalyst.[701]

Snyder et al.[706] have been unable to repeat Stephen's reductive cyclization of *o*-nitrobenzyl cyanide to indole[703] but obtained instead an unidentified substance which was tentatively considered to be *o*-aminophenylacetaldimine (**865**). They did find[706] that the Stephen reagent (dry stannous chloride in ether saturated with hydrogen chloride) readily converted ethyl 4-carbethoxy-2-nitrophenylcyanoacetate (**889**, R = $CO_2C_2H_5$) or ethyl 2,4-dinitrophenylcyanoacetate (**889**; R = NO_2) in reasonably good yield to the corresponding 2-amino-3-carbethoxyindole (**890**; R = $CO_2C_2H_5$ or NH_2) but failed to produce the expected 3-carbethoxyindoles **891** (Eq. 283). They also found[706]



(283)

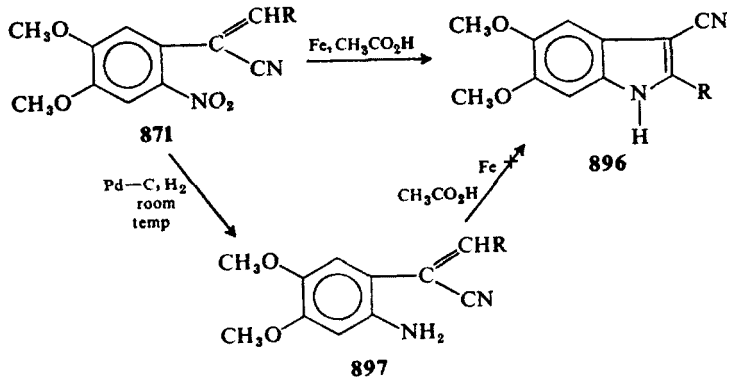
that palladium-carbon catalyzed hydrogenation of **889** (R = $CO_2C_2H_5$), provided 3,6-dicarbethoxyindole (**891**; R = $CO_2C_2H_5$) in 90% yield. A number of other *o*-nitrobenzyl cyanides, similarly reduced, gave the corresponding indoles, possessing no amino group at C-2. They discovered[706] that 2-amino-3,6-dicarbethoxyindole (**890**; R = $CO_2C_2H_5$) further hydrogenated with palladium-carbon catalyst under conditions more vigorous than those used to convert **889** to **891** was completely unchanged. This finding indicated that Walker's mechanism of the palladium-carbon reductive cyclization of *o*-nitrobenzyl cyanides to the indole, **879** → **880** → **881** → **884** → **886**, must be modified. It is suggested (Scheme 83)[706] that the *o*-aminobenzyl cyanide **880** is first reduced to the *o*-aminophenylacetaldimine **892** which then cyclizes to the 2-aminoindoline **885**. Subsequent loss of ammonia followed by



Scheme 83

tautomerization of the indolenine **893** would produce the indole **886**. Alternatively, the imine **892** could hydrolyze to **894**, cyclize to the 2-hydroxyindoline **895**, and then by loss of water and tautomerization form the indole **886**. The latter route would require only a catalytic amount of water.

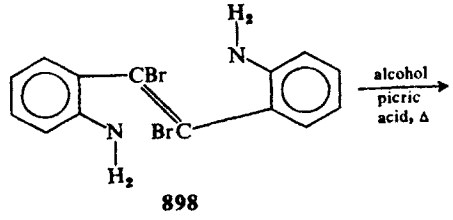
Suh and Puma[707] have shown that iron and acetic acid provides a means whereby 3-substituted-2-(4,5-dimethoxy-2-nitrophenyl)acrylonitriles **871** are reductively cyclized to 2,3-disubstituted indoles **896** in yields ranging from 39 to 83% (Eq. 284). It is significant that **871** (R = C_6H_5 or 3,4-dimethoxyphenyl), when reductively cyclized with palladium-carbon and hydrogen,



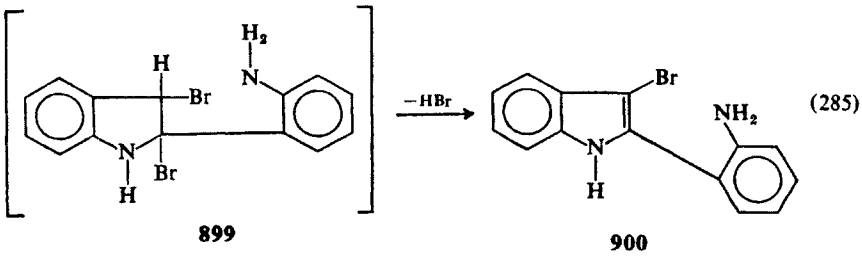
871 **896** **897** (284)

forms the indole **872** in which the cyano group has been involved in pyrrole ring formation,[701] while the action of iron and acetic acid on **871** (R = aryl) produces an indole in which the cyano group of **871** is retained intact as a substituent at C-3 in the indole **896**. The conversion of **871** → **896** has been successful with R as pyridyl, thienyl, furyl, substituted phenyl, or cyclohexyl.[707]

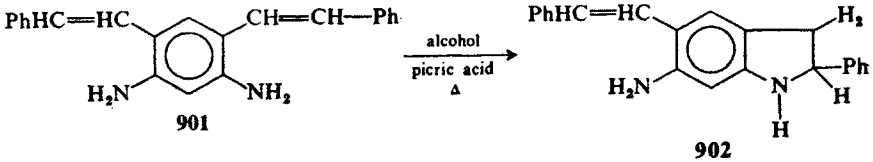
Since the amine **897**, obtained by room temperature hydrogenation of **871** with palladium-carbon, failed to produce an indole when treated with iron and acetic acid, it is considered that amine formation does not play a part in the conversion of **871** to **896** by iron and acetic acid.[707] It is known that phenylhydroxylamine is an intermediate in the reduction of nitrobenzene to aniline[710] and that *o*-aminostyrenes **898**, **901**[711, 712] are readily cyclized in the presence of an acid catalyst to the indolines, **899** and **902**, which could then form an indole if the indoline had a suitable leaving group at C-2 or C-3, e.g., **899** → **900** (Eqs. 285 and 286). On the basis of this information, Suh and Puma[707] proposed Scheme 84 as a route by which **871** is converted to **896**. The hydroxylamine **903** undergoes an internal Michael addition to form the indoline **904** which in turn loses water, no doubt catalyzed by the acid present, to provide first the indolenine **905** and subsequently the indole **896**.



898



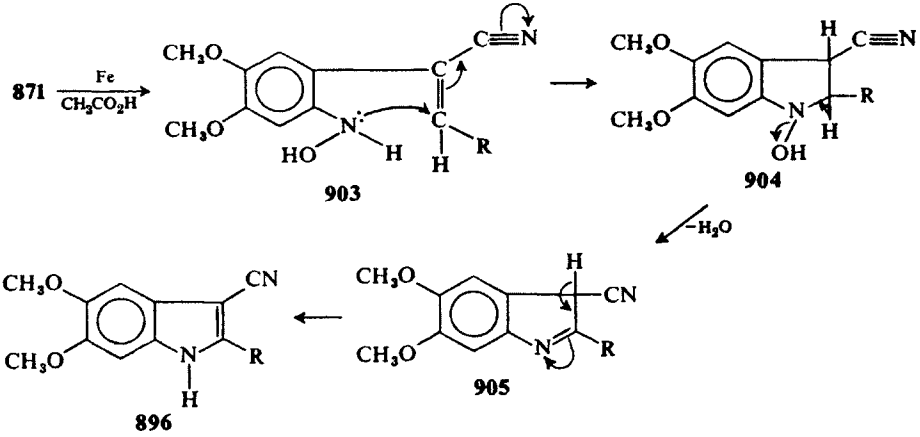
899 900 (285)



901 902

(286)

As in the case of the palladium-carbon catalyzed reductive cyclization of 2,β-dinitrostyrenes containing fluorine atoms in the aryl ring, similar reduction of 2-nitro-5-fluorobenzyl cyanide produces 5-fluoroindole in 84% yield,[380] thus showing that the fluorine atom is not removed under these circumstances.

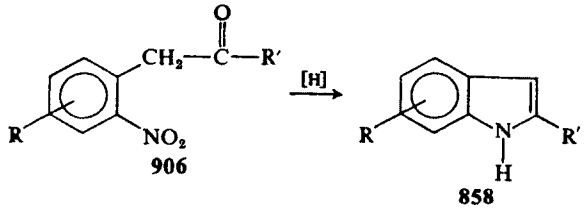


903 904 905 896

Scheme 84

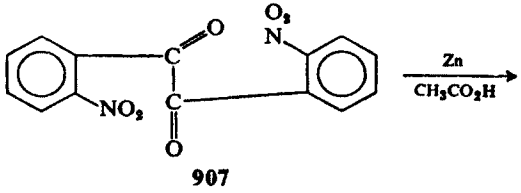
J. Indoles from the Reduction of *o*-Nitrobenzylcarbonyl Compounds

Closely related to the formation of indoles by reductive cyclization of 2,β-dinitrostyrenes and *o*-nitrobenzyl cyanides is the indole synthesis by reduction of *o*-nitrobenzylcarbonyl compounds. It had been shown before the turn of the century that zinc–ammonium hydroxide reduction of *o*-nitrobenzyl methyl ketone (**906**; R = H, R′ = CH_3) produced 2-methylindole (**858**; R = H, R′ = CH_3) though in 15% yield[713, 714] (Eq. 287). Similar reduction of *o*-nitrobenzyl phenyl ketone (**906**; R = H, R′ = Ph) gave 2-phenyl indole,[715] the same compound obtained by the pyrolysis of *N*-benzylidene-*o*-toluidine.[716] Stannous chloride reduction of 2,4-dinitrobenzyl phenyl ketone (**906**; R = 4-NO_2, R′ = Ph) has provided 6-amino-2-phenylindole (**858**;

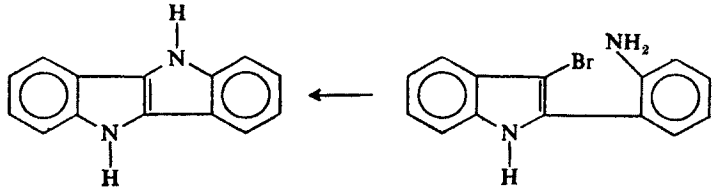


906 858 (287)

R = 6-NH_2, R′ = Ph),[717] while the same reducing agent has converted ethyl α-(2,4-dinitrophenyl)acetoacetate to ethyl 6-amino-2-methylindole-3-carboxylate in 10% yield.[217] The reaction of *o*,*o*′-dinitrobenzil (**907**) with zinc dust and acetic acid is reported[718] to give the diindole **908**, the same compound as was obtained by Ruggli[711] from 2-(*o*-aminophenyl)-3-bromoindole (**900**) (Eq. 288).



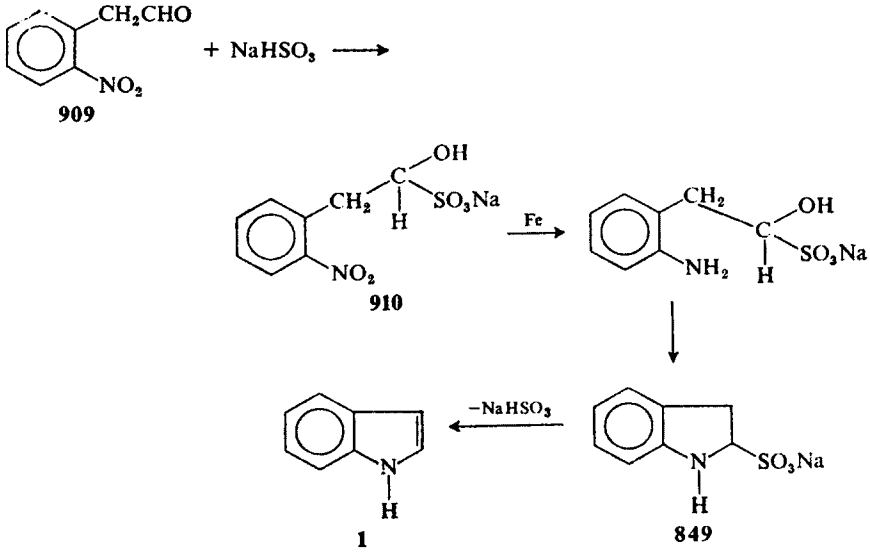
907



908 900 (288)

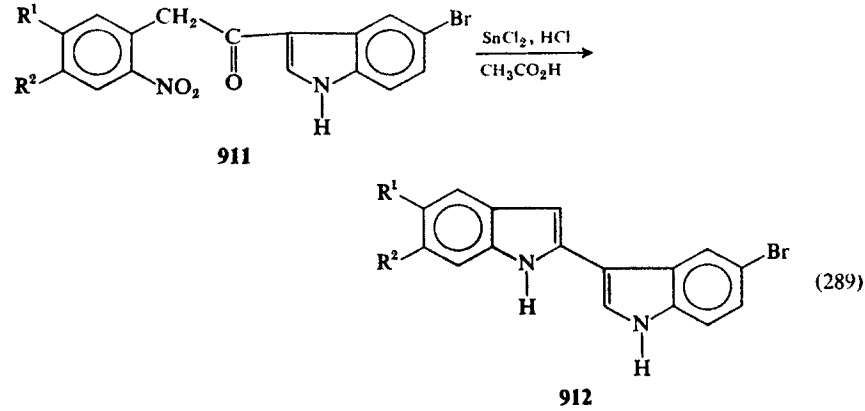
Weerman[719] had reduced *o*-nitrophenylacetaldehyde with iron powder in aqueous sodium bisulfite solution and obtained indole. Since aldehydes are known to add sodium bisulfite, Weerman proposed[720] that the *o*-nitrophenylacetaldehyde **909** first reacts with sodium bisulfite, and the adduct **910**

then is reduced to the amine which cyclizes to sodium indoline-2-sulfonate (**849**). This product then loses sodium bisulfite to become indole (Scheme 85).

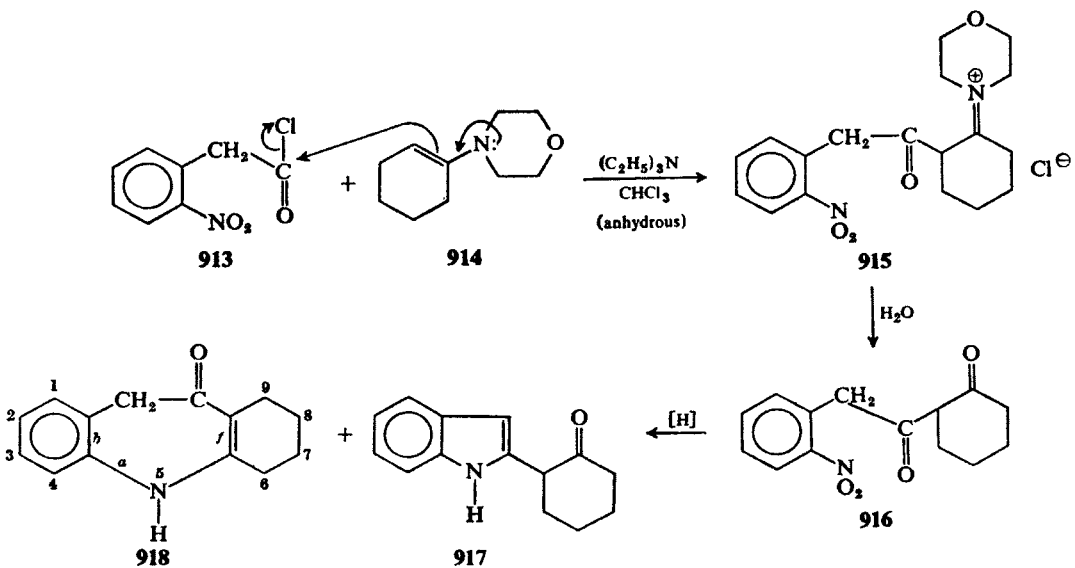


Scheme 85

Recently[279] 4- and 6-bromo-2-nitrobenzyl methyl ketone and 4- and 6-chloro-2-nitrobenzyl methyl ketone have been reduced with zinc dust and acetic acid to 6- and 4-bromo-2-methylindole and 6- and 4-chloro-2-methylindole, respectively, in yields from 51 to 91%. Stannous chloride reduction of 3-(4,5-dimethoxy-2-nitrophenylacetyl)-5-bromoindole (**911**; $R^1 = R^2 = CH_3O$) and 3-(4,5-methylenedioxy-2-nitrophenylacetyl)-5-bromoindole (**911**; $R^1-R^2 = OCH_2O$) has produced 5,6-dimethoxy-5′-bromo-2,3′-biindolyl (**912**; $R^1 = R^2 = CH_3O$) and 5,6-methylenedioxy-5′-bromo-2,3′-biindolyl (**912**; $R^1-R^2 = OCH_2O$) in 10 to 47% yield[721] (Eq. 289).



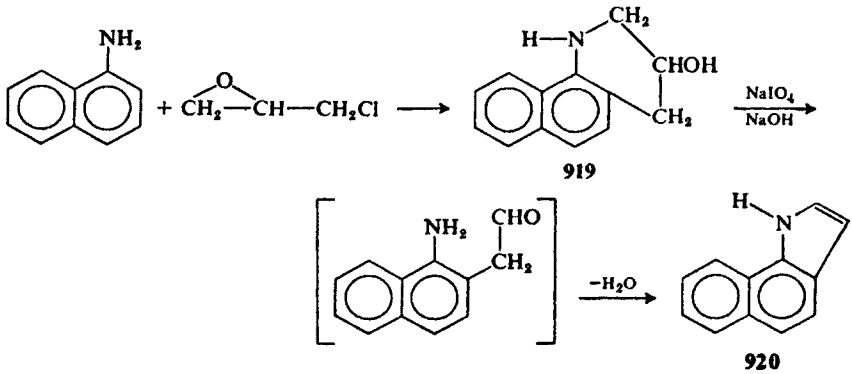
(289)



Scheme 86

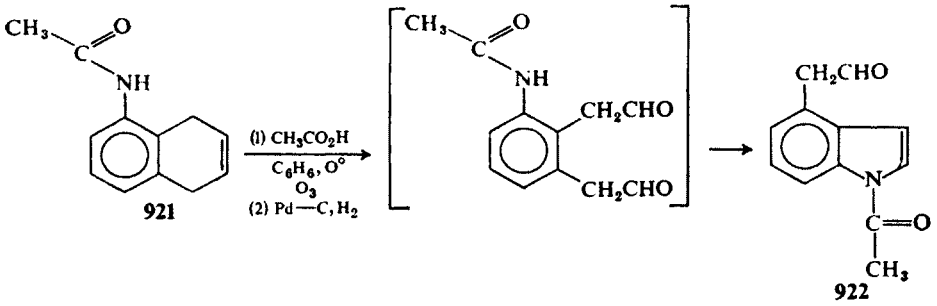
An interesting extension of the reductive cyclization of *o*-nitrobenzylcarbonyl compounds to indoles has been reported by Rosenmund and Haase.[722] Enamines obtained from the reaction of morpholine with ketones such as cyclohexanone, cyclopentanone, and acetophenone were allowed to react with *o*-nitrophenylacetyl chloride (**913**) to produce 1,3-diketones which in turn were reductively cyclized with palladium-carbon and hydrogen or preferably with anhydrous stannous chloride in ether to produce two products. The major product was a 2-substituted indole and the minor product was a benzazepin. This is illustrated in Scheme 86 by the reaction of 4-morpholinylcyclohexene (**914**) with *o*-nitrophenylacetyl chloride (**913**) to give the intermediate **915** which is decomposed with water to provide the 1,3-diketone **916**. The amino group, obtained by reduction, can react with the β-carbonyl group to produce the 2-(indolyl-2)-cyclohexanone (**917**) and with the δ-carbonyl group to give 10-oxo-6,7,8,9-tetrahydro-5*H*-dibenz[*b*,*f*]azepin (**918**) in yields of 72 and 10%, respectively, from **916**. The advantage of this sequence of reactions is that it provides a route to 2-substituted indoles that might otherwise be very difficult to prepare.

Related to the reactions above is the formation of 6,7-benzindole (**920**) in 27% yield from the sodium periodate oxidation of 7,8-benz-3-hydroxy-1,2,3,4-tetrahydroquinoline (**919**)[723] (Eq. 290). Similarly, oxidation of 5,6-benz-3-hydroxy-1,2,3,4-tetrahydroquinoline provides 4,5-benzindole in 30% yield.[723]



(290)

By using an improved procedure[724, 725] over that intially employed,[726] Plieninger and Suhr have treated 1-acetamino-5,8-dihydronaphthalene (**921**) with ozone followed by reduction of the ozonide with hydrogen in the presence of palladium-carbon catalyst[724, 725] or with Raney nickel[725] and obtained 1-acetylindole-4-acetaldehyde (**922**) in 70% yield (Eq. 291).

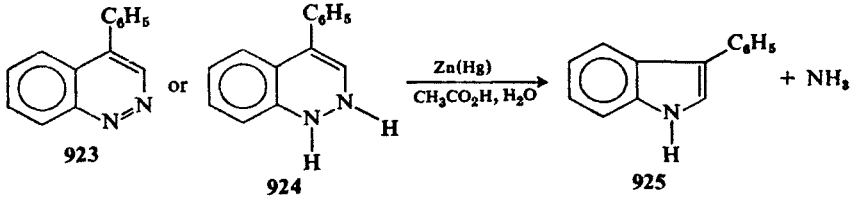


(291)

K. Miscellaneous Methods of Preparing Indoles

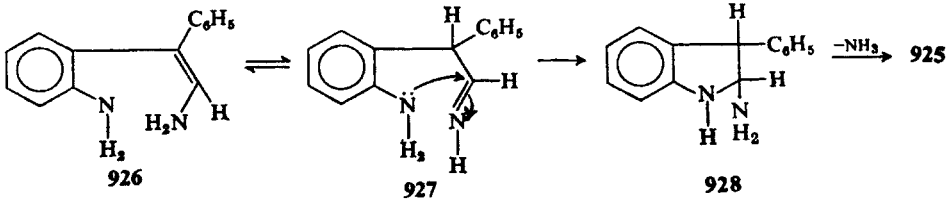
1. *Reduction of Cinnolines or Dihydrocinnolines*

Neber et al.[727] have shown that 4-phenylcinnoline (**923**) and its 1,2-dihydro derivative (**924**), when treated with amalgamated zinc and dilute aqueous acetic acid, are readily converted in good yield to 3-phenylindole (**925**) (Eq. 292). Reduction of the cinnoline **923** was thought[727] to provide first the 1,2-dihydro derivative **924** which then suffered cleavage of the N—N bond



(292)

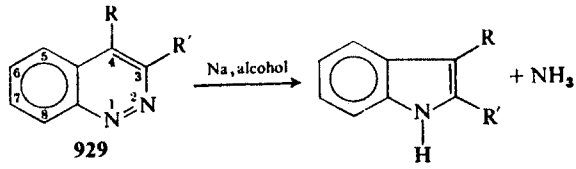
to form a diamine **926**. This diamine is similar to one of the intermediates in the mechanism proposed[160] for the Fischer indole synthesis.[9,10] The diamine **926** no doubt first tautomerizes to **927** which then cyclizes to the indoline **928**, a species that readily loses ammonia to form 3-phenylindole (**925**) (Eq. 293).



(293)

It was shown later[728] that several 4-substituted cinnolines could be converted to indoles by reduction with sodium in alcohol. The results obtained from these sodium and alcohol reductions are summarized in Table XI for the generalized structures **929** and **930**. The per cent ammonia evolved

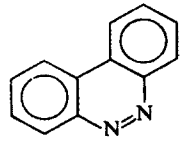
TABLE XI



929 **930**

Cinnoline			Cinnoline			
R	R′	NH_3 (%)	R	R′		NH_3 (%)
p-Anisyl	CH_3	58	*p*-Hydroxyphenyl	H		53
p-Hydroxyphenyl	CH_3	55	CH_3	H		65
p-Anisyl	C_6H_5	3	CH_3	H	6-Cl	57
p-Hydroxyphenyl	C_6H_5	1	CH_3	H	7-Cl	60
p-Anisyl	H	15				

represents the amount of the indole produced.[728] It is clear from the data that a phenyl group attached to C-3 of the cinnoline ring inhibits the conversion to the indole at some stage of the reaction, while a methyl group at either C-3 or C-4 generally facilitates the reaction, or at least fails to retard it. It is significant that if C-3 and C-4 of the cinnoline molecule form part of a fused ring system such as in 3,4-benzocinnoline (**931**), the molecule is much more stable to reduction, since such molecules are themselves produced from 2,2′-dinitrobiaryls by reduction, electrolytically, or in alkaline or acetic acid solution.[729–731] Regeneration of the pyridazine ring of compounds such as **931** from the corresponding 2,2′-diamines by diazotization and

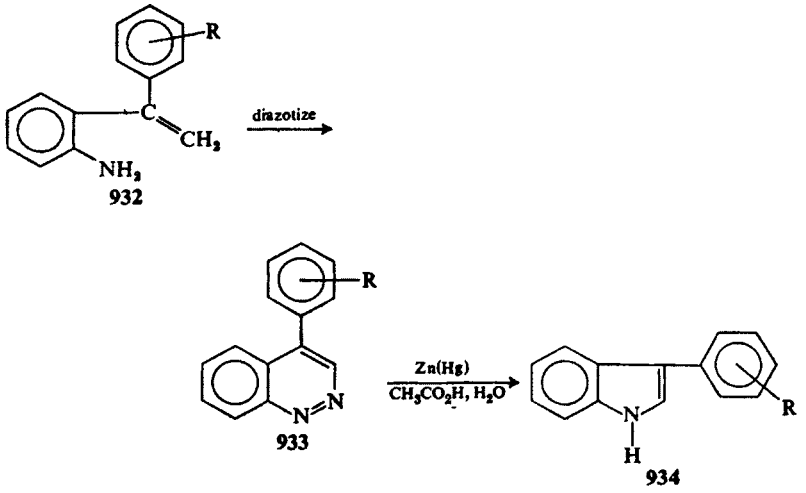


931

reduction appears to occur at least as readily as does the conversion of these diamines to the carbazoles.[732–735] These observations, as well as the results shown in Table XI, have led to the view[728] that steric as well as electronic factors must play a significant role in determining the ease of conversion of substituted cinnolines to indoles. It is to be noted that sodium in alcohol

reduction also removes the halogen atom when the 6- or 7-chlorocinnolines are cyclized to indoles.[728]

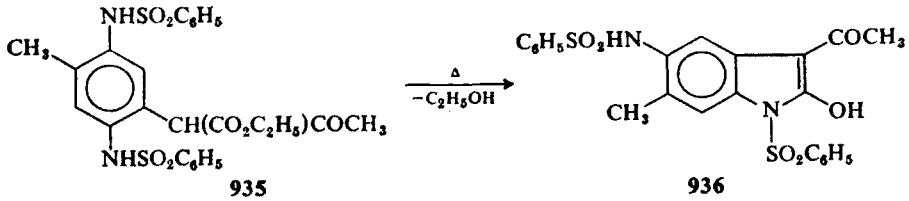
Recently the diazotization of several 1-(*o*-aminophenyl)-1-arylethylenes (**932**; R = H, 4-CH_3O, 2,5-di-CH_3O, 3,4-di-CH_3O, 2,3-di-CH_3O) has provided the corresponding 4-aryl- and 4-substituted(R)arylcinnolines **933**. These in turn have been reduced by zinc amalgam in aqueous acetic acid to give good yields of the corresponding 3-arylindoles **934**[736] (Eq. 294).



(294)

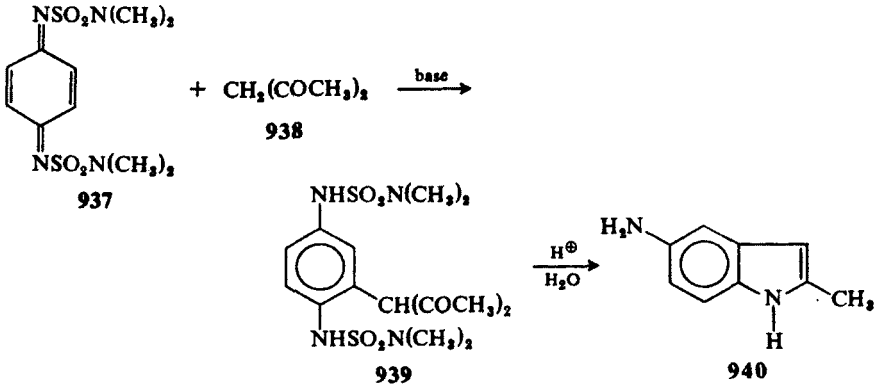
2. *Cyclization of p-Quinone Diimide Adducts to Indoles*

In a study of the addition of active methylene compounds such as β-diketones and β-ketoesters to *p*-quinone diimides, Adams and Blomstrom[737] had found that when the adduct, ethyl α-(2,5-dibenzenesulfonamido-4(?)-methylphenyl)-acetoacetate (**935**), was heated above its melting point it lost ethanol and was converted to 3-acetyl-5-benzenesulfonamido-6(?)methyl-oxindole (**936**) (Eq. 295). The exact orientation of the methyl group was not determined but believed to be *para* to the acetoacetate residue. Later work[738]



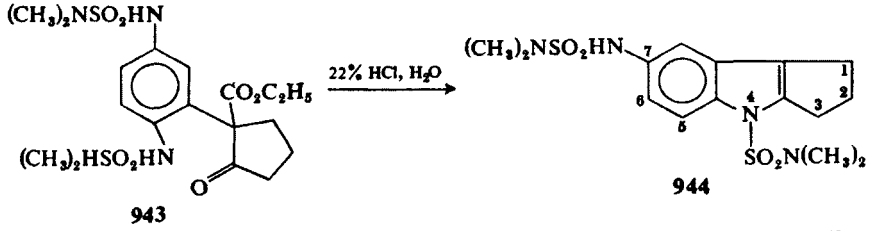
(295)

showed that the active methylene compound adducts of several *p*-quinonebis-(dimethylsulfamimides) or of 1,4-naphthoquinonebis-(dimethylsulfamimides), when heated in refluxing 48% hydrobromic acid or 22% hydrochloric acid, or treated with cold concentrated sulfuric acid, were converted readily to indoles. Thus, *p*-quinonebis(dimethylsulfamimide) (**937**) and acetylacetone (**938**) gave in nearly quantitative yield the adduct **939**, which in refluxing 48% hydrobromic acid or 22% hydrochloric acid was converted to 5-amino-2-methylindole (**940**) in 29 and 86.5% yield, respectively (Eq. 296). A number



(296)

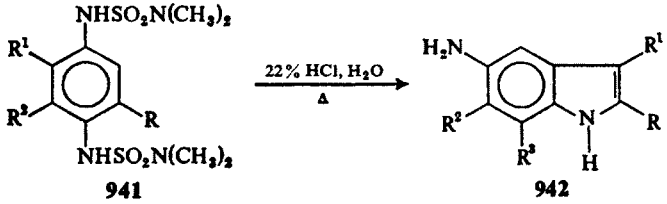
of such adducts were converted to the corresponding indoles when heated in refluxing 22% hydrochloric acid. These are shown in Table XII using the generalized structure of the adduct **941** and of the 5-aminoindole product **942**. The hot 22% hydrochloric acid generally removed both of the dimethylsulfamoyl groups as well as the substituent (acetyl, benzoyl, carbethoxy) at C-3. However, the adduct **943**, treated similarly, gave 7-dimethylsulfamoylamino-4-dimethylsulfamoyl-2,3-dihydro-1*H*-cyclopent[*b*]indole (**944**), (63% yield) (Eq. 297) with loss of only the carbethoxy group, while no groups were



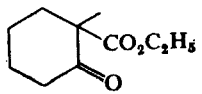
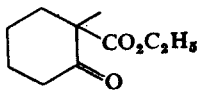
(297)

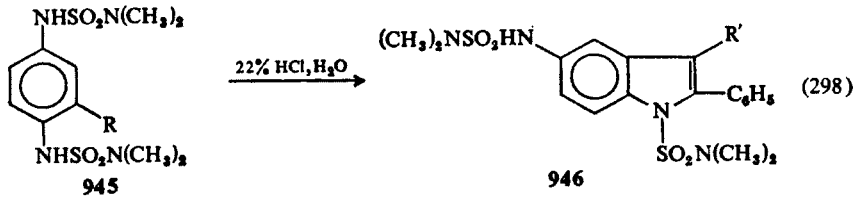
lost in the conversion of **945** [R = $CH(COC_6H_5)_2$ or $CH(COC_6H_5)CO_2C_2H_5$)] to **946** ($R^1 = COC_6H_5$, 88% yield; $R^1 = CO_2C_2H_5$, 84% yield, respectively) (Eq. 298).

TABLE XII

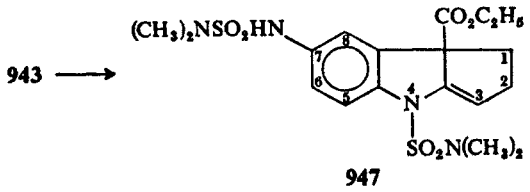


941 942

941			942				
R^1	R^2	R	R	R^1	R^2	R^3	942, % yield
H	H	—$CH(COCH_3)CO_2C_2H_5$	CH_3	H	H	H	86.5
H	H	—$CH(COCH_3)COC_6H_5$	CH_3	H	H	H	87
H	H	—$CH(COC_6H_5)CO_2C_2H_5$	C_6H_5	H	H	H	88.5
H	H		—$(CH_2)_4$—		H	H	79
H	H		—$(CH_2)_2CH(CH_3)CH_2$—		H	H	86.5
Cl	H	—$CH(COCH_3)_2$	CH_3	H	Cl (?)	H	71
$C_6H_5SO_2$	H	—$CH(COCH_3)_2$	CH_3	H	$C_6H_5SO_2$ (?)	H	55
Cl	Cl	—$CH(COCH_3)_2$	CH_3	H	Cl	Cl	83.5
Cl	Cl	—$CH(COC_6H_5)_2$	C_6H_5	H	Cl	Cl	55



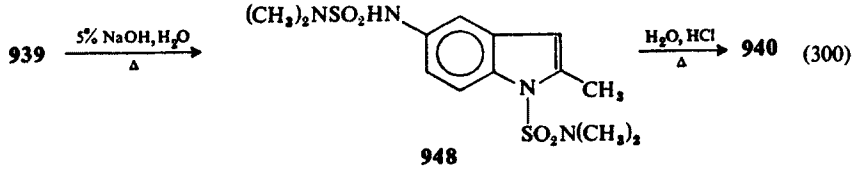
(298)



(299)

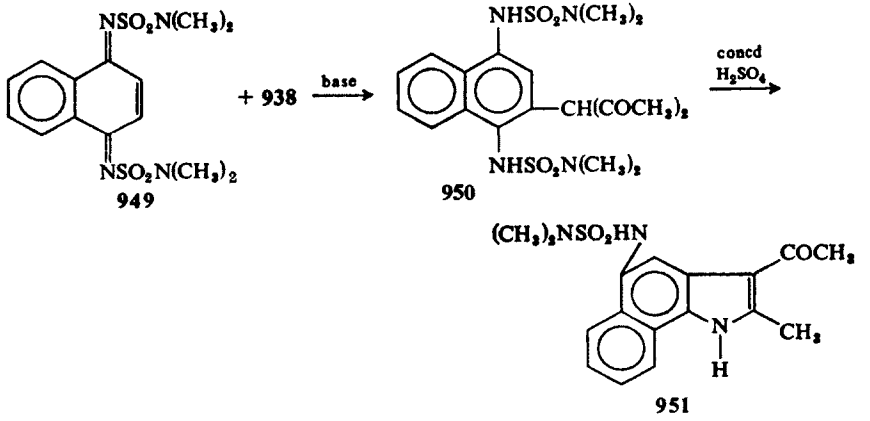
Cold concentrated sulfuric acid proved to be a much milder reagent and converted adducts **945** to the indole without removal of the 5-dimethylsufamoylamino group or the acetyl or benzoyl group at C-3, but generally removed the 1-dimethylsulfamoyl group and frequently a C-3 carbethoxy group. However, **943** under these conditions was converted to ethyl 4-(dimethylsulfamoyl)-7-[(dimethylsulfamoyl)amino]-2,4-dihydrocyclopent[*b*]-indole-8*b*(1*H*)carboxylate (**947**) in 90% yield (Eq. 299).

It is interesting that the adduct **939** when treated with hot 5% aqueous sodium hydroxide gave the indole **948** which could be hydrolyzed by hot dilute hydrochloric acid to 5-amino-2-methylindole (**940**) (Eq. 300).



(300)

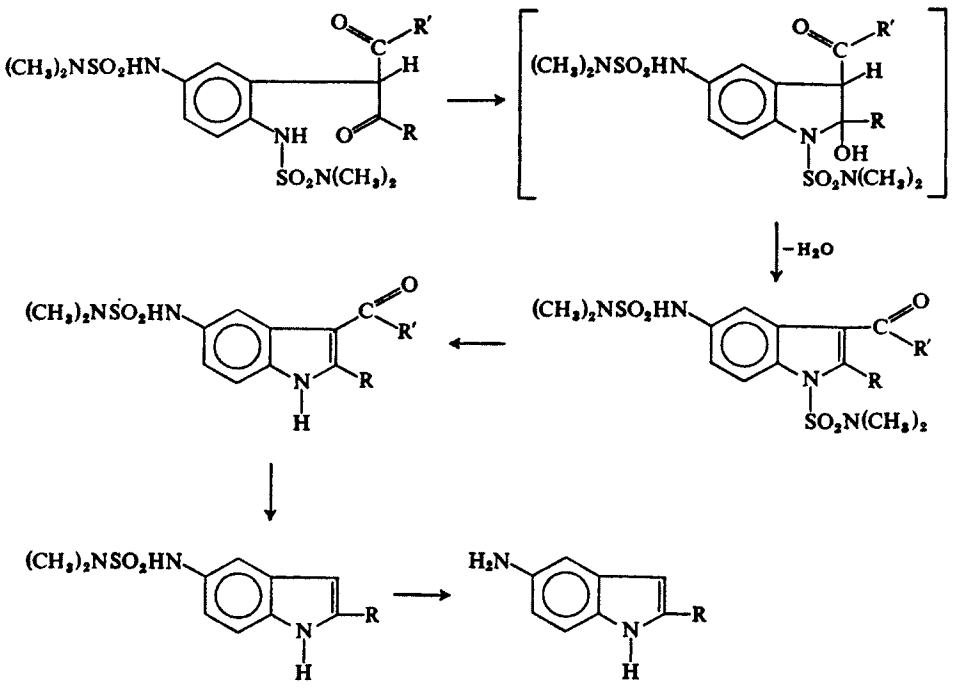
The adducts of 1,4-naphthoquinonebis(dimethylsulfamimide) (**949**) and acetylacetone (**938**) or the ethyl esters of acetoacetic acid or benzoylacetic acid failed to give an indole when heated in refluxing 20% hydrochloric acid. However, cold concentrated sulfuric acid converted **950** to 3-acetyl-5-dimethylsulfamoylamino-2-methyl-1*H*-benz[*g*]indole (**951**) (Eq. 301).



(301)

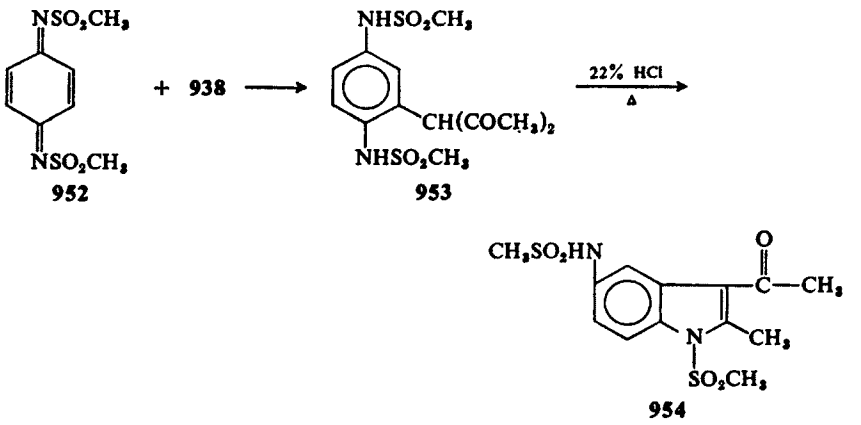
Adams and Samuels[738] have suggested Scheme 87 to describe the conversion of these quinone diimide adducts to the corresponding indoles, based upon the results of the experiments described above.

A subsequent publication[739] showed that the adduct **953** of *p*-quinonedimethanesulfonimide **952** and acetylacetone (**938**) gave 3-acetyl-5-methanesulfonamino-1-methanesulfonyl-2-methylindole (**954**) in yields of 90 and 48%,



R = CH_3 or C_6H_5; R′ = CH_3, C_6H_5, or OC_2H_5

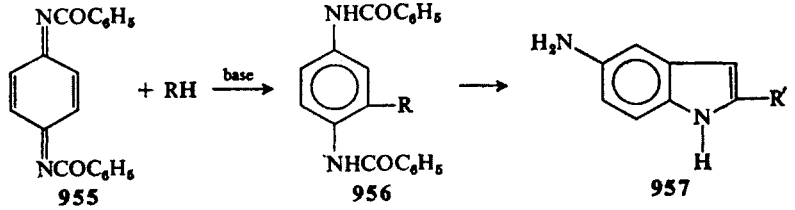
Scheme 87



952 953 954

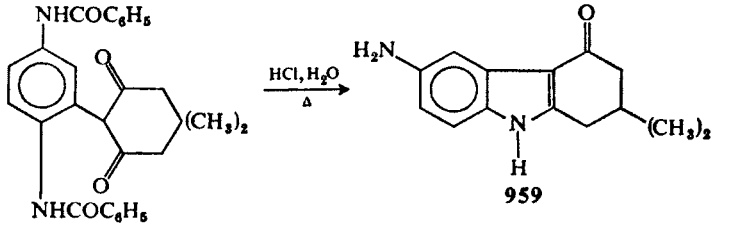
(302)

respectively, when heated in refluxing 22% hydrochloric acid or when treated with cold concentrated sulfuric acid (Eq. 302). Later work[740] showed that the adducts **956** [R = $CH(COCH_3)_2$ or $CH(COCH_3)COC_6H_5$] of *p*-benzoquinonedibenzimide **955** and acetylacetone or benzoylacetone, when heated in constant boiling hydrochloric acid, readily cyclized to the same 5-aminoindole **957** (R′ = CH_3) in excellent yield (Eq. 303). When the adduct



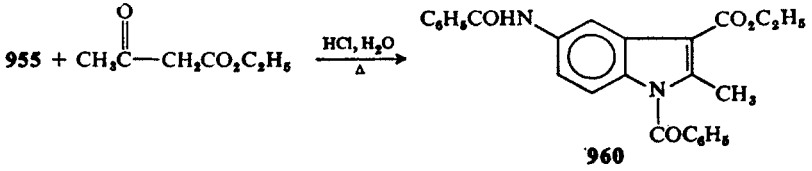
955 **956** **957** (303)

956 [R = $CH(COC_6H_5)_2$] was treated with warm concentrated sulfuric acid, the indole **957** (R′ = C_6H_5) was obtained. The methone adduct **958**, heated in constant boiling hydrochloric acid, gave in 60% yield a compound believed to be the carbazole derivative **959** (Eq. 304).



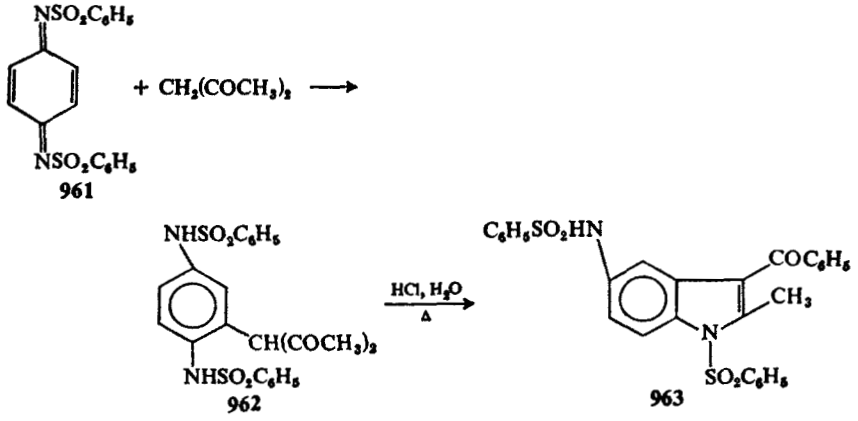
958 **959** (304)

No adduct of **955** and ethyl acetoacetate could be isolated, but if the *mixture* of **955** and ethyl acetoacetate was heated in constant boiling hydrochloric acid, the indole **960** was obtained (Eq. 305).



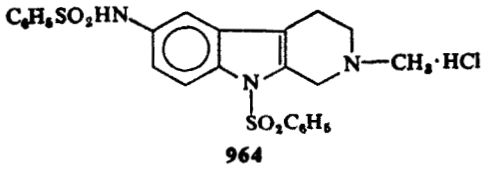
960 (305)

The adduct **962** of *p*-benzoquinonedibenzenesulfonimide (**961**) and acetylacetone, also heated in constant boiling hydrochloric acid, gave the indole **963**, which retained all the functional groups, while concentrated sulfuric acid gave the product **963** which had lost one of the benzenesulfonyl groups—considered to be that formerly attached to the pyrrole nitrogen (Eq. 306).



(306)

Treatment of an acetone solution of the 4-carbethoxy-1-methyl-3-piperidone adduct of **961** with constant boiling hydrochloric acid provided a product considered to be the hydrochloride of the β-carboline **964**, but all cyclization attempts on other heterocyclic adducts failed.[740]

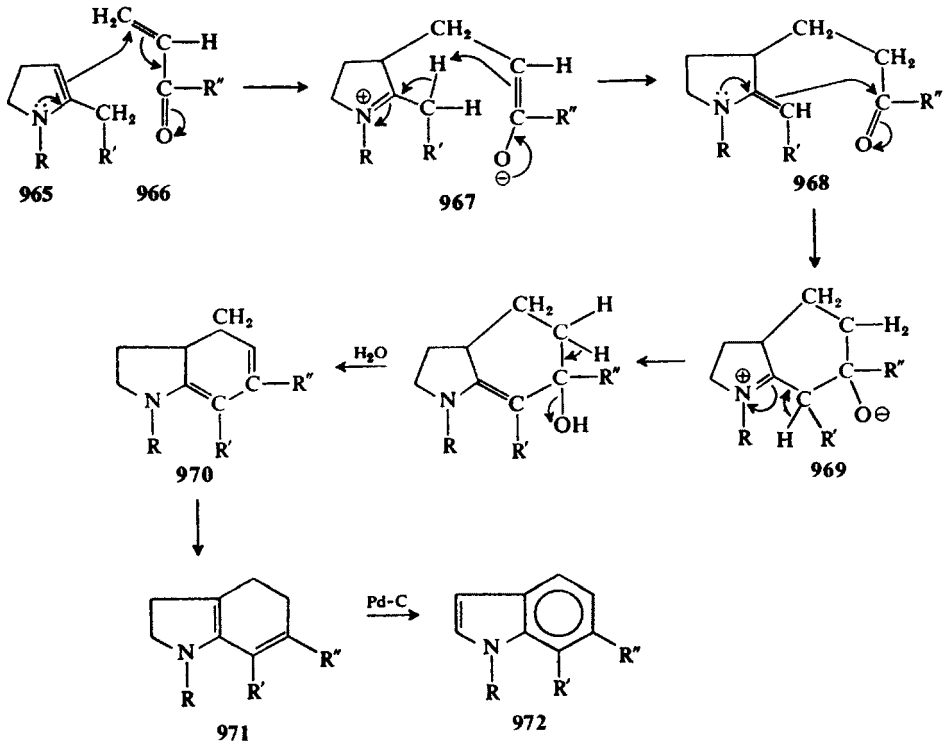


964

3. *From the Reaction of Enamines with α,β-Unsaturated Carbonyl Compounds*

A novel synthesis of *N*-alkylindoles has been reported,[741] involving a Michael-type condensation of cyclic enamines with α,β-unsaturated carbonyl compounds. The specific type of enamine required is the 1,2-dialkyl-Δ^2-pyrroline **965**. When **965** was heated in tetrahydrofuran with an α,β-unsaturated carbonyl compound **966**, an unstable base was obtained whose structure was considered to be that of **971** on the basis of its ir spectrum (Scheme 88). A similar structure has been suggested for the intermediate obtained when 2-methylindole reacted with methyl vinyl ketone to form 2-methylcarbazole eventually.[742]

Dehydrogenation of this base **971** in mesitylene with palladium on carbon provides the indole **972**. Yields of **972** were improved markedly if the base **971** was not first isolated. Thus, by condensing the enamine **965** (R = CH_3, R′ = H) with **966** (R″ = CH_3) in *p*-cymene, followed by addition of the



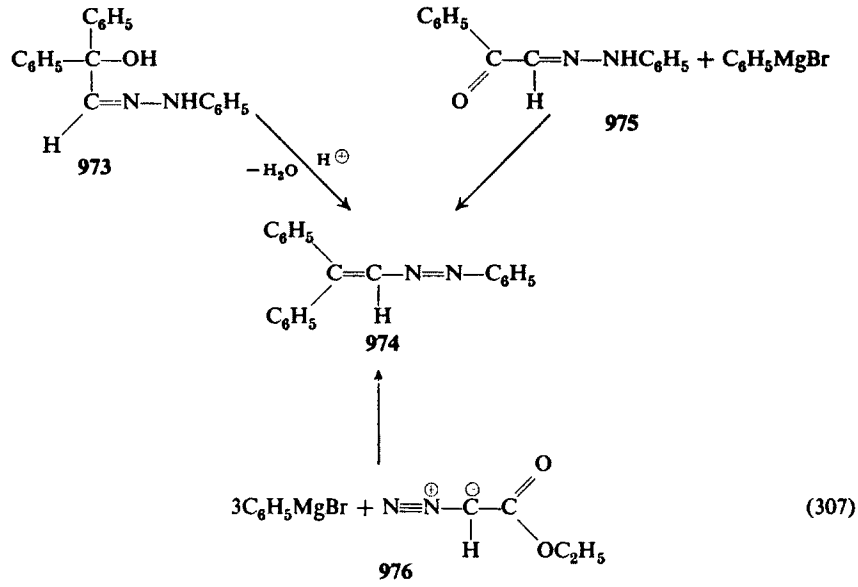
Scheme 88

palladium-carbon catalyst to the resulting solution to effect dehydrogenation, the yield of 1,6-dimethylindole (**972**; R = R″ = CH_3, R′ = H) was increased to 62 from 28%. By this modified method 1-methylindole, 1-methyl-6-phenylindole, and 1,7-dimethylindole were obtained in yields of 35, 46, and 33%, respectively, from the combinations of **965** (R = CH_3, R′ = H) and **966** (R″ = H); **965** (R = CH_3, R′ = H) and **966** (R″ = C_6H_5); and **965** (R = R′ = CH_3) and **966** (R″ = H).

The course of the reaction can be reasonably considered to follow the sequence **967** → **970** involving two enamine alkylations (Scheme 88).

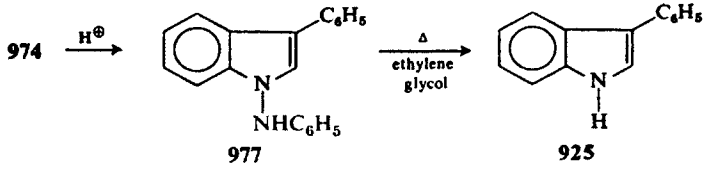
4. *Indole Ring Formation from β,β-Diphenylethyleneazobenzene*

It has been shown[743] that β,β-diphenylethyleneazobenzene (**974**) (Eq. 307) obtainable from the dehydration of diphenylglycolaldehyde phenylhydrazone (**973**) or the reaction of phenylmagnesium bromide with phenylglyoxal



(307)

phenylhydrazone (**975**) or the reaction of excess phenylmagnesium bromide with ethyl diazoacetate (**976**), when heated with warm acetic acid containing some sulfuric acid, was converted to 1-anilino-3-phenylindole **977** (Eq. 308).

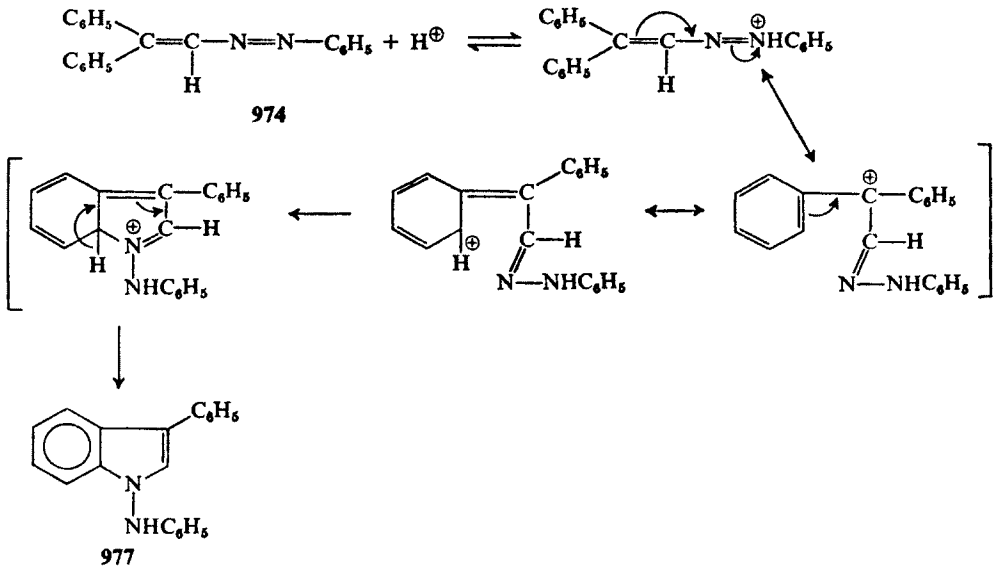


(308)

When **977** was heated in ethylene glycol, 3-phenylindole (**925**) was formed. The conversion of **974** to **977** is considered[743] to occur by the route given in Scheme 89.

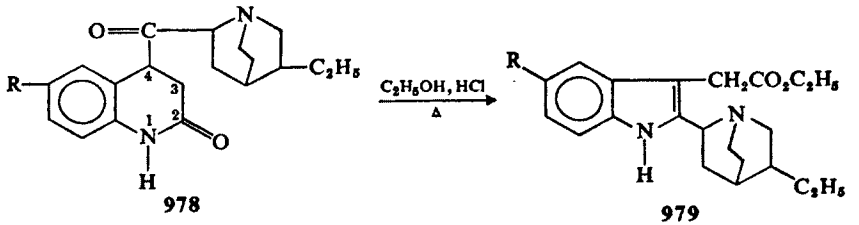
5. *Synthesis of Indole-3-acetic Acids from Quinoline*

The discovery[744] that the 2-oxo-1,2,3,4-tetrahydrocinchoninone (**978**; R = H or CH_3O), heated in ethanol containing hydrogen chloride, could be converted in good yield to the corresponding ethyl 2-(3′-ethyl-8′-quinuclidyl)-indole-3-acetate (**979**; R = H or CH_3O) has provided a new route to the formation of derivatives of ethyl indole-3-acetate from hydrocarbostyrils that have a carbonyl group at the C-4 position[745–753] (Eq. 309).



Scheme 89

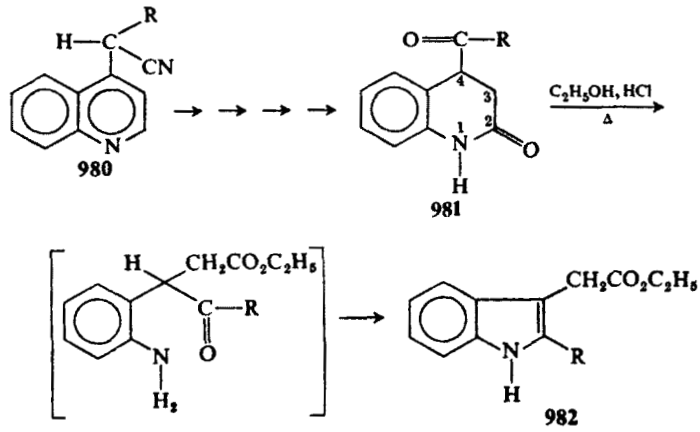
Both 4-(phenylcyanomethyl)quinoline (**980**; R = C_6H_5) and 4-(2′-pyridylcyanomethyl)quinoline (**980**; R = 2′-pyridyl) have been converted first to the 4-aroyl-3,4-dihydrocarbostyril (**981**) and this in turn, when heated in dry



(309)

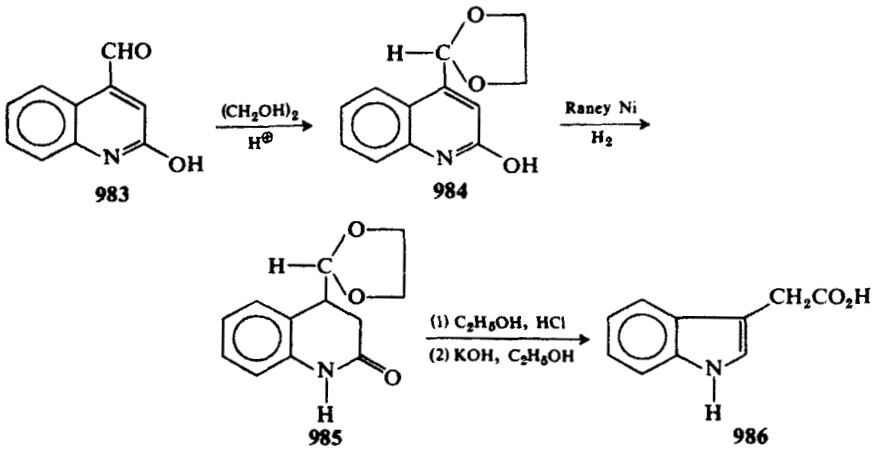
ethanol containing hydrogen chloride, formed ethyl 2-phenylindole-3-acetate (**982**; R = C_6H_5)[745] and ethyl 2-(2′-pyridyl)indole-3-acetate (**982**; R = 2′-pyridyl),[747] respectively. 4-Acetylquinoline has been converted by similar treatment[745] to ethyl 2-methylindole-3-acetate (**982**; R = CH_3) (Scheme 90).

By starting with 4-formyl-2-hydroxyquinoline (**983**) and protecting the formyl group of **983** by conversion to the ethylene acetal **984**, a reduction of **984** with Raney nickel and hydrogen provided 4-formyl-3,4-dihydrocarbostyril ethylene acetal (**985**). Subsequent reaction of **985** with alcoholic hydrogen chloride followed by treatment of the reaction product with potassium



Scheme 90

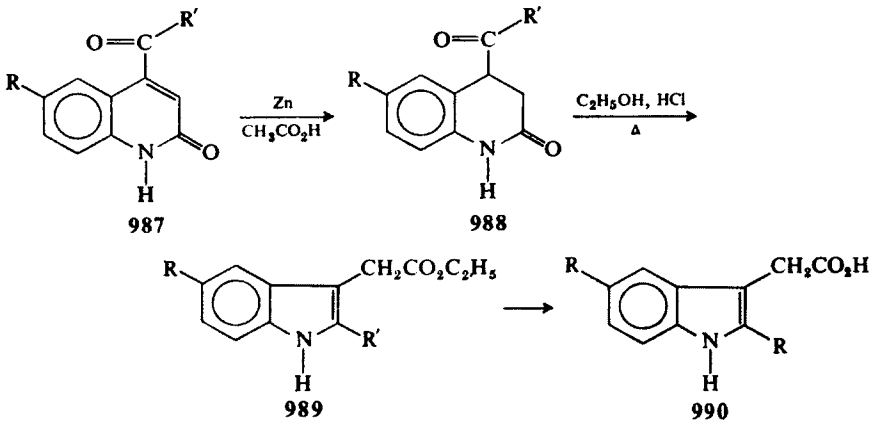
hydroxide and ethanol gave indole-3-acetic acid **986** without a substituent at C-2[750] (Scheme 91). The low yield of **986** obtained could be improved somewhat by prior benzoylation of **985**.[750]



Scheme 91

The reduction of 4-acetyl-6-methoxycarbostyril (**987**; R = CH_3O, R′ = CH_3) with zinc and acetic acid has produced 4-acetyl-6-methoxy-3,4-dihydrocarbostyril (**988**; R = CH_3O, R′ = CH_3) which was converted to ethyl 2-methyl-5-methoxyindole-3-acetate (**989**; R = CH_3O, R′ = CH_3) when heated in ethanolic hydrogen chloride.[749] This was then converted to the free acid **990** by hydrolysis with potassium hydroxide. Later work[751] showed that if the 3,4-dihydrocarbostyril **988** was heated with 47% hydrobromic acid or with concentrated hydrochloric acid, the yield of the

indole-3-acetic acid **990** was greatly improved. By this means, the following substituted indole-3-acetic acids **990** were obtained where R and R′, respectively, are H, C_6H_5; H, CH_3; CH_3O, CH_3; NO_2, CH_3; and CH_3O, C_6H_5[751] (Scheme 92).



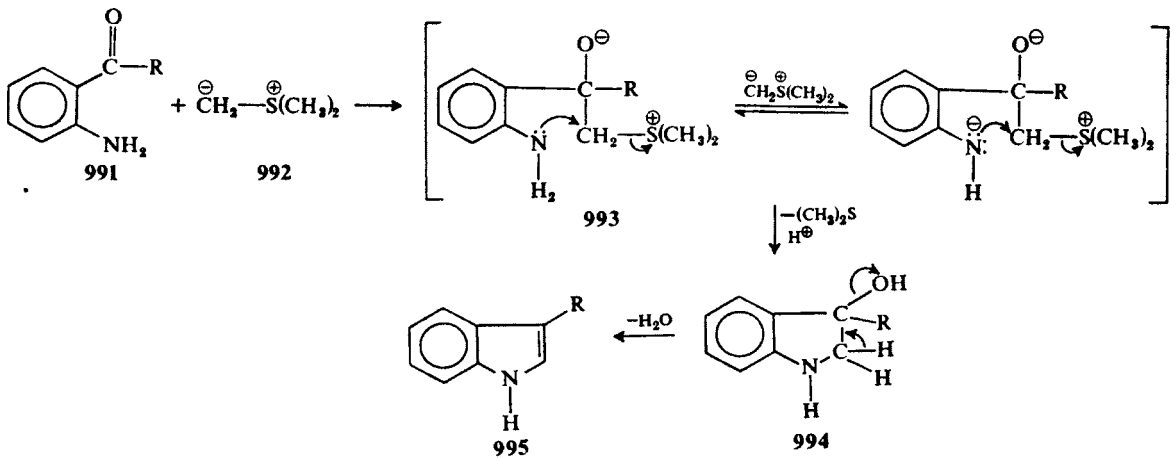
987 **988** **989** **990**

Scheme 92

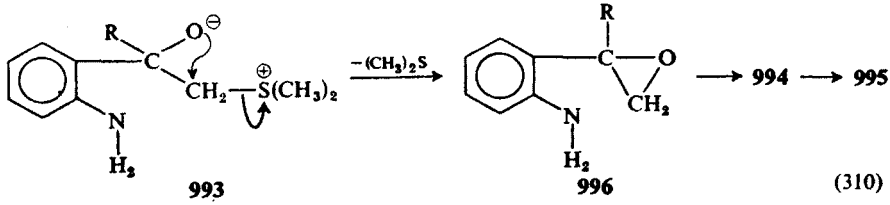
6. *Indoles from the Reaction of Dimethylsulfonium Methylide with Aromatic o-Aminocarbonyl Compounds*

The reaction of dimethylsulfonium methylide (**992**) with aromatic *o*-aminocarbonyl compounds **991**, carried out in tetrahydrofuran at −5°, has provided a number of indoles in yields of 5 to 95%.[752] The reaction is considered[752] to proceed by attack of the methylide **992** at the carbonyl moeity of **991** to produce an intermediate **993** which then, by an intramolecular attack either by the nucleophilic amino group or its anion, cyclizes to form the indoline **994** and dimethyl sulfide. Loss of water from **994** gives the indole **995** (Scheme 93).

Although the reaction of **992** with carbonyl compounds such as ketones is known to produce epoxides, the failure to obtain an epoxide such as **996** has led to the view[752] that it does not form, probably because of the greater nucleophilicity of the amine or amido group, and/or the lower energy required to form the five-membered dihydropyrrole ring compared to that necessary to form the three-membered oxirane ring. However, one cannot rule out the possibility that the oxirane **996** does form, and in turn reacts rapidly with, the amino group (or its anion) to form **994** (Eq. 310).


O
C—R
NH2
991
+ ⊖CH2—⊕S(CH3)2
992
O⊖
C—R
N
H2
CH2—⊕S(CH3)2
993
⊖CH2⊕S(CH3)2
O⊖
C—R
⊖N:
H
CH2—⊕S(CH3)2
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H⊕
OH
C—R
N
H
C—H
H
994
−H2O
R
N
H
995

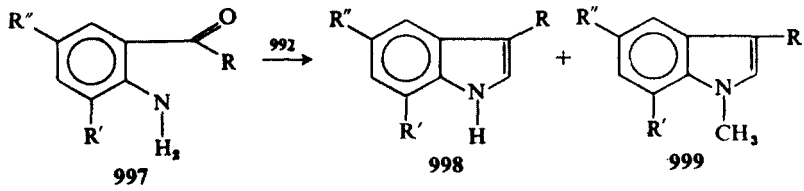
Scheme 93



(310)

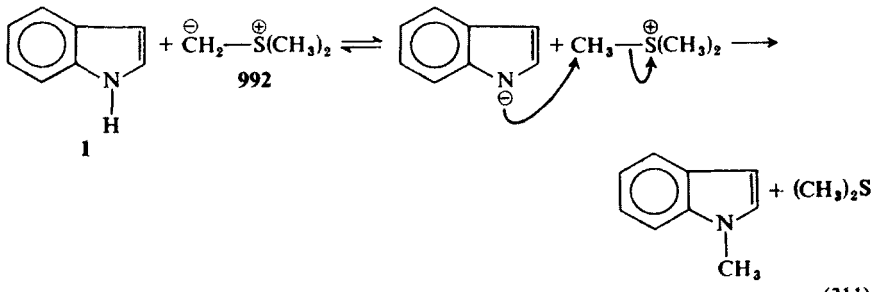
Indoles prepared by this method are shown in Table XIII using the generalized structures **997**, **998**, and **999**. In some cases the *N*-methyl derivative **999** is also formed. This might occur by methylation of the indole **998**[752] although

TABLE XIII



R	R″	R′	% yield of **998**	% yield of **999**
H	H	H	5	15
CH_3	H	H	80	14
C_6H_5	H	H	69	Trace
C_6H_5	Cl	H	72	0
COOH	H	H	40	0
COOH	Br	H	60	0
COOH	H	CH_3	61	0
COOH	Br	CH_3	95	0

prior methylation of the amino group of **997** is possible. Indole itself can be methylated at the nitrogen by reaction with dimethylsulfonium methylide (**992**), possibly by the sequence shown in Eq. (311).



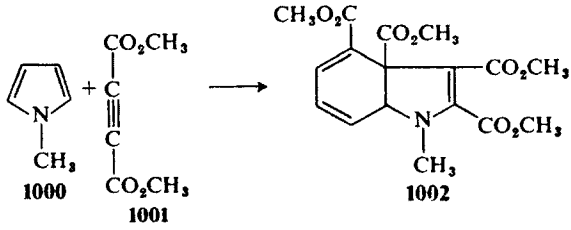
(311)

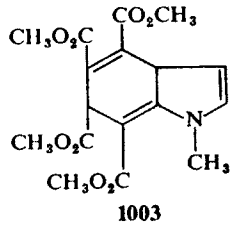
Dimethyloxosulfonium methylide $\overset{\ominus}{C}H_2—\overset{\oplus}{S}O(CH_3)_2$ was found to be much less effective in converting the *o*-aminocarbonyl compounds **991** to the indole **995**.[752]

This reaction appears to be quite useful for the preparation of C-3 and benzene ring-substituted indoles.

7. *Indoles from Reactions of Dimethyl Acetylenedicarboxylate*

a. WITH 1-ALKYLPYRROLES. The reaction of 1-methylpyrrole **1000** with dimethyl acetylenedicarboxylate **1001** at 0° for 48 hr gave in 70% yield the yellow 2:1 adduct tetramethyl 3*a*,7*a*-dihydro-1-methylindole-2,3,3*a*,4*a*-tetracarboxylate (**1002**[752a]) (Eq. 312). The same yellow product had been obtained from this reaction by Diels et al.[753] who considered its structure to be that shown by **1003**. However the nmr and ir data as well as the reactions of this adduct are in accord with structure **1002**. Oxidation of **1002** with

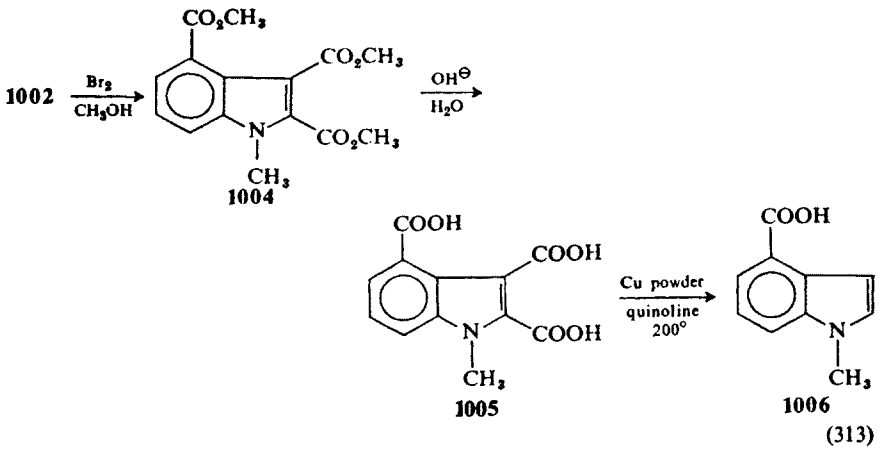




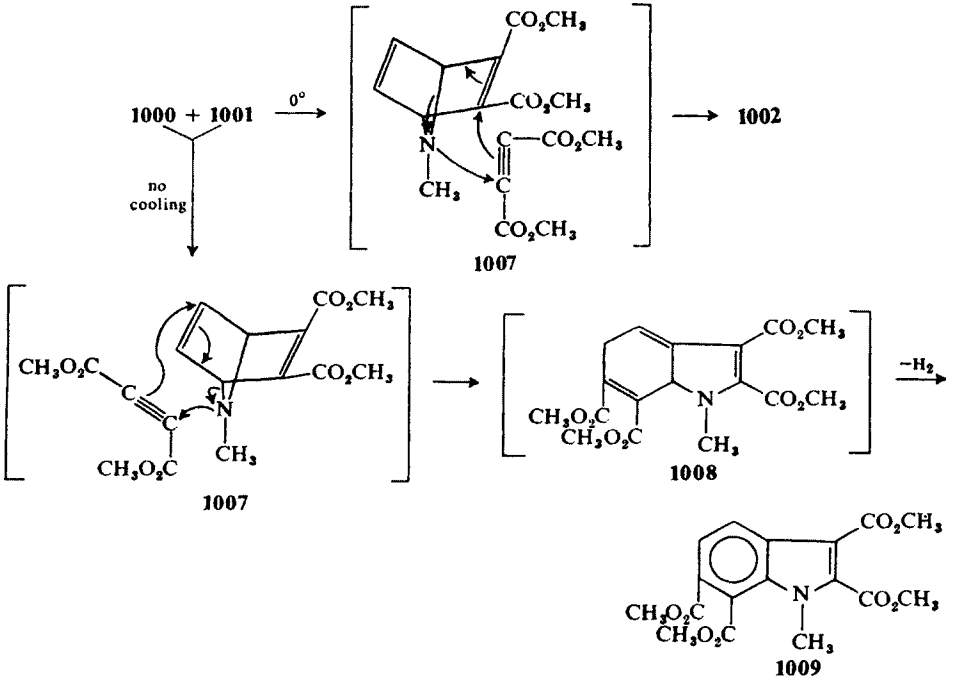
(312)

bromine in methanol produced trimethyl 1-methylindole-2,3,4-tricarboxylate (**1004**) which could be saponified to the tricarboxylic acid **1005** and decarboxylated to 1-methylindole-4-carboxylic acid (**1006**[752a]) (Eq. 313).

It is considered[752a] that the reaction of **1000** with **1001** to produce **1002** involves, as the first step, the Diels Alder 1:1 adduct **1007** given in Scheme 94. This has not been isolated but is believed to react with a second molecule of the ester **1001** by a type of Michael addition to form **1002**. The reaction is more vigorous if carried out without cooling, and produces several products among which is found tetramethyl 1-methylindole-2,3,6,7-tetracarboxylate (**1009**). This is believed to arise by the reaction of the 1:1 adduct **1007** with



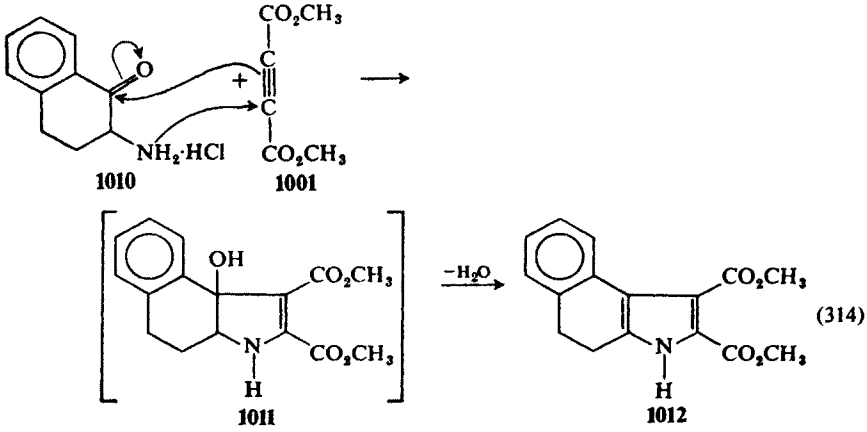
(313)



Scheme 94

the ester **1001** as indicated to form the 2:1 adduct **1008** which has not been isolated but is considered to dehydrogenate spontaneously under the reaction conditions to form **1009**.

b. WITH α-AMINOCYCLOHEXANONES. The known reaction of dimethyl acetylenedicarboxylate (**1001**) with α-aminoketones to produce pyrroles[754, 754a, 755] has led to the synthesis of 4,5-benz-6,7-dihydroindole systems by the reaction of the diester **1001** with α-aminocyclohexanones.[756] A methanolic solution of 2-aminotetralone-1 hydrochloride (**1010**) reacted with dimethyl acetylenedicarboxylate at 0° to produce a mixture consisting largely of dimethyl 4,5-benz-6,7-dihydroindole-2,3-dicarboxylate (**1012**). The product **1012** no doubt is formed by a Michael addition of the α-aminoketone to the acetylene diester **1001** to form first the unstable intermediate **1011**[754, 755] (Eq. 314).

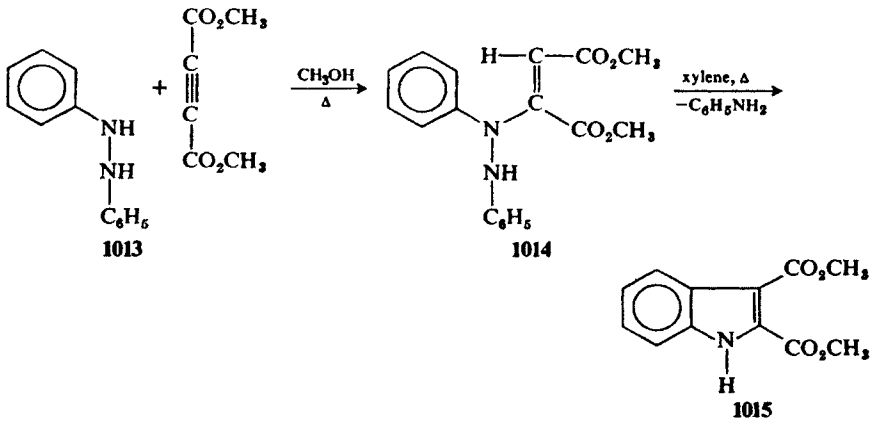


(314)

Although **1012** was not converted to the indole,[756] this could be accomplished quite readily by dehydrogenating agents such as chloranil.

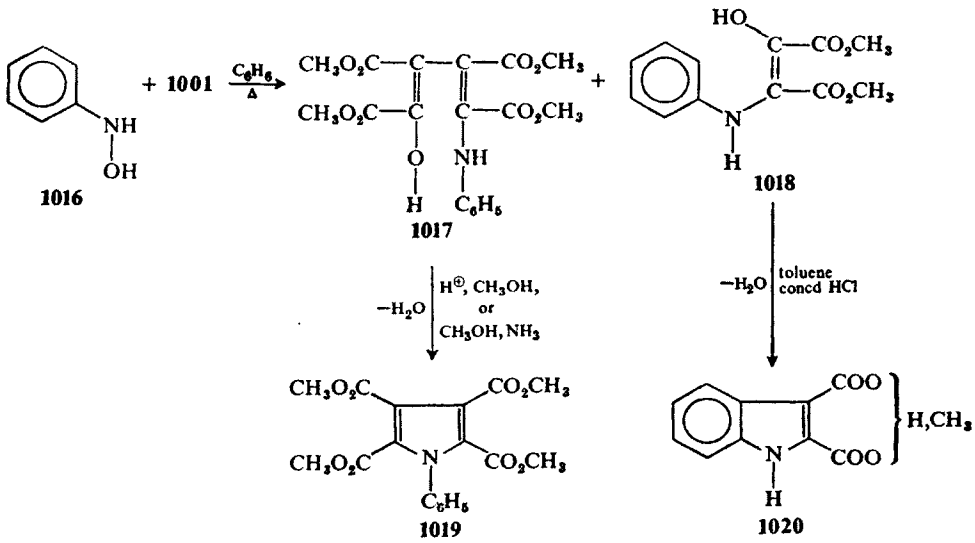
c. WITH HYDRAZOBENZENE OR *N*-PHENYLHYDROXYLAMINE. The reaction of hydrazobenzene (**1013**) and dimethyl acetylenedicarboxylate (**1001**) in hot methanol[757] has provided a 1:1 adduct **1014**, which when heated in boiling xylene produces a good yield of dimethyl indole-2,3-dicarboxylate (**1015**) with simultaneous expulsion of aniline (Eq. 315).

In an extension of this reaction, a later report[758] showed that a 1:2 molar proportion of *N*-phenylhydroxylamine (**1016**) and the diester **1001**, heated in refluxing benzene, gave a crystalline 1:2 adduct along with an orange, oily 1:1 adduct, which are considered[758] to have the structures **1017** and **1018**, respectively (Scheme 95). Treatment of **1017** with cold concentrated sulfuric acid, methanolic ammonia at room temperature, or refluxing methanol containing 1% hydrogen chloride gave tetramethyl 1-phenylpyrrole-2,3,4,5-tetracarboxylate **1019** in excellent yield. The orange oil **1018**, when dissolved in toluene and acidified with concentrated hydrochloric acid, gave a 46%



(315)

yield of the monomethyl ester of indole-2,3-dicarboxylic acid (**1020**). Similar results were obtained from the reaction of *N-p*-tolylhydroxylamine with dimethyl acetylenedicarboxylate.[758]

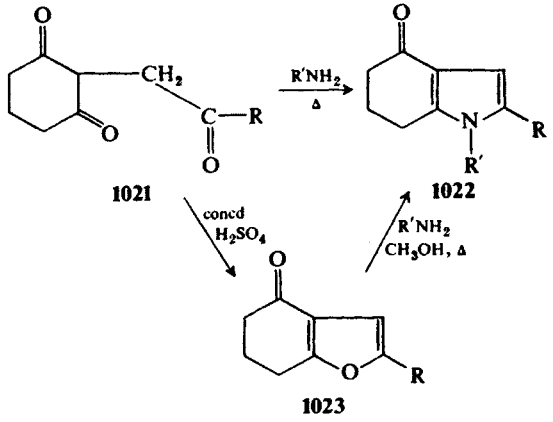


Scheme 95

8. *The Reaction of Primary Amines with the Condensation Product of* 1,3-*Cyclohexanediones and* α-*Haloketones*

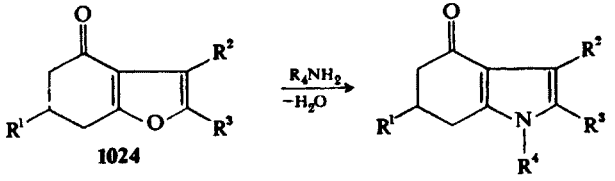
It has been shown[759, 760] that ammonia or primary amines can react with 1-phenacyl-2,6-cyclohexanedione (**1021**; R = C_6H_5) or with 1-acetonyl-2,6-cyclohexanedione (**1021**; R = CH_3) to form 4-oxo-4,5,6,7-tetrahydroindoles

1022 (R = C_6H_5, R′ = H or C_6H_5; R = CH_3, R′ = H, CH_3, or C_6H_5) in good yield (Eq. 316). If **1021** is first cyclized by concentrated sulfuric acid



(316)

to the 2-substituted 4-oxo-4,5,6,7-tetrahydrocoumarone **1023** and this is heated in methanol with ammonia or a primary amine, the 4-oxo-4,5,6,7-tetrahydroindole **1022** is obtained in even better yield.[760] The 4-oxo-4,5,6,7-tetrahydroindoles **1025** listed in Eq. (317) have been obtained from the

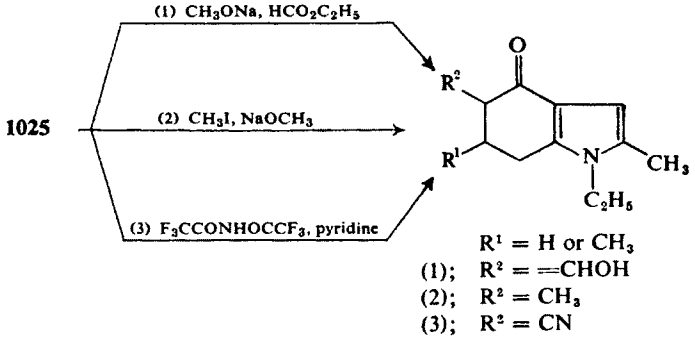


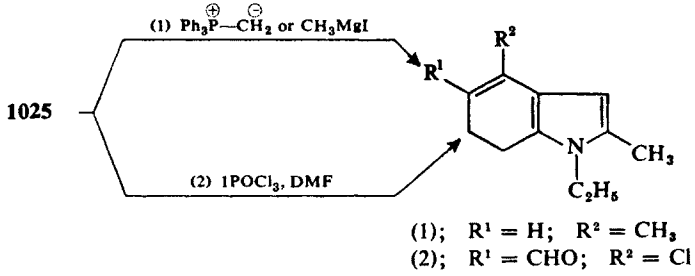
(317)

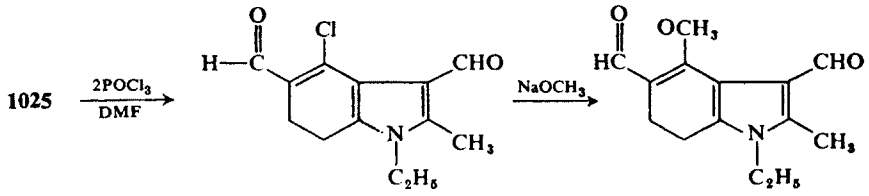
R^1	R^2	R^3	R^4
H	H	CH_3	H
H	H	CH_3	CH_3
H	CH_3	H	H
H	CH_3	H	CH_3
CH_3	H	CH_3	H
H	CH_3	CH_3	H
CH_3	CH_3	H	H
CH_3	CH_3	CH_3	H

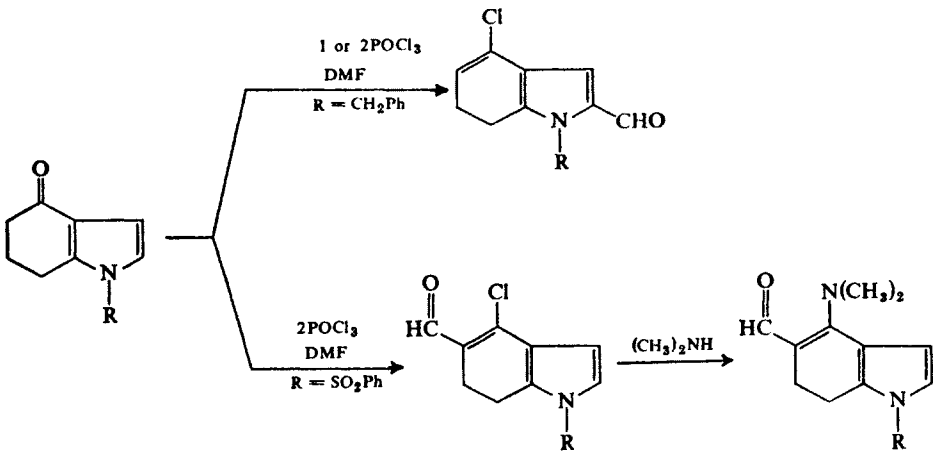
respective 4-oxo-4,5,6,7-tetrahydrocoumarones **1024** ($R^2 = R^3 = CH_3$ or COOH) in this way.

The coumarones **1024**, having a carboxyl substituent as R^2 or R^3, are decarboxylated during this conversion to the 4-oxo-4,5,6,7-tetrahydroindole **1025** ($R^2 = R^3 = H$).


(1) CH_3ONa, $HCO_2C_2H_5$
1025
(2) CH_3I, $NaOCH_3$
(3) $F_3CCONHOCCF_3$, pyridine
R^1 = H or CH_3
(1); R^2 = =CHOH
(2); R^2 = CH_3
(3); R^2 = CN


(1) $Ph_3\overset{\oplus}{P}-\overset{\ominus}{C}H_2$ or CH_3MgI
1025
(2) $POCl_3$, DMF
(1); R^1 = H; R^2 = CH_3
(2); R^1 = CHO; R^2 = Cl


1025
$2POCl_3$
DMF
$NaOCH_3$


1 or $2POCl_3$
DMF
R = CH_2Ph
$2POCl_3$
DMF
R = SO_2Ph
$(CH_3)_2NH$

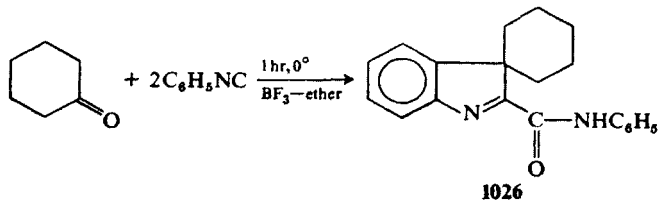
Scheme 96

The formation of 4-oxo-4,5,6,7-tetrahydroindoles in this manner has been utilized to develop a versatile method of synthesizing indoles,[761, 762] particularly those having substituents at C-4 or at both C-4 and C-5 as well as at C-2 and/or C-3 or on the nitrogen atom. This is due to the fact that the 4-oxo-4,5,6,7-tetrahydroindoles lend themselves readily to a number of substitution reactions. Those involving base catalysis are successful only if the nitrogen atom of **1025** is substituted. Dehydrogenation of these substituted 4-oxo-4,5,6,7-tetrahydroindoles then provides the substituted indole. The reactions given in Scheme 96 illustrate the scope of this method.

Dehydrogenation of these 4-oxo products is accomplished best with 10% palladium on carbon in refluxing cumene to give the corresponding 4-hydroxyindoles in yields of ~ 40–45%. The yield of the 4-hydroxyindole is decreased if a methyl group is attached to C-5. The use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as dehydrogenating agent[763] was unsuccessful except in the cases which contained a formyl substituent.

9. *Indoles from the Reaction of Ketones with Aromatic Isocyanides*

Zeeh[764, 765] had reported that the reaction of aromatic isocyanides with cycloalkanones in the presence of boron trifluoride etherate at low temperatures produced indolenines in fair yield. Thus cyclohexanone and phenyl isocyanide gave spiro[indolenine-3,1′-cyclohexane]-2-carboxanilide (**1026**) in 40% yield (Eq. 318). Similarly spiro[indolenine-3,1′-cycloheptane]-2-

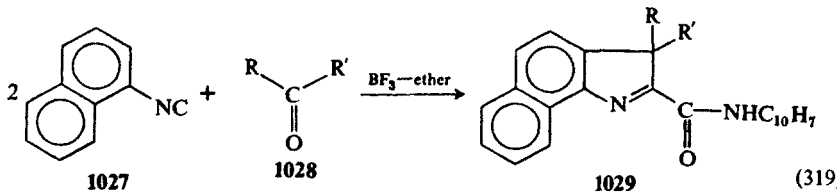


(318)

1026

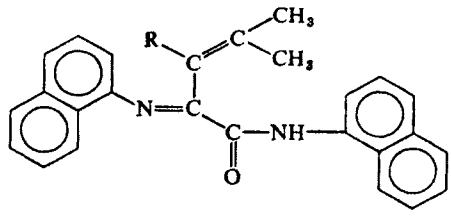
carboxanilide was obtained in 30% yield from cycloheptanone.

The same system applied to the reaction of 1-naphthyl isocyanide (**1027**) with a series of aliphatic ketones **1028** gave 3*H*-benz[*g*]indole-2-carboxylic acid naphthyl amides **1029** (Eq. 319).[766] If the substituents R or R[1] of the



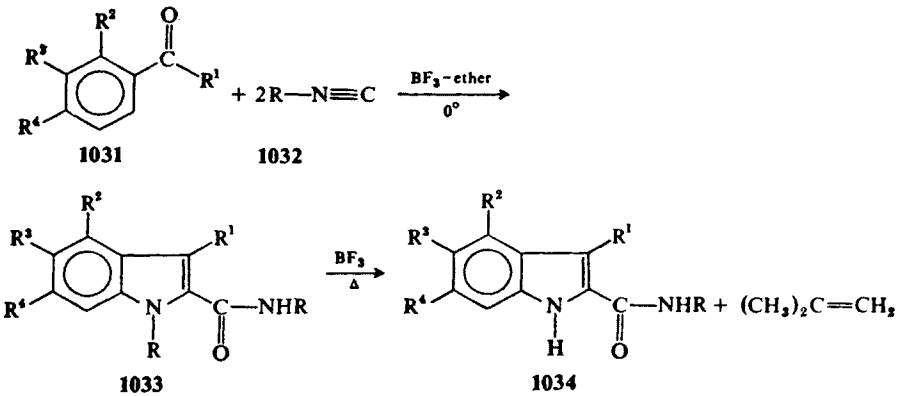
1027 **1028** **1029** (319)

ketone **1028** are bulky, then cyclization to the indolenine is hindered or even completely suppressed,[766] and in such cases the alterntive product **1030** is formed (e.g., for R′ = *i*-C_3H_7).



1030

When the reaction was extended to aromatic ketones, indoles were obtained in 15–40% yield.[767, 768] The reaction of benzophenone (**1031**; $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = H$) with *t*-butyl isocyanide (**1032**; R = *t*-C_4H_9) provided 1-*t*-butyl-3-phenylindole-2-carboxylic acid *t*-butylamide in 30% yield based on the isocyanide, or 90% yield based on the benzophenone consumed. If the product **1033** is warmed with the boron trifluoride etherate, the *t*-butyl substituent on the nitrogen atom is readily removed as isobutylene. In some cases the loss of the *t*-butyl group from the pyrrole nitrogen occurs during the cyclization reaction. Base-catalyzed hydrolysis of the product **1034** produces the indole-2-carboxylic acid (Eq. 320).



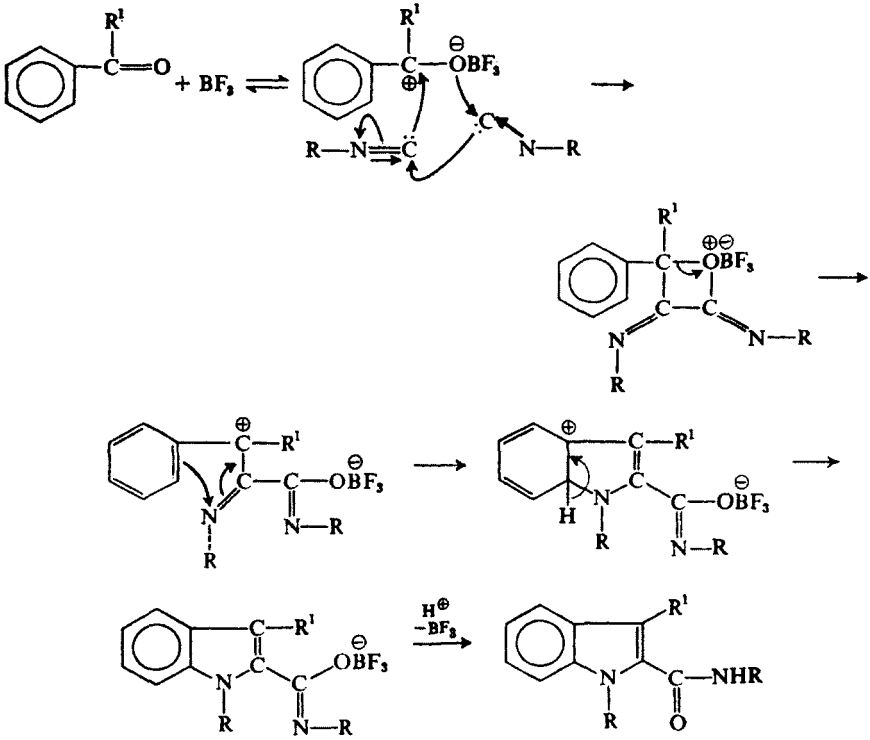
1031 **1032** **1033** **1034**

(320)

The isocyanide reaction provides a simple route to the indole structure under mild conditions. The indoles listed in Table XIV have been prepared by this method.[767, 768] The mechanism in Scheme 97 has been suggested[768] to explain the course of this reaction.

TABLE XIV

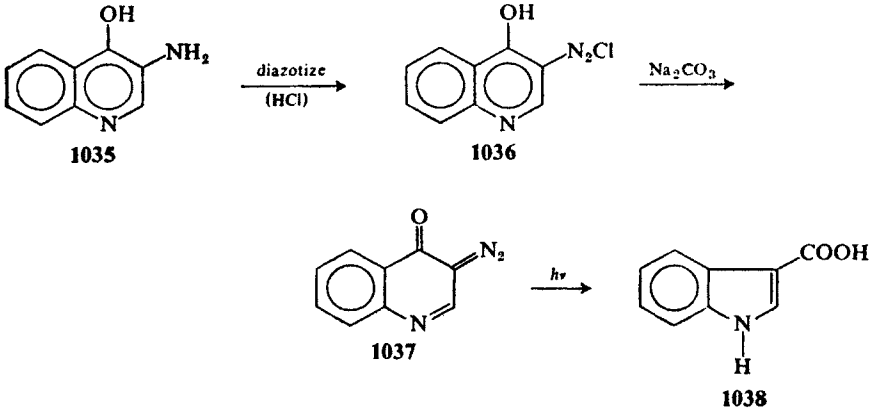
R^1	R^2	R^3	R^4
C_6H_5	H	H	H
COC_6H_5	H	H	H
CH_3	H	H	H
CH_3	H	H	C_6H_5
CH_3	H	H	Cl
CH_3	OCH_3	H	H
CH_3	H	H	OCH_3
CH_3	H	t-C_4H_9	OH
└$(CH_2)_3$┘		H	H



Scheme 97

10. *Indoles from Light Irradiation of o-Quinone Diazides*

It has been shown that *o*-quinone diazides obtained from suitably substituted quinolines, when irradiated, experience a ring contraction, and this provides a route for the conversion of quinoline to indole.[769] The quinoline required for this purpose was 3-amino-4-hydroxyquinoline (**1035**) which gave a solid isolable diazonium salt **1036**. Treatment of **1036** with sodium carbonate solution gave quinoline 3,4-quinone-3-diazide **1037**, a crystallizable solid which upon irradiation was converted smoothly to indole-3-carboxylic acid **1038** in about 50% yield based on **1037** (Eq. 321). Since a number of substituted 3-amino-4-hydroxyquinolines are readily prepared, this method is useful

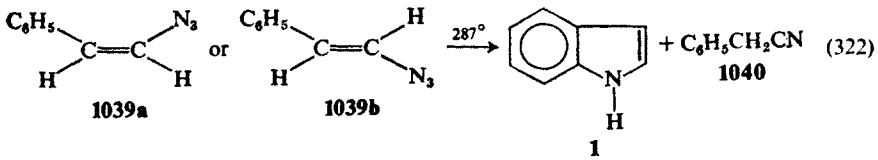


(321)

for the preparation of benzene ring-substituted indoles. Both 5-chloro- and 5,7-dimethoxyindole-3-carboxylic acid have been thus prepared.[769] The reaction has also been extended to the preparation of 5,6-benzindole.[769]

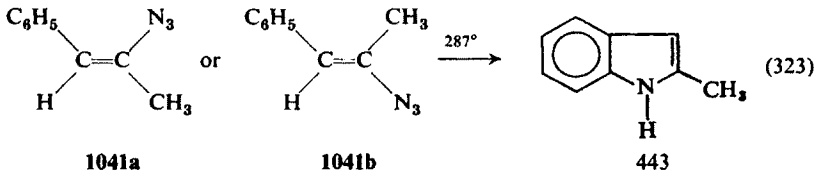
11. *Indole Formation by Pyrolysis of β-Styrylazides*

Dropwise addition of *cis*- or *trans*-β-styrylazide **1039a** or **b** into boiling (287°) *n*-hexadecane produced in 85% yield a 1:1 mixture of indole **1** and phenylacetonitrile (**1040**)[770] (Eq. 322). Similar pyrolysis of either the *cis* or



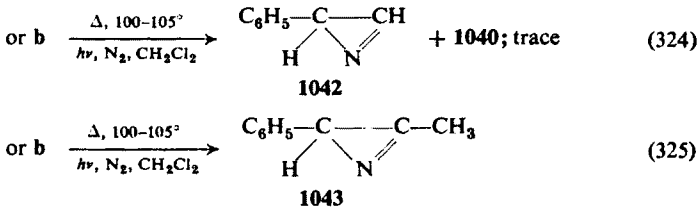
(322)

trans isomer of β-methyl-β-styrylazide **1041a** or **b** gave only 2-methylindole **443** (yield, 85%) (Eq. 323).



1041a **1041b** **443** (323)

Pyrolysis at 100–105° or photolysis in methylene chloride under nitrogen of **1039a** or **b** gave 2-phenyl-2*H*-azirine (**1042**) along with just a trace of phenylacetonitrile (Eq. 324), while similar treatment of **1041a** or **b** gave 2-phenyl-3-methyl-2*H*-azirine (**1043**) quantitatively (Eq. 325). Since thermal treatment



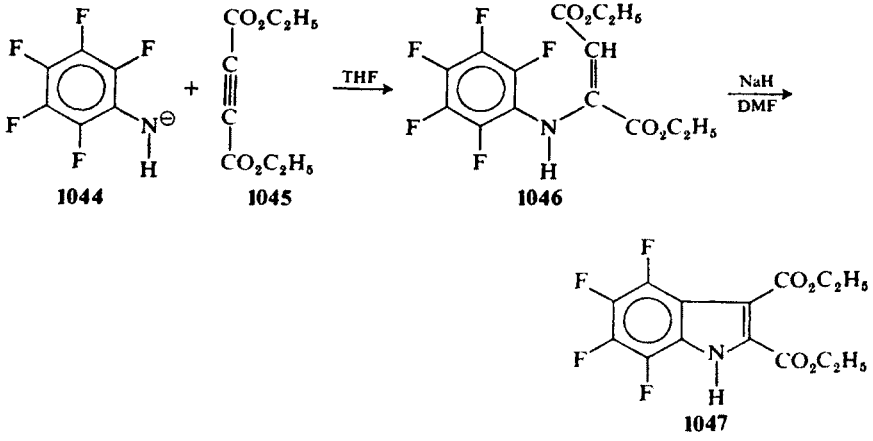
1042 (324)

1043 (325)

of the azirine **1042** by its addition to boiling *n*-hexadecane gave an equimolar proportion of indole and phenylacetonitrile, while the azirine **1043**, similarly treated, gave only 2-methylindole, it is believed[770] that azirine formation is one step in the conversion of the β-styrylazides to indoles. Although firm evidence is lacking, it is felt that β-styrylnitrenes are also involved in the mechanism.[770]

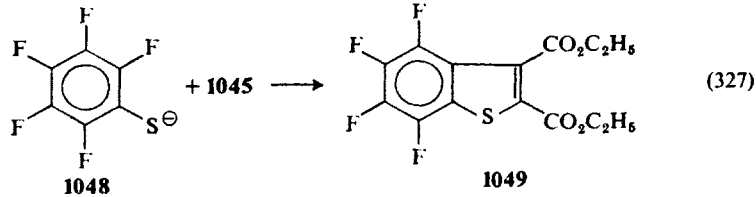
12. *Tetrafluoroindoles*

a. From the Reaction of Pentafluoroaniline with Diethyl Acetylenedicarboxylate. When pentafluoroaniline was treated with sodium hydride in tetrahydrofuran (THF) and the resulting anilide (**1044**) allowed to react with diethyl acetylenedicarboxylate (**1045**), a *trans* addition occurred, providing only the aminofumarate **1046**[771] (Eq. 326). This reaction failed to yield an isolable cyclized product even when carried out at ~150°,[771] although it is known[772] that lithium pentafluorobenzenethiolate (**1048**) reacts by *cis* addition to the acetylene diester **1045** to form 2,3-diethoxycarbonyl-4,5,6,7-tetrafluorobenzo[*b*]thiophene (**1049**) as the result of displacement of a



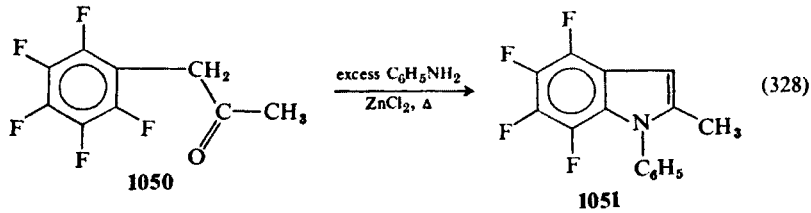
(326)

nuclear fluorine atom by a carbanion (Eq. 327). Treatment of the aminofumarate **1046** with sodium hydride in *N*,*N*-dimethylformamide (DMF) at reflux temperature did produce **1047**, but only in < 3% yield.[771]



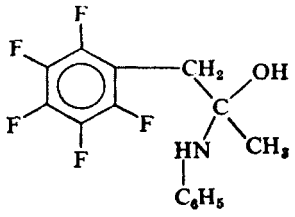
(327)

b. From the Reaction of Pentafluorophenylpropan-2-one with Aniline. Recently,[773] 2′,3′,4′,5′,6′-pentafluorophenylpropan-2-one (**1050**) was heated in refluxing, excess aniline containing anhydrous zinc chloride and gave 2-methyl-1-phenyl-4,5,6,7-tetrafluoroindole (**1051**) in < 10% yield (Eq.

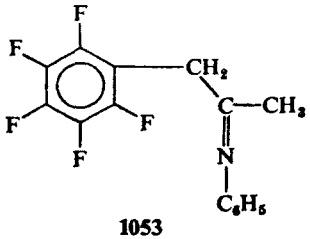


(328)

328). The yield could be raised to 47% if a mixture of the ketone **1050**, aniline hydrobromide, zinc chloride, and aniline was heated under reflux for 2 hr. Neither of the two possible intermediates, the adduct **1052** or the Schiff base **1053**, could be obtained.

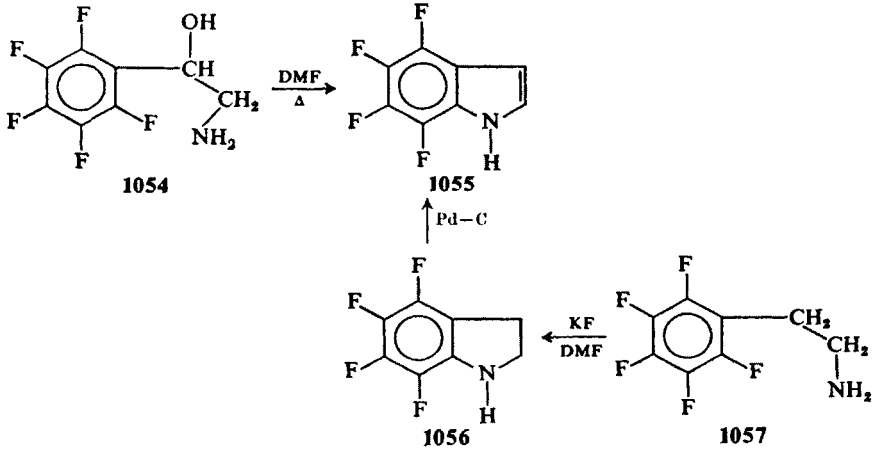


1052



1053

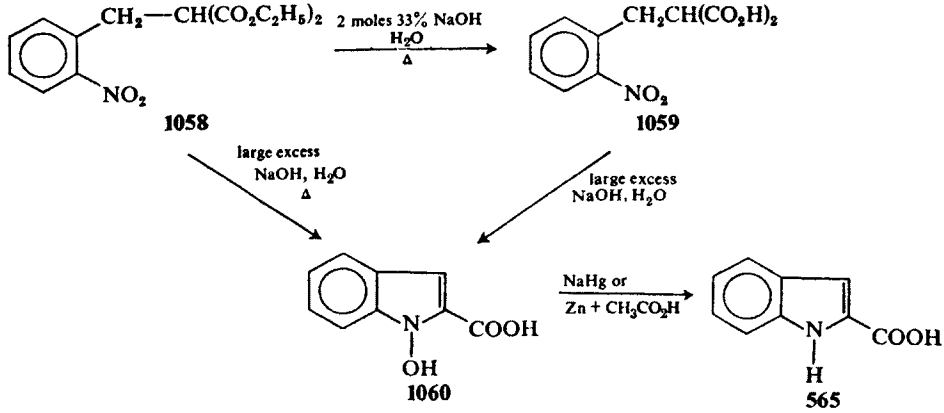
c. From the Reaction of β-Pentafluorophenyl-β-hydroxyethylamine. A recent report[774] describes the preparation of 4,5,6,7-tetrafluoroindole (**1055**) in excellent yield by merely heating β-pentafluorophenyl-β-hydroxyethylamine (**1054**) in refluxing *N*,*N*-dimethylformamide. The same indole could be obtained by Pd-C dehydrogenation of 4,5,6,7-tetrafluoroindoline (**1056**) obtained by heating β-(pentafluorophenyl)ethylamine (**1057**) with potassium fluoride in *N*,*N*-dimethylformamide[774] (Eq. 329).



(329)

13. *Base Catalyzed Cyclization of o-Nitroaryl Compounds to 1-Hydroxyindoles*

Reissert[775] had shown that diethyl *o*-nitrobenzylmalonate (**1058**) heated with 2 moles of aqueous sodium hydroxide (33%) gave *o*-nitrobenzylmalonic acid (**1059**) (Scheme 98). However, when either **1058** or **1059** was heated with a large excess of this aqueous base, 1-hydroxyindole-2-carboxylic acid (**1060**)

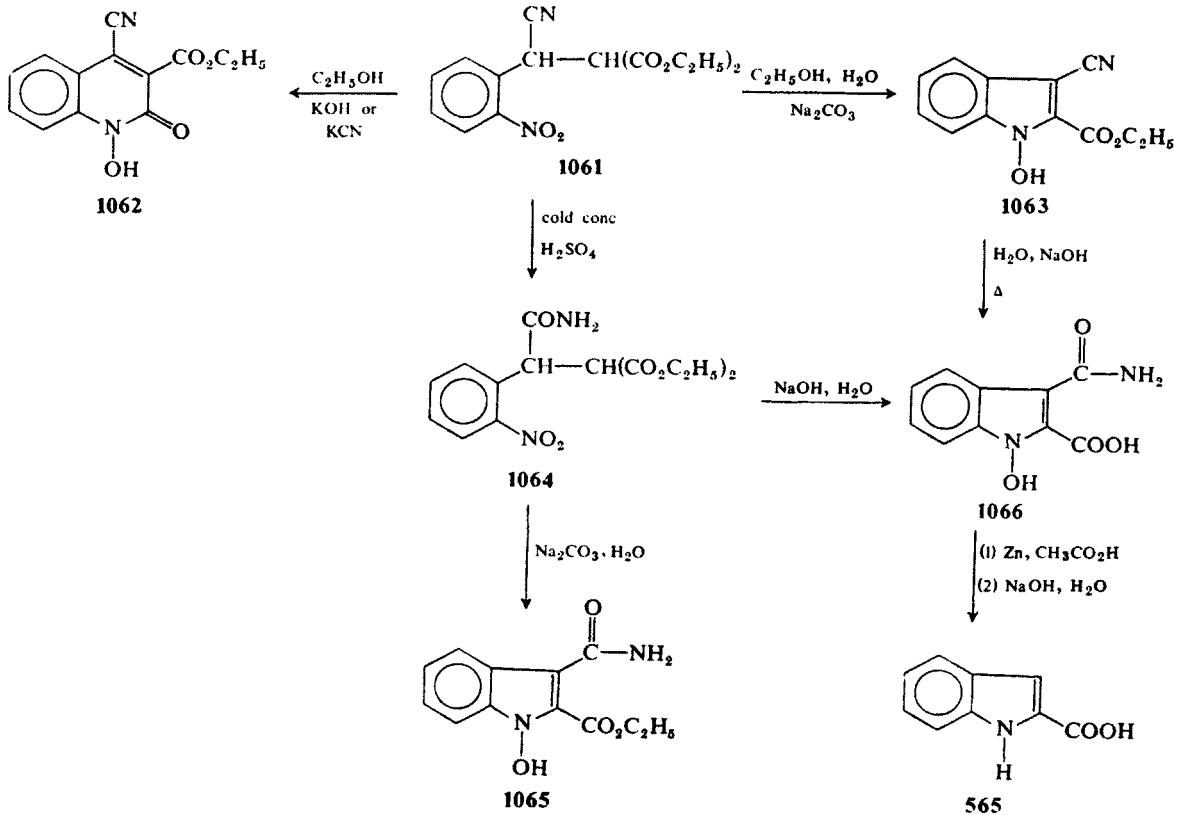


was obtained and this could be converted readily to indole-2-carboxylic acid (**565**) by reduction with sodium amalgam or preferably with zinc dust and acetic acid. When **1058** was shaken for 10–15 min with a tenfold excess of 3% aqueous potassium hydroxide, the ethyl ester of **1060** was obtained in fair yield.[776] Hydriodic acid in the presence of zinc chloride converted this ester to the ethyl ester of **565**.[776]

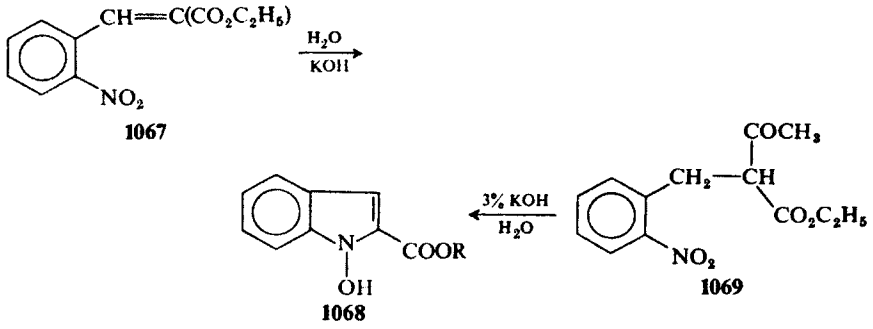
The reduction of *o*-nitrophenylpyruvic acid with sodium amalgam is reported to form **565**.[426]

In a study of the reaction between an aryl nitro group with an *ortho* side chain to produce a heterocyclic ring, Loudon and Wellings[777] found that in strongly alkaline media (ethyl alcohol containing potassium hydroxide or potassium cyanide) diethyl (α-cyano-*o*-nitrophenyl)malonate (**1061**) gave the 1-hydroxy-2-quinolone **1062** while in weakly alkaline media (sodium carbonate in aqueous ethanol) the adduct **1061** formed ethyl 3-cyano-1-hydroxyindole-3-carboxylate (**1063**). Cold concentrated sulfuric acid converted **1061** to the diester amide **1064** which could be cyclized to the 1-hydroxyindoles **1065** or **1066** under the conditions indicated (Scheme 99).

Treatment of diethyl *o*-nitrobenzylidenemalonate (**1067**) with aqueous alkali[777] gave 1-hydroxyindole-3-carboxylic acid (**1068**; R = H (Eq. 330). The ethyl ester of this same compound **1068** (R = C_2H_5) was obtained when ethyl α-*o*-nitrobenzylacetoacetate (**1069**) was shaken with 3% aqueous potassium hydroxide.[776] It is interesting that the presence of a cyano group in **1061** has such a pronounced effect on the course of reaction followed by **1061**, a course which depends upon the strength of the base used. Both weakly alkaline and strongly alkaline media give the 1-hydroxyindole when the relevant precursors **1058**, **1059**, **1067**, and **1069** do not have the cyano substituent.

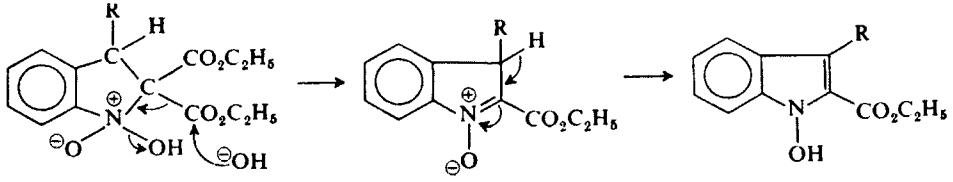

CN
CO2C2H5
N
O
OH
1062
C2H5OH
KOH or
KCN
CN
CH—CH(CO2C2H5)2
NO2
1061
C2H5OH, H2O
Na2CO3
CN
CO2C2H5
N
OH
1063
cold conc
H2SO4
H2O, NaOH
Δ
CONH2
CH—CH(CO2C2H5)2
NO2
1064
NaOH, H2O
O
C—NH2
COOH
N
OH
1066
Na2CO3, H2O
(1) Zn, CH3CO2H
(2) NaOH, H2O
O
C—NH2
CO2C2H5
N
OH
1065
COOH
N
H
565

Scheme 99



(330)

The formation of the indole is thought to occur[777] by the formation and decomposition of an intermediate such as **1070** (Eq. 331).

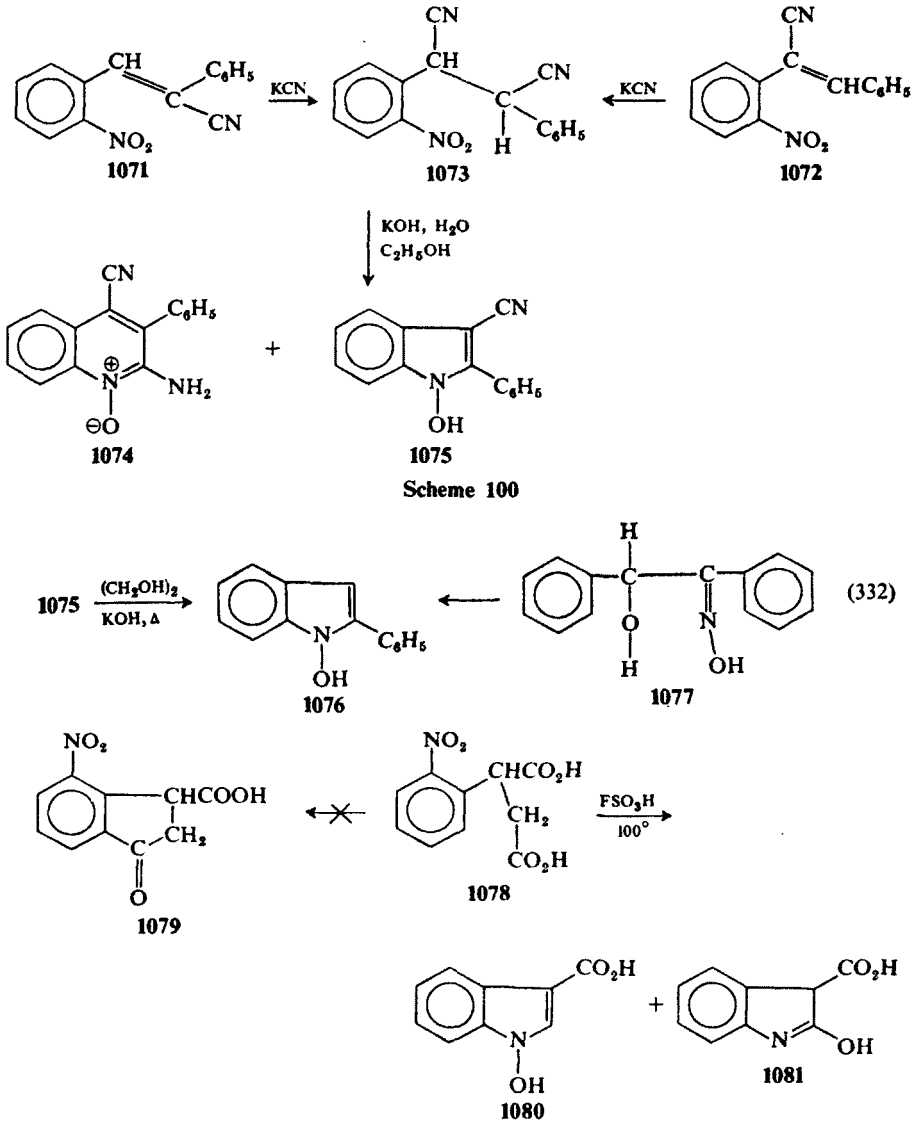


(331)

In a subsequent report[778] it was shown that either 2-nitro-α-phenylcinnamonitrile (**1071**) or α-(*o*-nitrophenyl)cinnamonitrile (**1072**) when treated with potassium cyanide in aqueous ethanol gave the same mixture of products, hence the same intermediate adduct (not isolated) **1073** is considered to have been formed first.[778] The reaction mixture contained two major products, 2-amino-4-cyano-3-phenylquinoline-1-oxide (**1074**) and 3-cyano-1-hydroxy-2-phenylindole (**1075**), whose proportions could be changed at will by altering the reaction conditions (Scheme 100).

By hydrolysis under forcing conditions (hot ethylene glycol containing potassium hydroxide), **1075** was converted to 1-hydroxy-2-phenylindole (**1076**), the same compound obtained by cyclodehydration of benzoin oxime (**1077**)[779] (Eq. 332).

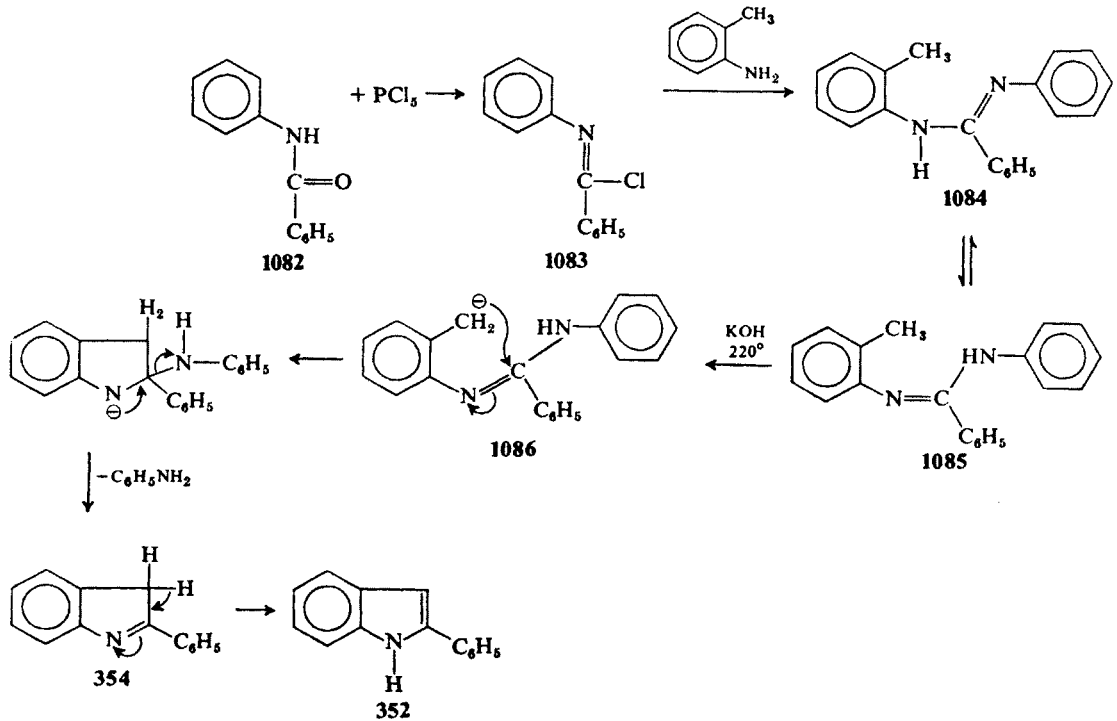
In an attempt to cyclize *o*-nitrophenylsuccinic acid (**1078**) or its anhydride to form the indanone **1079**, using the usual Friedel-Crafts catalysts, either no reaction or tar formation occurred.[780] However, if **1078** was heated with fluorosulfonic acid on a steam bath, the two compounds 1-hydroxyindole-3-carboxylic acid (**1080**) and oxindolic acid (**1081**) were formed in good yield (Eq. 333). This appears to be another example of a nitro substituent reacting with a neighboring *ortho* group—a subject reviewed recently by Loudon and Tennant.[781]



Scheme 100

14. *Cyclization of N-o-Tolylbenzamidines*

A route to the preparation of 2-phenylindoles has been described.[782] Benzanilide (**1082**) is first converted to the imido chloride **1083** which with *o*-toluidine forms *N*-phenyl-*N'*-*o*-tolylbenzamidine (**1084**). This amidine or its tautomer **1085**, heated with potassium hydroxide at 220°, produces 2-phenylindole (**352**) in 30% yield. This reaction **1085** → **1086** → **352** can be

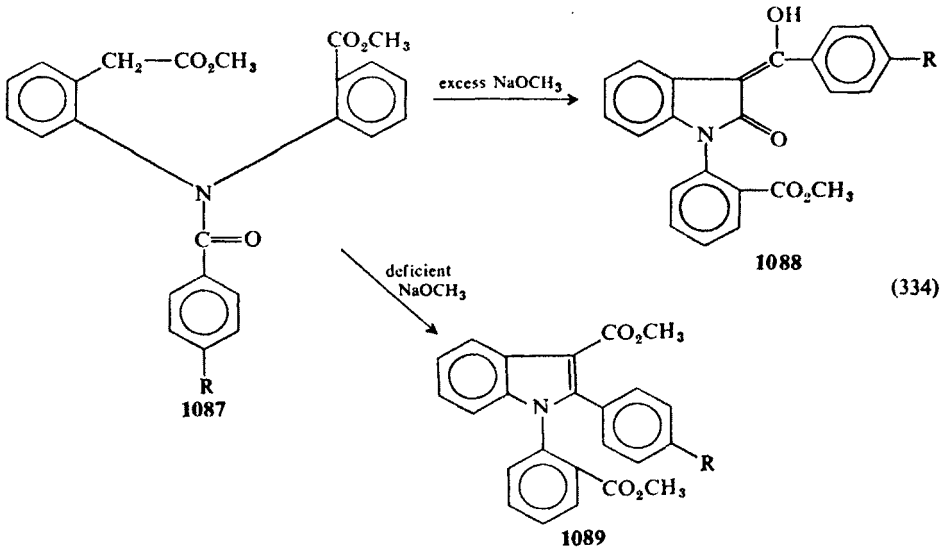


Scheme 101

considered as a modification of the Madelung indole synthesis (see pp. 394–395) and probably forms the indole by the route **1085** → **1086** → **354** → **352** (Scheme 101) similar to that advanced by Lorenz et al.[403] for the conversion of the amidine **557** to 7-azaindole **560**.

15. *The Reaction of Methyl N-Benzoyl-N-[o-(methoxycarbonylmethyl)-phenyl]anthranilate with Sodium Methoxide*

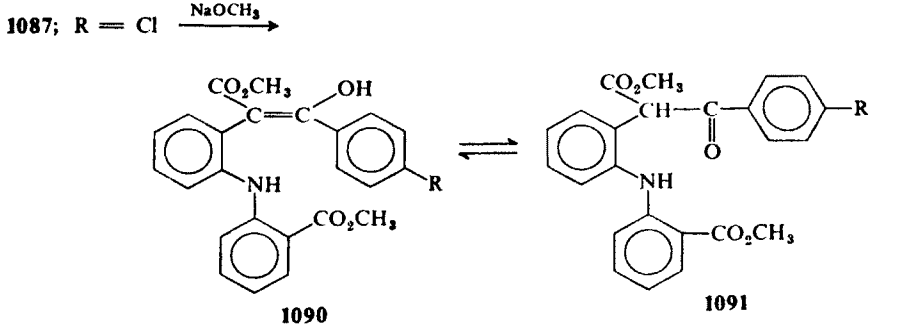
The reaction of this anthranilate **1087** (R = H) with excess sodium methoxide[783] has produced 1-(*o*-carbomethoxyphenyl)-3-benzoyloxindole (**1088**; R = H), while a deficiency of sodium methoxide converts **1087** (R = H) to methyl 1-(*o*-carbomethoxyphenyl)-2-phenylindole-3-carboxylate (**1089**; R = H)[783, 784] (Eq. 334). Further study of this reaction[784] revealed



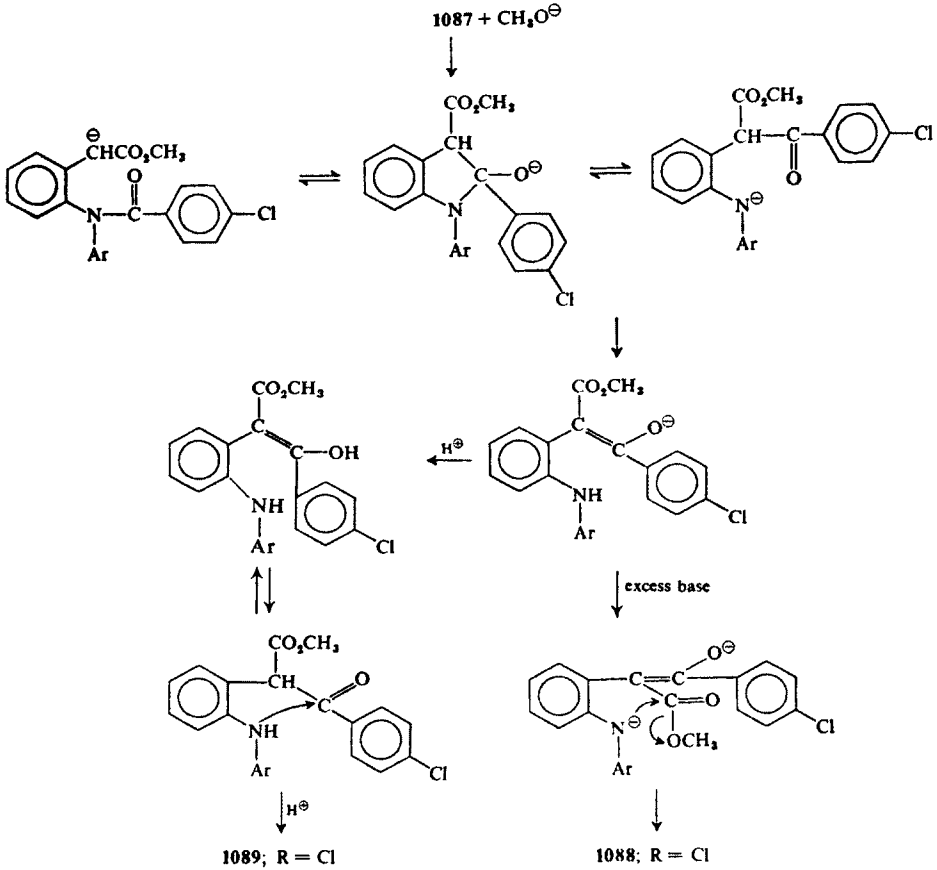
(334)

that in the presence of a deficiency of base, **1087** (R = Cl) suffered a base-catalyzed acyl migration to form the enol **1090** (R = Cl) which could be converted partly to the keto tautomer **1091** (R = Cl) by crystallization from methanol (Eq. 335). This keto tautomer **1091** (R = Cl) could be obtained in 68% yield by heating **1090** (R = Cl) in boiling methanol and allowing the solution to cool with the addition of seed crystals of **1091** (R = Cl). Equilibration of **1090** with **1091** (3:7) could be attained rapidly if triethylamine was added.

Treatment of either tautomer **1090** or **1091** (R = Cl) with excess sodium methoxide gave the oxindole **1088** (R = Cl) in 71% yield, while treatment of **1090** or **1091** (R = Cl) with trifluoroacetic acid gave the indole **1089** (R = Cl).



(335)

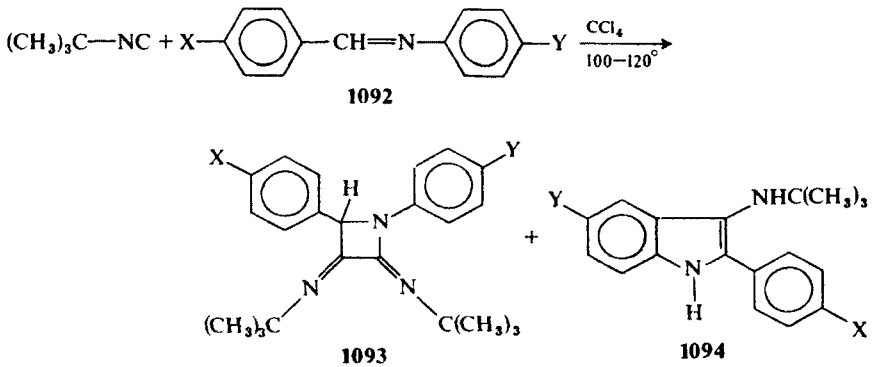


Scheme 102

The course of the reaction is believed[784] to follow the route shown in Scheme 102.

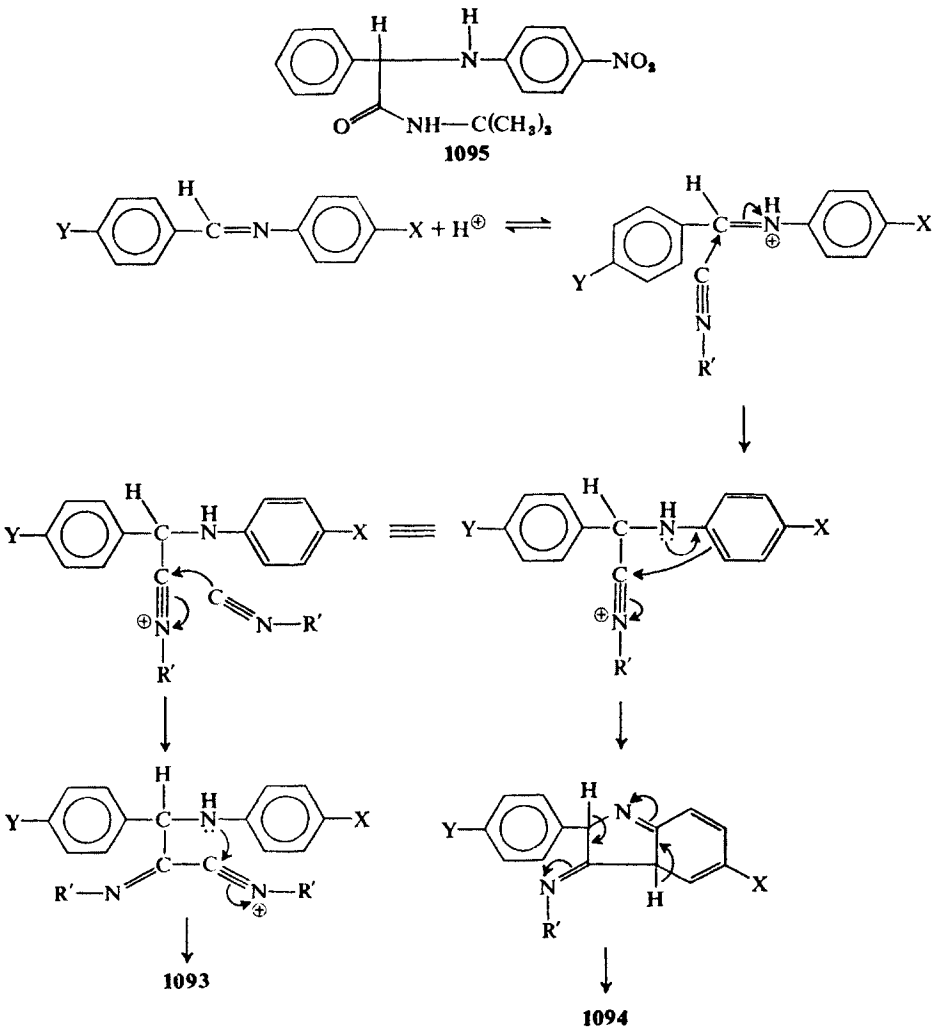
16. *Reaction of Imines with t-Butyl Isocyanide*

It has been found[785] that when a carbon tetrachloride solution of *t*-butyl isocyanide and an imine of structure **1092** was heated in a sealed tube at 100–120°, two major products were obtained. The relative proportions and yields of these two products were highly dependent upon the substituents X and Y. One of the products was a 2:1 adduct (51–70%) while the other was a 1:1 adduct (27–41%) of the isocyanide and the imine. On the basis of their ir, proton magnetic resonance, and mass spectra as well as chemical degradation, these adducts were assigned the structures **1093** and **1094**, respectively (Eq. 336).



(336)

Since the imines and isocyanide did not condense in polar solvents, including *t*-butyl isocyanide itself, the possibility of an acid-catalyzed reaction was indicated. It is known that trace amounts of acid present in nonpolar halocarbon solvents have a large effect on reactions in these solvents. In fact, **1092** (X = H, Y = NO_2) reacted with *t*-butyl isocyanide in the presence of some trifluoroacetic acid at room temperature to form chiefly **1093** (X = H, Y = NO_2) along with an uncyclized product of structure **1095**. It is found that in the sealed tube reactions the imines **1092** with Y = NO_2 form preferentially the 2:1 adduct **1093**, hence this acid-catalyzed reaction would not be suitable for indole preparation. The reactions given in Scheme 103 have been suggested[785] to account for the formation of the products **1093** and **1094**.



1095

1093

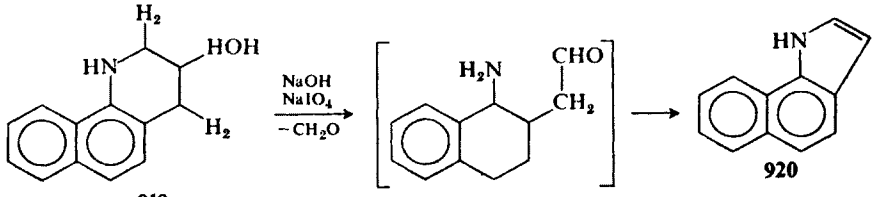
1094

Scheme 103

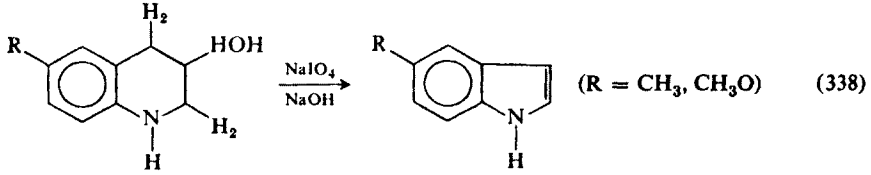
17. *Indoles from the Periodate Oxidation of* 3-*Hydroxy*-1,2,3,4-*tetrahydroquinolines*

The discovery that the 3-hydroxy-1,2,3,4-tetrahydroquinolines **919** and **1096**, obtained from the reaction of a primary arylamine with epichlorohydrin, could be converted to indoles **920** and **1097** by periodate oxidation[723, 786] led to a general study of the conditions best suited to form these

3-hydroxy-1,2,3,4-tetrahydroquinolines, as well as the application of this method to prepare a number of indoles[787] (Eq. 337, 338).

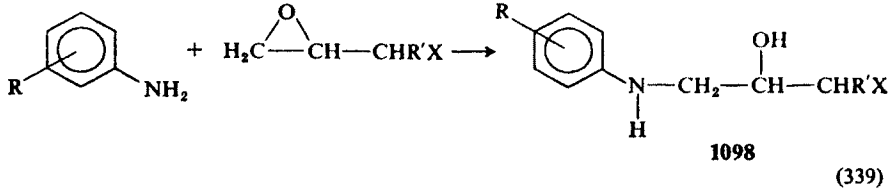


919 920 (337)



1096 1097 (338)

Condensation of the amine with epichlorohydrin to form the 1-arylamino-3-halo-2-propanols **1098** was best accomplished at room temperature in methanol containing hydrochloric acid as catalyst,[788] although water-soluble amines could be condensed satisfactorily in aqueous media at 40–50° (Eq. 339). The cyclization reaction to form the 1,2,3,4-tetrahydroquinoline-3-ols **1096** was done most satisfactorily by several days' reflux of a dilute



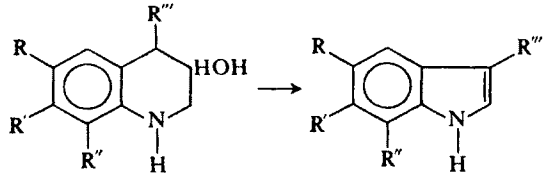
1098 (339)

solution of **1098** in bromobenzene or *o*-dichlorobenzene. The addition of a tertiary amine such as diethylaniline or pyridine improved the yields and prevented formation of undesirable byproducts. The order of reactivity of the halide X in **1098** is I > Br > Cl > F, but compounds obtained with epichlorohydrin were generally easier to purify.

The simplicity of the reaction and availability of starting materials makes this an attractive procedure especially since this permits the conversion of primary amines to indoles in yields competitive with those obtained by the Fischer indole synthesis.

The indoles prepared by this method are shown in Table XV using the generalized structures **1099** and **1100**.

TABLE XV

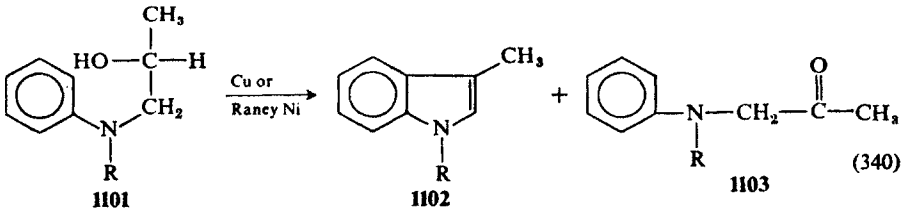


1099 1100

R	R′	R″	R‴	Yield (%)
H	H	H	H	47
CH_3	H	H	H	57
OCH_3	H	H	H	~10
H	OCH_3	H	H	43
CH_3	H	H	CH_3	70
H	H	CH_3	H	52
H	H	OCH_3	H	35

18. *Indoles from the Catalytic Dehydrogenation of N-Alkyl N-aryl-1-amino-2-propanols*

The catalytic dehydrogenation of *N*-alkyl-*N*-aryl-1-amino-2-propanols **1101** with copper powder occurs quantitatively[789] and gives a mixture of two main components, *N*-alkyl-3-methylindole **1102** and the arylaminoketone **1103** along with a small amount of a secondary amine (Eq. 340). Raney



1101 1102 1103 (340)

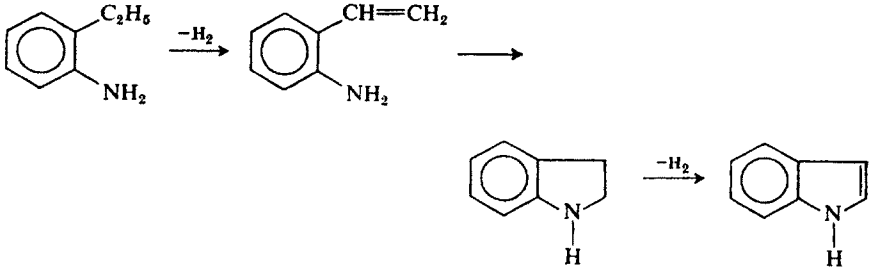
nickel is more active than is copper powder, but leads to a mixture of the products mentioned above along with some *N*-substituted anilines.

19. *Dehydrocyclization of N-Alkylanilines and o-Alkylarylamines to Indoles*

The early work of Baeyer and Caro[790] had shown that ethyl aniline could be converted to indole by passage through a red-hot iron tube. Further work[791]

showed that the yield of indole obtained depended upon the type of substituted aniline used. Whereas ethylaniline gave only a trace of indole, diethylaniline, ethylmethylaniline, or *N*-acetyl-*N*-methylaniline gave somewhat better yields of indole. Dimethyl-*o*-toluidine and diethyl-*o*-toluidine provided indole in fair and good yield, respectively, while dimethyl-*p*-toluidine gave no indole. Pyrolyses carried out later also showed that *N*-methyl-*o*-toluidine[792] and *N*,*N*-dimethyl-*o*-toluidine[793] formed indole.

Gresham and Bruner[794] reported the successful dehydrocyclization of *o*-ethylaniline to indole by means of a titania gel catalyst at 550–750°. Hansch and Helmkamp[795] repeated the work of Gresham and Bruner but used a chromium-copper-on-charcoal catalyst.[796] They found that at the optimum temperature of 670°, *o*-ethylaniline could be converted to indole in 32% yield with very little decomposition of either substance. At temperatures below 600°, only *o*-aminostyrene was formed (65% at 560°). This information along with other evidence[797, 798] suggested that the course of the reaction was most likely that shown in Eq. (341), involving initial dehydrogenation of *o*-ethylaniline to *o*-aminostyrene followed by cyclization to the indoline and then conversion of the latter compound to indole.



(341)

Extension of this dehydrocyclization[795] to *o*-isopropylaniline was much less satisfactory. It did provide skatole (3-methylindole) in 7.3% yield but also gave a 16% yield of indole. Since 2,4-diaminoethylbenzene and its isopropyl homolog both suffered very extensive decomposition under these conditions, the conclusion was made[795] that dehydrocyclization of *o*-alkylanilines would be of little use as a method of synthesizing indoles other than indole itself.

A number of reports have appeared since that of Hansch and Helmkamp describing the results of pyrolytic methods of obtaining indoles. In the presence of carbon or silica gel-Al_2O_3 catalyst, 2-aminoethylbenzene has been converted to indole at 650–700°.[799] A catalyst containing titanium dioxide has converted *o*-nitroethylbenzene at 650° to indole (10–15%).[800] At 500–700°, a chromium-copper-on-carbon catalyst or iron-zinc catalyst rearranged *o*-ethylaniline to indole in 34% yield.[801] A 30% yield of skatole was obtained

by the catalytic dehydrocyclization of *o*-ethyl-*N*-methylaniline using a copper catalyst at 580°.[802] The chromium-copper-on-carbon catalyst[796] has been used to convert a mixture of styrene and ammonia to indole (14.3%).[803]

Some other modifications of these catalytic systems have been fruitful. Indole, skatole, and 2-methylindole have been prepared when a mixture of aniline with ethyl alcohol, isopropyl alcohol, or *n*-propyl alcohol was passed over an alumina and ferric oxide-alumina catalyst at elevated temperatures.[804]

A kaolin-alumina catalyst has isomerized *o*-aminostyrene at 400° to indole.[805] The reaction of *o*-nitrocinnamic acid with excess molten potassium hydroxide containing iron filings no doubt forms *o*-aminostyrene which then cyclizes under the conditions employed.[806]

20. *Indole from the High Temperature, Catalyzed Reaction of Ethylene or Acetylene with Aniline*

The passage of aniline in a stream of ethylene over ferric oxide and alumina at 620–670° has produced indole.[807] A mixture of acetylene and aniline, passed through a hot aluminum tube filled with one of the catalysts, zinc or cadmium acetate, zinc or cadmium phosphate, mercuric sulfate or cuprous chloride gave indole.[808] The yield of indole depends upon the catalyst employed, being greatest (22%) with zinc phosphate. The observation[809] that the addition of tetraethyl lead to the high temperature reaction of aniline with acetylene increased the yield of indole by a factor of 2.6, indicated that the reaction involved free radicals. The mechanism is believed[810] to involve the formation of the ethynyl radical $HC{\equiv}C\cdot$, which then attacks the aniline at the position *ortho* to the amino group to produce *o*-ethynylaniline, a substance which then cyclizes to indole. Support for this latter step was obtained from the observation that authentic *o*-ethynylaniline, heated to 500–700°, did form indole.[810]

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