San Fernando Valley State College

THE SYNTHESIS OF 2-(INDOL-3-YL)ETHANE DERIVATIVES

A thesis submitted in partial satisfaction of the requirements for the degree of Master of Science in

Chemistry

by

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June, 1969
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Committee Chairman

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June, 1969
To my wife, Jo-Ellen, 
who made this possible 
and worthwhile
ACKNOWLEDGMENT

My deepest indebtedness is to Dr. Ricardo A. Silva, who helped me greatly with this work from the moment of its inception through the many stages of its development and, most of all, for his friendship and the opportunity to learn from him during this time.

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ABSTRACT

THE SYNTHESIS OF 2-(INDOL-3-YL)ETHANE DERIVATIVES

by

Pirouz Tahbaz

Master of Science in Chemistry
June, 1969

In this project, tryptophol was made by reaction of indole with oxalyl chloride followed by esterification with ethanol and reduction of the ester with lithium aluminum hydride. The halogen, benzoate, and tosylate derivatives of tryptophol were obtained. The attempted synthesis of the 2-(indol-3-yl)ethyl azide via benzoate and tosylate of tryptophol were singularly unsuccessful. However, it was possible to arrive at the azide by nucleophilic substitution of both 2-(indol-3-yl)ethyl iodide and 2-(indol-3-yl)ethyl bromide.

The photolysis and thermolysis of the azide resulted in similar decomposition to one or more products which could not be identified. In addition v-triazoles were prepared by allowing the azide to react with methyl propiolate and dimethyl acetylenedicarboxylate.

Physical constants for all these derivatives were obtained and analyzed in this work.
CHAPTER I

INTRODUCTION

This research was performed to obtain some information about the chemistry of some 2-(indol-3-yl)ethane derivatives.

The 2-(indol-3-yl)ethyl group has been found in many naturally occurring compounds of great chemical and biochemical interest. Essentially, all of the indole alkaloids contain a β-ethanolamine indole group. Several specific examples are tryptophan, serotonin, bufotenine, eserine, and lysergic acid.

![Chemical structures of tryptophan, serotonin, and bufotenine]
Some of the uses of the above are as follows: tryptophan is a nutrient which is effective in preventing and treating pellagra; serotonin, which is present in the human brain, has been used experimentally in psychopharmacology as a lysergic acid diethylamide antagonist; eserine is used as a parasympathomimetic agent; and bufotenine and the diethylamide derivative of lysergic acid are hallucinogenic agents which have been used in the experimental production of temporary psychoses.

The \( \pi \)-electron densities at the various positions on the indole ring have been calculated by molecular orbital methods.\(^1\)

\[
\begin{array}{c}
1.009 \\
1.015 & 1.013 \\
1.010 & 1.066 & 1.059
\end{array}
\]

\( \pi \)-electron densities calculated by molecular orbital method
By referring to the \( \pi \)-electron density values for the indole ring, one would expect the 3-position to be the most apt to undergo electrophilic substitution. In this work, the 3-ethyl indole derivatives were made through electrophilic substitution with oxalyl chloride. The indol-3-yl-glyoxalyl chloride was further converted to the desired derivatives according to the reaction sequence on the following page.

Originally, it was anticipated that the azide (X) would be potentially the most useful intermediate for the synthesis of various indolic compounds since the azide could be made to undergo thermolysis or photolysis or to become involved in 1,3-dipolar addition to various dipolar-philes.

The attempted synthesis of the azide (X) via the benzoate or tosylate derivatives of tryptophol were singularly unsuccessful. However, it was possible to arrive at (X) by nucleophilic substitution of both the bromo and iodo derivatives of tryptophol.

The photochemical behavior of alkyl azides is not clearly delineated at the present time. Barton and Morgan\(^2\) reported a partial synthesis of the steroidal alkaloid, conessine, by the photolytic cyclization of a suitable alkyl azide to a pyrrolidine. More recently in 1965, Barton and Starratt\(^3\) reported that they could not perform similar cyclizations with \( \text{n-butyl} \) and \( \text{n-octyl} \) azides under
\[
\begin{align*}
&\text{I} \rightarrow \text{II} \rightarrow \text{III} \\
&\text{CH}_2-\text{CH}_2-\text{R} \leftarrow \text{CH}_2-\text{CH}_2-\text{OH} \\
&\text{V, } R = \text{OCOC}_6\text{H}_5 \\
&\text{VI, } R = \text{OTS} \\
&\text{VII, } R = \text{Cl} \\
&\text{VIII, } R = \text{Br} \\
&\text{IX, } R = \text{I} \\
&\text{X, } R = \text{N}_3 \\
&\text{XVa, } R = \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \text{COOCH}_3 \\
&\text{XIV, } R = \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \text{COOCH}_3 \\
&\text{X} \rightarrow \text{XVb, } R = \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \text{COOCH}_3 \\
&\text{XI} \\
&\text{miscellaneous material}
\end{align*}
\]
the conditions used earlier even though they employed a large variety of lamps. These workers also report that Smolinsky (Bell Telephone Lab) independently was unable to repeat the partial synthesis of conessine, whereas Moriarity was able to cyclize n-octyl azide to 2-butylpyrrolidine. In contrast, the photochemistry of aryl azides is well defined. Photolysis of biphenyl-2-azide leads clearly to carbazole. On the basis of the foregoing, it was felt that photolysis of 2-(indol-3-yl)ethyl azide might lead to generation of a nitrene followed by cyclization to XII or XIII.

In this work the photolysis and thermolysis of the tryptophol azide was performed in order to obtain the desired pyrrolidine (XII) or alternatively, to the pyrrolidine (XIII).
The compound XII contains the basic ring system of eserine, while XIII is a variant of part of the lysergic acid skeleton. It was found that both photolysis and thermolysis of the azide (X) resulted in similar decomposition to one or more products which could not be identified but which are unequivocally not (XII) or (XIII).

Our attention was next directed to the fact that the azide could undergo 1,3-dipolar cycloaddition with alkynes to form v-triazoles, which are of physiological value as growth antagonists and inhibitors and as anti-acetylcholine esterase agents. Since v-triazoles are readily prepared from aromatic azides by 1,3-dipolar cycloaddition to unsaturated acids and esters, the azide, (X), was allowed to react with methyl propiolate, and dimethyl acetylenedicarboxylate. In the first case, compounds XVa and XVb were obtained and, in the latter, compound XIV was synthesized. Physical constants for all these derivatives were obtained and analyzed in this work.
CHAPTER II

DISCUSSION OF RESULTS

The Alcohol Synthesis

Tryptophol, 2-(indol-3-yl)ethanol, is of considerable interest as an intermediate in indole chemistry. It has been prepared by the lithium aluminum hydride reduction of ethyl 3-indolylacetate in a near quantitative yield. This ester of the indole, however, is rather difficult to obtain via gramine, indolylacetonitrile, and indolylacetic acid. This six-step synthesis gives an overall yield of only 59%. The new procedure of Johnson and Crosby produces indolylacetic acid in a 90% yield and from this acid, tryptophol can be obtained in an overall yield of 79%. This method requires the use of a concentrated potassium hydroxide solution, and a heating period of 14-22 hr at 250°C in an autoclave. In this project, tryptophol was prepared by the method of Nogrady and Doyle. Although Nogrady and Doyle claim an overall yield of 85% for the tryptophol, the alcohol could not be obtained in better than an 80% yield. The alcohol obtained by this method is pure enough for making its derivatives.
Up to 1954, it was believed that the reaction of oxalyl chloride and indole would lead to 2-indole oxalyl chloride.\textsuperscript{9} This belief has been proven to be incorrect by Speeter and Anthony.\textsuperscript{1} Proof of the position of the glyoxylyl chloride substituent on the indole ring was obtained by lithium aluminum hydride reduction of the amide, which was obtained from the acid chloride and ammonia, to yield tryptamine [3-(2-amino-ethyl)-indole], while a similar reduction of the ethyl ester of glyxolic acid yielded tryptophol.
It is clear from the above mechanism that electrophilic attack is the more likely at the 3-position of the indole ring, because of the involvement of the electrons on the nitrogen atom. The structure of tryptophol obtained in this work was proven by nmr (Figure 1), ir and reported melting point. 8

Benzoate, Tosylate, and Halides of Tryptophol

The pure benzoate of tryptophol (80% yield) was finally made by using the method on page 33. Using either more than two equivalents of pyridine or the Schotten-Baumann method did not result in a pure benzoate or good yields. Ehrlich 10 claimed that a good yield of pure benzoate was obtained by using the Schotten-Baumann method, but this work could not be duplicated in this lab.

![Chemical Structures]

The purity of the benzoate (V) was affirmed by ir, nmr, and the reported melting point. 10

In this work the tosylate of tryptophol was not obtained in good yield, but its structure was affirmed by its nmr spectrum. Addition of cold 3 N HCl in the regular work-up for the preparation of the tosylate resulted in no
tosylate, but yielded instead the indole-3-(2-chloro-ethane). One could explain this reaction by either $S_{n}^{2}$ displacement of OTs by Cl$^{-}$ or by the formulation of a spiro compound followed by the opening of the spiro ring to form the chloro compound as shown below.

![Diagram](image)

The halogen derivatives of tryptophol were made in 60-70% yield, and their nmr spectra were studied. The bromo derivative of tryptophol (VIII) was made by means of PBr$_{3}$ in ether. It is very heat and light sensitive. In contrast to the alcohol, the nmr of the bromide (Figure 2) did not show two clean triplets for the protons of the two methylene groups (Figure 1). This nmr has departed from the first-order $A_{2}X_{2}$ pattern to the higher order $A_{2}B_{2}$ pattern.

The iodo derivative of tryptophol was made in excel-
lent yield and purity with PI₃ by using CS₂ instead of ether as solvent. The iodide (IX) exhibited a rather interesting nmr (Figure 3). It showed a sharp singlet (integrated for four hydrogens) at 3.35 δ. All values for nmr signals are expressed as ppm downfield (δ) tetramethylsilane. The signal due to the CH₂-CH₂ protons has deviated from the first order A₂X₂ pattern to the higher order nearly A₄ type. The chemical shift of the CH₂ group connected to the indole rings is evidently equivalent to the chemical shift of the CH₂ group next to iodine.

\[
\begin{align*}
\text{CH}_2\text{-CH}_2\text{OH} & \xrightarrow{\text{PX}_3} \text{CH}_2\text{-CH}_2\text{X} \\
& X = \text{I, Br}
\end{align*}
\]

Table 1
Nmr Values (δ) for Methylene Protons in 3-Ethylindole Compounds

<table>
<thead>
<tr>
<th>R</th>
<th>CH₂</th>
<th>CH₂</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indol-3-yl</td>
<td>2.75</td>
<td>3.75</td>
<td>OH</td>
</tr>
<tr>
<td>&quot;</td>
<td>3.22</td>
<td>3.68</td>
<td>OTs</td>
</tr>
<tr>
<td>&quot;</td>
<td>3.20</td>
<td>3.75</td>
<td>Cl</td>
</tr>
<tr>
<td>&quot;</td>
<td>3.35</td>
<td>3.35</td>
<td>I</td>
</tr>
<tr>
<td>&quot;</td>
<td>2.80</td>
<td>3.25</td>
<td>N₃</td>
</tr>
<tr>
<td>&quot;</td>
<td>3.20</td>
<td>4.55</td>
<td>O-COOC₆H₅</td>
</tr>
</tbody>
</table>
The nmr assignments in the above table were made as follows. Considering the case for \( X = \text{Cl} \) and \( X = \text{I} \), the higher electronegativity of Cl should shift the signal due to the protons on the methylene group attached to Cl to lower field than for I. Thus, it is clear that the triplet at 3.75 (for \( X = \text{Cl} \)) is due to the methylene protons attached to Cl and the triplet at 3.20 must be due to the \( \text{CH}_2 \) attached to the indole ring. For \( X = \text{I} \), the chemical shifts of the protons on both methylene groups have the same chemical shift (3.35). Electronegativity differences between the halogens would account for the higher field value for \( \text{CH}_2 \) on I compared to Cl (see Table 2).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>( \text{CH}_3 )</th>
<th>( \text{CH}_2 )</th>
<th>( X )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.22</td>
<td>3.70</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>1.48</td>
<td>3.57</td>
<td>Cl</td>
<td></td>
</tr>
<tr>
<td>1.67</td>
<td>3.43</td>
<td>Br</td>
<td></td>
</tr>
<tr>
<td>1.83</td>
<td>3.20</td>
<td>I</td>
<td></td>
</tr>
</tbody>
</table>

The signals obtained for the \( \text{CH}_2 \) groups attached to the ring must be due to some other factor since that for the iodo compound is at lower field than that for the chloro. This has been studied previously\(^{12,13}\) and it was found that a correlation was obtained between the difference in chem-
ical shift for the $CH_3$ and $CH_2$ protons in ethyl halide and the Huggins electronegativity values. This condition was found to be linear.\textsuperscript{14} In this work, it was not possible to obtain an exact value for chemical shifts of the $CH_2$ protons of bromo derivatives, VIII, and hence such a condition could not be made with high precision, even though there seems to be no a priori reason why this should be so.

**Synthesis of the Azide**

The halogen derivatives of tryptophol were converted to the azide (X) by nucleophilic substitution with sodium azide. The yield of the azide from the iodo compound, IX, was found to be superior to that from the bromo compound, VIII. This is not unexpected since iodine is much more subject to nucleophilic substitution than bromine. In addition, the greater sensitivity of the bromo compound towards heat led to much decomposition of starting bromide, thus lowering the yield of azide.

In the literature, methanol/water mixtures are generally used as the solvent for the preparation of azides from alkyl halides.\textsuperscript{15} In this work, it was found that better yields were obtained when dimethyl formamide/water mixtures were used as the solvent.
In contrast to the iodo and bromo derivatives, the benzoate of tryptophol (V) could not be converted to the azide by any method attempted. Temperatures above 120°C or longer periods of heating in the preparation of the azide, gave some decomposition product along with the azide. The azide also decomposed during vacuum distillation. However, it could be purified by molecular distillation. The product (X) is very heat and light sensitive, therefore it was stored in the dark and at low temperatures.

**Photolysis and Thermolysis of the Azide**

Morgan and Barton² have observed that the thermal and photochemical properties of azides are much the same. The first step in either type of decomposition is the loss of nitrogen with the formation of some reactive species (nitrene, azene, etc.).¹⁵ They observed that all products obtained could be rationalized in terms of subsequent stabilization of the reactive species by a variety of routes: (1) hydrogen abstraction from the carbon by nitrogen to form an imine; (2) hydrogen abstraction from the 4- or 5-position followed by ring closure to produce...
pyrrolidines and piperidines, respectively; and (3) hydrogen abstraction from the solvent resulting in amine formation.

\[
\begin{align*}
\text{RCH}_2\text{CH}_2\text{CH}_2\text{N}_3 & \xrightarrow{-\text{N}_2} \text{R-CH}_2\text{CH}_2\text{CH}_2\text{N}: \\
\text{R-CH}_2\text{CH}_2\text{CH}_2\text{NH}_2 & \xrightarrow{(3)} \text{R-CH}_2\text{CH}_2\text{CH}_2\text{N}: \xrightarrow{(1)} \text{R-CH}_2\text{CH}_2\text{CH}=\text{NH} \\
& \xrightarrow{(2)} \text{R-CH-CH}_2\text{CH}_2-\text{NH} \\
& \xrightarrow{} \text{R} \begin{array}{c} \text{N} \\ \text{H} \end{array}
\end{align*}
\]

Considering the observations of Morgan and Barton, the following compounds would be expected by photolyzing or thermolyzing the azide \((X)\).
Low temperature photolysis of the azide resulted in no product and recovery of the starting material. When photolysis was done with heating, the solution resulted in a brown solid (20% yield) and the remainder of the reaction mixture was starting material. This photolysis product could not be identified. Recrystallization and chromatography of the solid were not successful.

Thermolysis of the azide yielded the same decomposi-
tion product as was obtained by photolysis. To identify this product, further work is needed. Not too much is clear from the ir of the solid except that the band around 3400 cm\(^{-1}\) is still present and the azide band at around 2100 cm\(^{-1}\) is no longer present. Because of the impurity of the sample, a good nmr spectrum could not be obtained. This material will remain unidentified pending further work.

**Synthesis of the Triazoles**

Azides and acetylene derivatives through 1,3-dipolar cycloaddition result in triazoles.\(^{16}\) The addition of the azide (X) to dimethyl acetylenedicarboxylate in a high boiling inert solvent (\(p\)-dioxane) resulted in the 4,5-di-substituted triazole (XIV).

\[
\text{CH}_2\text{CH}_2\text{N}_3 + \text{CH}_3\text{O-}\text{C-}\text{C\equiv}\text{C-}\text{OCH}_3 \rightarrow \text{XIV}
\]

The triazole XIV was obtained in 80% yield. The nmr of this compound (Figure 5) indicates two singlets for the
two methyl groups with different chemical shifts at 3.54 and 3.87. The singlet at 3.54 was assigned to the methyl of the carboxyl group attached to position 4 of the triazole ring.

From the drawing below, it is clear that the unshared electron pair on the 3-nitrogen lies in a $p$-orbital in the plane of the triazole ring. The protons of the methoxycarbonyl group at the 4-position may interact with the unshared electron pair of the 3-nitrogen resulting in shielding of these protons and a shift of the NMR signal to higher field.

![Drawing of triazole structure]

Such shielding is not possible for the protons of the methoxycarbonyl group at the 5-position. (It must be remembered that the unshared electron pair on N-1 occupies a $p$-orbital which is perpendicular to the plane of the ring and thus is unable sterically to interact strongly with the methoxycarbonyl protons on C-5.) The above argument was substantiated by the NMR (Figure 6) of triazoles XVa and XVb, which were obtained by the reaction of methyl
propiolate with the azide X.

The nmr of the mixtures of isomers obtained from the propiolate reaction reveals two singlet signals of unequal intensity at 8.20 and 8.35. Upon purification, the major product can be separated and its nmr reveals a singlet signal at 8.35 attributable to the hydrogen at C-4. In addition, the protons of the methoxycarbonyl group of the major product yield a clean singlet at 3.74. The nmr of the mixture of isomers yields two singlets at 3.74 and 3.60. Employing the same argument as previously, namely, that the protons of the methoxycarbonyl at C-4 should be shielded relative to those of the methoxycarbonyl at C-5, the major product must have methoxycarbonyl at C-5.

Sterically, XVa is expected to be the major product, and this is proven by its nmr (Figures 6 and 7). Because
of electronic effects, the signal for the hydrogen at carbon 4 is expected to be at a lower field than that for the hydrogen at carbon 5. This type of electronic effect is analogous to that observed for pyridine and pyrrole.\textsuperscript{11}

\[
\text{H} \quad 8.60 \quad \text{N} \quad 6.60
\]

It is highly probable then that from a mechanistic viewpoint and from analysis of the spectral data, the major product of the reaction between methyl propiolate and the azide, X, is XVa and the minor, XVb.
CHAPTER III

NUCLEAR MAGNETIC RESONANCE SPECTRA

All the nmr spectra were obtained in deuterated chloroform at 34°C unless specified otherwise. The scale of the spectral reproductions is 1 cm = 30 Hz. All values for nmr signals are expressed as ppm downfield (δ) from tetramethylsilane. Chemical shifts for multiplets were obtained by first-order analysis only.
COMPOUND IX

sweep width 120 Hz
COMPOUND X

Fig. 4
COMPOUND XIV

SOLVENT — PYRIDINE

TEMPERATURE — 70 °C
COMPOUND XVa

SOLVENT -- PYRIDINE

TEMPERATURE __ 70°C
CHAPTER IV

EXPERIMENTAL

General

All melting points were obtained on a Thomas-Hoover melting point apparatus. The values are uncorrected, and they were observed for samples in open capillary tubes.

The infrared spectra were obtained with a Beckman IR-8 Infrared Spectrophotometer equipped with a diffraction grating. All infrared spectra were run in nujol unless otherwise specified.

The nuclear magnetic resonance spectra were recorded on an Hitachi R-20 NMR Spectrometer operating at 60 MHz.

The ultraviolet spectra were taken with a Perkin-Elmer Model 202 in methanol and ethanol solutions.

Procedures

Indole 3-Oxalyl Chloride (II)

A total of 50.0 g of oxalyl chloride (396 mmoles) in a sealed ampoule was cooled in an ice bath and then added to 350 ml of anhydrous ether in a 2-liter, round-bottomed flask equipped with stirrer, dropping funnel, thermometer, and condenser with drying tube. The reaction vessel was
immersed in an ice bath and after the temperature had reached approximately 0°C, 43.9 g of indole (372 mmoles) in 200 ml of anhydrous ether was added over a 45-min period at 0-5°C. After addition of 20 ml of the ether-indole solution, a yellow precipitate was formed. The reaction mixture was stirred in an ice bath at 5-10°C for 30 min after the completion of the addition of the indole solution, and then it was stirred for a period of 1 hr at room temperature. The yellow mixture was filtered and washed with two 100-ml portions of ether, and then it was immediately dried in vacuo at 60°C to give 75.0 g (98.5%) of a yellow crystalline solid, mp 136-137°C, ir: (nujol) 3200, 1780, 1730, 1615 cm⁻¹. The solid was insoluble in ether, chloroform, and ethyl alcohol, and it was highly hygroscopic and darkened when exposed to air.

**Ethyl-2-(Indol-3-yl)glyoxylate (III)**

To 7.20 g of freshly prepared 2-(indol-3-yl)glyoxylychloride (345 mmoles) in a round-bottomed flask equipped with an addition funnel, condenser with a drying tube, and a stirrer was slowly added 50.4 ml (364 mmoles) of triethylamine and 420 ml of absolute ethanol and the whole refluxed for 30 min. The mixture was cooled in an ice bath and filtered, and the filtrate was washed with two 30-ml portions of cold absolute ethanol. The pale green, flaky solid was dried in vacuo at 70°C overnight to give a total of 76.5 g of the product (98%). The solid melted at 185-
$186^\circ$C, ir: (nujol) 3950, 3200, 1730, 1615, 1260 cm$^{-1}$. It can be recrystallized from methanol to give a melting point of $186.0-186.5^\circ$C (lit.$^8$ mp 184-186°C).

2-(Indol-3-yl)ethanol (Tryptophol) (IV) Method A

In the following procedure the tetrahydrofuran used was dried and distilled over lithium aluminum hydride. Into a 5-liter flask equipped with stirrer, reflux condenser with drying tube, and a dropping funnel through which a nitrogen stream could be introduced was placed 46.2 g (1.12 mole) of LiAlH$_4$ and 1 liter of previously dried tetrahydrofuran. A suspension of 72.0 g of the ethyl-2-(indol-3-yl)glyoxylate in 1 liter of tetrahydrofuran was added dropwise over a 45-min period to the LiAlH$_4$ mixture by maintaining a gentle reflux. After completion of the addition the mixture was refluxed for 3 more hr, then the mixture was cooled to room temperature and 100 ml of H$_2$O was added cautiously and slowly over 45 min with vigorous stirring. After all the gray matter was converted to a white mixture, the substance was filtered and washed well with three 150-ml portions of hot tetrahydrofuran. The filtrate was dried to a light yellow oil in vacuo. The light yellow oil was later converted to a white solid by adding 50.0 ml of benzene and drying it in vacuo. It gave 44.3 g of tryptophol (82%) which melted at 55-56°C. It could be distilled at 170°C and 1.50 mm Hg (lit.$^{10}$ 174°C C/2 mm Hg). Some decomposition of the product occurred.
during the distillation. On standing, the oily product crystallized to give solid material melting at 57-58°C (lit.² mp 59°C). Tryptophol could also be chromatographed with CHCl₃ and activated alumina to give a white crystalline product, mp 58-59°C, ir (CHCl₃): 3510 (OH), 3040, 1600, 1040 cm⁻¹, nmr: 2.20 (OH proton), 2.80 (CH₂ attached to O), 3.75 (CH₂ attached to the ring), 8.10 (NH proton). When shaken with D₂O bands at 2.20 and 8.10 were changed in intensity.

2-(Indol-3-yl)ethanol (Tryptophol) (IV) Method B

The same procedure used for making this compound from ethyl-2-(indol-3-yl)glyoxylate was used for 1.00 g of indole-3-acetic acid. A total of 0.500 g (55%) of the tryptophol was obtained, mp 50-52°C, ir: identical to the ir of previously made tryptophol.

2-(Indol-3-yl)ethylbenzoate (V)

To a 10-ml, round-bottomed flask were added 1.00 g of the tryptophol (6.00 mmoles) and 0.960 g of pyridine (12.0 mmoles). To the above solution was added 1.00 g of benzoyl chloride (7.00 mmoles). Heat was evolved, then the warm, cloudy solution was shaken and allowed to sit at room temperature for 3 hr. The mixture was filtered through 5.00 g of activated alumina and the solution was evaporated to dryness in vacuo. To the yellow oil were added to portions of 20.0 ml of toluene and the mixture evaporated to dryness in vacuo. Each time, a pale white solid was
obtained which was washed with 10.0 ml of petroleum ether and dried in vacuo at 40°C overnight. A yield of 1.30 g of white crystals were obtained (80%), melting point 75.5-75.8°C (lit. mp 76°C), ir: 3420, 1710 cm⁻¹, nmr: 3.20 (CH₂ on the ring), triplet at 4.55 (OCH₂), multiplet between 6.80-8.10 (aromatic protons). It can be recrystallized from ether/petroleum ether.

2-(Indol-3-yl)ethyl p-Toluene Sulfonyl Chloride (VI) and (VII)

To a 25-ml, round-bottomed flask were placed 2.01 g of p-toluene sulfonyl chloride (10.0 mmoles), 10.0 ml of pyridine, and 0.900 g of the tryptophol (5.00 mmoles). The above solution was kept at 5°C for 48 hr, then cold water was added to it, and it was extracted with CHCl₃. The chloroform extract was washed well with two 20.0-ml portions of water and then dried over magnesium sulfate, filtered, and the solution was evaporated to 1.00 g of an oil. By adding ether to the oil and triturating, a light brown solid was obtained which was determined by nmr to be an excess of p-toluene sulfonyl chloride (singlet at 2.25 and no triplet for any CH₂ groups). The brown solid weighed 250 mg.

The ether soluble portion was evaporated to a dark oil which weighed 700 mg, ir: 3450, 2400, 1900, 1600 cm⁻¹, nmr: triplet at 3.22 (CH₂ on indole ring), triplet at 3.68 (CH₂ on OTs), multiplet from 6.90-7.50 (ring protons).
This is compound VI.

In the work-up of this compound when 3 N HCl was used instead of H₂O to eliminate pyridine, 2-(indol-3-yl)-ethyl chloride was obtained with no trace of the indole tosylate. The melting point is 72-73°C, ir: 3410, 1600, 1550 cm⁻¹, nmr: triplet at 3.20 (CH₂ on indole ring), triplet at 3.75 (CH₂ on Cl), multiplet from 6.90-7.80 (ring protons).

This is compound VII.

2-(Indol-3-yl)ethyl Bromide (VIII)

To a 250-ml, round-bottomed flask equipped with stirrer, addition funnel, and condenser with drying tube were placed 3.00 g of tryptophol (18.6 mmoles) and 150 ml of anhydrous ether. To the above solution 0.600 ml of PBr₃ (6.30 mmoles) in 20.0 ml of anhydrous ether was added in 2 min. Immediately after the addition of the PBr₃, a dark oily precipitate was formed. The mixture was stirred at room temperature overnight, then the ether solution was decanted and the precipitate was washed with two 10-ml portions of ether. All the ether solutions were added together and washed with cold water twice, dried over magnesium sulfate, filtered, and evaporated to a light pink solid which was recrystallized from n-hexane to give 3.00 g (70%) of 2-(indol-3-yl)ethyl bromide. The melting point was 98.0-98.3°C (lit.¹⁹ mp 98.5-99.0°C), ir: 3420 cm⁻¹, nmr: multiplet from 3.10-3.70 (methylene protons), multiplet from 7.00-7.65 (ring protons). The tlc showed one
spot in benzene and silica gel. The bromide is both heat and light sensitive.

2-(Indol-3-yl)ethyl Iodide (IX)

To a 150-ml, round-bottomed flask were placed 50 ml of CS₂ and 0.546 g of red phosphorous (20.0 mmoles), then 6.70 g of I₂ (67.0 mmoles) was added in five portions within 10 min. The mixture was stirred for 1 hr and then it was added to a solution of 7.20 g of the tryptophol (45.0 mmoles) in 150 ml of CS₂, and the mixture was stirred overnight at room temperature. The solution was decanted and the brownish red precipitate was washed with CS₂. All the CS₂ solutions were added together and washed with three 100-ml portions of saturated sodium thiosulfate, followed by two 100-ml portions of water. The CS₂ extract was dried over magnesium sulfate, filtered and the CS₂ was distilled in vacuo. A pale white solid was obtained which weighed 7.50 g (61.5%) and the melting point was found to be 115.5-115.7°C, ir: 3420 cm⁻¹, nmr: a sharp singlet at 3.35 (methylene protons), multiplet from 6.95-8.20 (ring protons). The tlc showed one spot near the solvent front in benzene and silica gel.

Anal. Calcd for C₁₀H₁₀NI: C, 44.30; H, 3.72; I, 46.81; N, 5.17. Found: C, 44.30; H, 3.74; I, 46.71, N, 5.04.

The 2-(indol-3-yl)ethyl iodide was also made with various PI₃ to alcohol ratios and also with ether as a sol-
vent, but the most pure material and the best yield was obtained with the exact procedure as described above.

Reduction of 2-(Indol-3-yl)ethyl Iodide

The hydrogenation of 2-(indol-3-yl)ethyl iodide with Raney nickel and Pd/C with and without heating was unsuccessful and in all the above reactions starting material was obtained.

Reduction with LiAlH₄ and also with Zn and HCl resulted in an unidentified oil.

2-(Indol-3-yl)ethyl Azide (X) Method A

To a round-bottomed flask equipped with condenser and stirrer were placed 50.0 ml of 70% solution of water/methanol and 81.0 mg (1.10 mmoles) of sodium azide. Then 224 mg (1.00 mmole) of the 2-(indol-3-yl)ethyl bromide in 2.00 ml of methanol was added to the above solution. The milky solution was heated at 90°C overnight and was then cooled to room temperature, extracted with ether, and washed with two 20.0-ml portions of H₂O. The ether extract was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 130 mg of light brown oil (70.5%), ir (film): 2100 cm⁻¹ (azide), nmr: triplet at 2.80 (CH₂ connected to indole ring), triplet at 3.25 (CH₂ attached to N₃), multiplet from 6.58-7.55 (ring protons).

2-(Indol-3-yl)ethyl Azide (X) Method B

To a 150-ml, round-bottomed flask were placed 10.8 g (40.0 mmoles) of 2-(indol-3-yl)ethyl iodide and 70.0 ml of
dimethyl formamide. Then 5.20 g of sodium azide (80.9 mmoles) in 20 ml of H₂O was added to the above solution. It was found that the elimination of H₂O from the solvent resulted in lower yields. The solution was heated at 100-110°C for 2 hr. Temperatures above 120°C or longer periods of heating tend to decompose the azide. Most of the remaining DMF was then distilled in vacuo. The remaining cloudy mixture was added to 100 ml of ice water and a brown oil settled down. The water/oil mixture was extracted with two 100-ml portions of ether and the ether extracts were washed with three 100-ml portions of water. The extract was then dried over magnesium sulfate, filtered, and evaporated in vacuo to 3.55 g of a light brown oil (96%). The ir and the nmr were identical to the azide made by Method A.

Attempted fractional distillation in vacuum was not successful. The azide decomposed to a dark brown solid during the distillation.

The azide was successfully distilled to a colorless oil by molecular distillation.²⁰ The ir (film) and nmr were identical to that of the azide made by Method A. The uv showed a band at 290 μm.

Anal. Calcd for C₁₀H₁₀N₄: C, 64.51; H, 5.41; N, 30.10. Found: C, 64.50; H, 5.48; N, 28.67.

Photolysis of 2-(Indol-3-yl)ethyl Azide

Irradiations were carried out in a quartz flask.

To a quartz flask were placed 300 mg (1.60 mmoles) of
2-(indol-3-yl)ethyl azide and 100 ml of redistilled and dried p-dioxane and the solution was irradiated for five days with a 450-watt mercury lamp 6-10 cm from the flask. The reaction temperature stayed around 100°C during the irradiation. The solvent was removed in vacuo and the residue was washed well with water. It was then dissolved in 50.0 ml of methanol and dried over magnesium sulfate, filtered and distilled in vacuo to give 250 mg of a dark oil. From the oil a brown precipitate was formed by adding 20.0 ml of ether, filtering, and drying in vacuo. This yielded 50.0 mg. It did not have a sharp melting point, but decomposed around 160-165°C. Attempts to find a solvent for recrystallization were not successful. The ir showed a band at 3430 cm\(^{-1}\) (NH), but a band around 2100 cm\(^{-1}\) (azide) was not present. The nmr spectrum in dimethyl sulfoxide was not very clear. The uv spectrum was similar to that of azide. Attempted chromatography was not successful. This material remained unidentified (XI).

Photolysis of the azide at room temperature resulted in the starting material. The solution of ether which did not give any precipitate showed a sharp band at 2120 cm\(^{-1}\) in the ir which indicates the presence of starting material.

**Thermolysis of 2-(Indol-3-yl)ethyl Azide**

To a three-necked, round-bottomed flask equipped with an adapter which was connected to a dry ice trap was placed
1.00 g of 2-(indol-3-yl)ethyl azide. A nitrogen stream was introduced to the flask throughout the reaction. The reaction vessel was heated in an oil bath at 200-240°C for 3 hr. A black, gummy substance was formed which, upon the addition of ether and stirring, was converted to a black solid. The black solid was dissolved (most of it) in hot methanol, charcoaled, and filtered over celite. The filtrate was charcoaled, heated, and filtered over celite three more times. The solution was evaporated in vacuo to a brown solid which weighed 500 mg. Recrystallization of the solid was not successful because of failure to find an appropriate solvent. The thermolysis product had a similar ir, uv and nmr as the photolysis product. It did not have a sharp melting point but decomposed around 160-167°C. As in the case of the photolysis product, this compound was unidentified (XI).

**1-[2-(Indol-3-yl)ethyl]-4,5-bis-Methoxycarbonyl-v-Triazole (XIV)**

To a three-necked, round-bottomed flask equipped with stirrer, addition funnel, and a condenser with drying tube were placed 1.00 g of the 2-(indol-3-yl)ethyl azide (54.0 mmoles) and 10.0 ml of p-dioxane. To the above solution was added a solution of 1.00 g dimethyl acetylenedicarboxylate (71.0 mmoles) and 5.00 ml of p-dioxane in a 3-min period. The solution was heated at 100°C for 5 hr; then the p-dioxane was removed in vacuo. A light yellow solid
was obtained which was washed with 10.0 ml of ice cold ether, filtered, and dried to give 1.40 g of light yellow product (80%). The triazole was recrystallized from methanol using charcoal to give a melting point of 127.0-127.5°C, ir: 3360, 1715, 1690, 1200 cm⁻¹, uv (methanol): 220, 275, 283, 292 mu, nmr (deuterated pyridine): triplet from 3.25-3.45 (CH₂ on indole ring), singlet at 3.45 (CH₃ on oxygen connected to C-4 of triazole ring), singlet at 3.75 (CH₃ on oxygen connected to C-5 of triazole ring), triplet at 4.75-5.01 (CH₂ on triazole ring), multiplet at 6.95-7.75 (ring protons).

Addition of dimethyl acetylenedicarboxylate to the azide without using any solvent resulted in an uncontrolably violent reaction. When ether was used as the solvent, the reaction did not go to completion. The triazole made by using p-dioxane as a solvent (above procedure) was sent for analysis.

_Anal._ Calcd for C₁₆H₁₆N₄O₄: C, 58.54; H, 4.91; N, 17.07. Found: C, 58.55; H, 5.07; N, 16.98.

1-[2-(Indol-3-yl)ethyl]-4- and -5-Methoxycarbonyl-v-Triazole (XV)

Methyl propiolate and the 2-(indol-3-yl)ethyl azide were allowed to react according to the procedure used for compound XIV. An 81% yield of triazoles was obtained. From the observed tlc (CHCl₃ and a drop of methanol with silica gel) and from the nmr, it was determined that the
product was a mixture of the 4- and 5-isomers. The mixture melted at 150-165°C (could not obtain good melting points), ir: 3250-3350 cm⁻¹ (N-H), 3150 cm⁻¹ (triazole H), 1720 cm⁻¹ (ester carbonyl), nmr (deuterated pyridine): triplet from 3.26-3.55 (CH₂ on indole ring), singlet at 3.65 (CH₃ on oxygen connected to C-4 of triazole ring), singlet at 3.70 (CH₃ on oxygen connected to C-5 of triazole ring), triplet from 4.65-4.85 (CH₂ on the triazole ring), multiplet from 7.10-7.75 (ring protons), singlet at 8.30 (H on C-5 of triazole ring), singlet at 8.50 (H on C-4 of triazole ring).


Separation of 4- and 5-Isomers of Compounds XV, XVa and XVb

The mixture of two isomers was dissolved in hot methanol and cooled to approximately 10°C. This process was done ten times and all the crystals obtained were collected and recrystallized with methanol again. The crystals obtained were dried and set aside for identification (compound XVa). All the methanol filtrates were collected and run through an alumina column followed by a silica gel column using CHCl₃ as an eluting solvent. The CHCl₃ solutions were evaporated to dryness to give a mixture of both 4- and 5-isomers by nmr and tlc (CHCl₃ and a drop of MeOH in silica gel). The minor isomer could not be isolated (XVb). Compound XVa was identified by nmr, tlc and melting
point to be the major product which is 1-[2-(indol-3-yl)ethyl]-5-methoxycarbonyl-1H-triazole. The uv was similar
to the uv of compound XIV, and the ir was the same as com-
 pound XV, nmr (deuterated pyridine): triplet from 3.26-
3.55 (CH$_2$ on the indole ring), singlet at 3.70 (CH$_3$ on
oxygen connected to C-5 of triazole ring), triplet from
4.70-4.90 (CH$_2$ on triazole ring), multiplet from 7.15-7.75
(ring protons), singlet at 8.50 (H on C-5 of triazole ring).

Anal. Calcd for C$_{14}$H$_{14}$N$_4$O$_2$: C, 62.20; H, 5.22;
N, 20.73. Found: C, 60.65; H, 5.48; N, 20.49.
BIBLIOGRAPHY


