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The Wittig Reaction with Carbohydrates and the Addition of Benzenesulfonyl Azides to Indoles

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THE WITTIG REACTION WITH CARBOHYDRATES AND
THE ADDITION OF BENZENESULFONYL AZIDES TO INDOLES

by

George R. Wellman

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Doctor of Philosophy

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The author wishes to thank Dr. George Slomp of the Upjohn Company for his aid in the interpretation of nmr spectra including the computer simulated spectrum of one compound.

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INTRODUCTION

This dissertation is divided into two parts. The first part discusses some Wittig reactions of stabilized phosphonium ylids with aldehydo carbohydrates.

In order to determine if the basicity of the ylids could be correlated with the eventual success of the Wittig reactions involving carbohydrates, a series of ylids were prepared and their relative basicities determined. Each ylid was then reacted with two aldehydo carbohydrates.

In the course of this work, the preparation of 2-acetamido-3,4,5,6-tetra-O-acetyl-2-deoxy-aldehydo-D-glucose as an example of an aldehydo amino sugar was attempted. This compound could not be prepared, but a discussion of the chemistry involved in the products obtained in the attempt is included.

In the second part, the chemistry of the addition of substituted benzenesulfonyl azides to indoles is discussed. In the case of the addition to 1-methylindole, two products were obtained from each reaction. The normal 2-substituted products showed a tautomeric equilibrium which was substituent and solvent dependent. The 3-substituted products did not show a tautomeric equilibrium. The preparation and properties of certain model compounds used to help assign the proper structures to the products is also discussed.
PART I

THE WITTIG REACTION
WITH CARBOHYDRATES
HISTORICAL

In 1919, Staudinger\textsuperscript{1} discovered that the reaction of a carbonyl compound \((1)\) with a phosphorous ylid \((2)\) produced an olefin \((3)\) and a phosphine oxide \((4)\).

\[
\begin{array}{c}
\text{R-C-R'} + \text{R''}_3\text{PCH} \\
\text{R} \text{CH} \end{array} \rightarrow \begin{array}{c}
\text{R'-C=CH} + \text{R''}_3\text{P-O} \\
\text{R} \end{array}
\]

This reaction was later named the Wittig reaction after George Wittig who extensively studied the reaction in the 1940's and 1950's.\textsuperscript{2}

Since Wittig's work, many other people have studied the reaction and its applications.\textsuperscript{3}

Phosphorous ylids are generally very reactive compounds and are generated for use in situ by treatment of a phosphonium salt with a strong base under anhydrous conditions. This is known as the "salt method" and choice of a suitable base depends upon the acidity and structure of the phosphonium salt.\textsuperscript{4} Strong electron withdrawing groups on an ylid such as \(\text{2}\) confer much stability to the system. When \(\text{R''}\) is an electron withdrawing group such as acetyl, the resulting ylid is stable enough to be isolated and stored. Such ylids are termed "stabilized ylids".\textsuperscript{5}

Since the first step in the Wittig reaction is the nucleophilic attack on the carbonyl by the ylid, it has been suggested that measuring the basicity of the ylid would shed light on its reactivity.
For the "stabilized ylids" this initial attack is believed to be the slow step in the reaction.\textsuperscript{15} The method that has been used to determine the relative basicities of the ylids has been the potentiometric titration of the ylid with aqueous acid. The resulting data is reported as the pK\textsubscript{a} value of the ylid conjugate acid. Therefore the higher the pK\textsubscript{a} value, the greater the basicity of the ylid.\textsuperscript{16}

It was stated earlier that electron withdrawing groups, properly placed, can greatly stabilize an ylid. This can be readily understood by consideration of the important resonance structures (5, 6 and 7) of the ylids.

\[
\begin{align*}
R'\text{3P-C\text{-CH-C-R}} & \rightleftharpoons R'\text{3P-C\text{-CH-C-R}} \\
5 & \rightleftharpoons 6 \\
6 & \rightleftharpoons 7
\end{align*}
\]

The greater the charge localization on carbon as in 5, the greater the basicity and nucleophilicity of the ylid.\textsuperscript{32} Likewise, resonance structures such as 6 ought to stabilize the ylid and reduce its nucleophilicity and basicity. As structure 6 becomes more important in the resonance hybrid, the infrared band for the carbonyl group shifts to longer wavelengths, corresponding to increased carbon-oxygen single bond character in the carbonyl group. Speziale and Ratts\textsuperscript{17} have used these measurements as a guide to ylid reactivity.

The Wittig Reaction with Carbohydrates

A wide variety of carbonyl compounds have been studied although...
the reaction is normally considered with aldehydes and ketones. The use of carbohydrate derivatives as the carbonyl component of the reaction was first reported in 1963 by Kochetkov and Dmitriev. They studied the Wittig reaction of carbethoxymethylenetriphenylphosphorane \((\mathcal{S}, R' = \text{phenyl, } R = \text{OCH}_2\text{CH}_3)\) with a variety of monosaccharides as well as with some acetylated aldehydo carbohydrates. Other workers have shown that certain ylids reacted with acetal and ketal protected aldehydo carbohydrates.

Generally the presence of other functional groups in the aldehyde or ketone does not interfere with the Wittig reaction. Bohlmann and Inhoffen were able to carry out the Wittig reaction with an aldehyde that also contained an ester function. Thus it is not surprising that successful Wittig reactions have been applied to ester protected aldehydo carbohydrates.

It has been observed that two cyclic ylids, succinimidenetriphenylphosphorane \((8)\) and its N-phenyl derivative \((9)\) did not react smoothly with 2,3,4,5,6-penta-O-acetyl-aldehydo-D-glucose.\(^{12}\)

\[\begin{array}{c}
\phi_3P = \text{N-H} \\
8 \\
\phi_3P = \text{N-}\phi \\
9 \\
\phi_3P = \text{O} \\
10
\end{array}\]
Heyda and Theodoropulos\textsuperscript{13} observed that ylids 8 and 2 reacted normally with aldehydes while the related ylid 10 gave tarry reaction mixtures. Hauser et al\textsuperscript{14} have suggested that the basic ylids can catalyze aldol condensations and polymerizations. However, it is not clear whether this explains the unsuccessful reaction of 2,3,4,5,6-penta-O-acetyl-aldehydo-D-glucose with 5 and 6 since the more basic ylid, carboxethoxy-methylidenetriphenylphosphorane, reacted normally with this aldehyde.\textsuperscript{12}

The purpose of the present work was to explore more fully the reaction of stabilized ylids with aldehydo carbohydrates. It was desired to prepare a large number of ylids possessing a wide range of reactivity. The aldehydes selected were the well-known 2,4,3,5-di-O-benzylidene-aldehydo-D-ribose and 2,3,4,5,6-penta-O-acetyl-aldehydo-D-glucose. In addition, as an example of an aldehydo amino sugar, 2-acetamido-3,4,5,6-tetra-O-acetyl-2-deoxy-aldehydo-D-glucose was chosen because it was reported in the literature and the starting materials were readily available. This latter compound could not be prepared but the chemistry of its attempted synthesis was quite interesting.
DISCUSSION

Preparation and Reactivities of the Ylids

The ylids used in this study are listed in Table 1. They were all prepared via the "salt method". The phosphonium salts (13a-e) were obtained by reaction of triphenylphosphine (11) with the appropriate α-halo carbonyl compound (12a-e) in benzene.

\[
\text{11} \quad \text{12a-e} \quad \text{13a-e} \quad \text{14a-e}
\]

\[\text{R} \in \{\text{NH}_2, \text{OEt}, \text{CN}, \text{CH}_3, \text{Phenyl}\}, \quad \text{X} \in \{\text{Br, Cl}\}\]

The phosphonium salts were then dehydrohalogenated using sodium hydroxide in water to give the ylids (14a-e).

The pKa values of the ylid conjugate acids were determined by the method of Speziale and Ratts. The ylids are listed in decreasing order of relative basicity in Table 1. The carbonyl absorption peaks in the ir spectra of 14a, b, d and e are also listed. The ylid reactivities predicted from infrared data roughly parallel those
obtained by consideration of their relative basicities.

Table 1

Relative Basicities of Ylids and their Carbonyl Infrared Peaks

<table>
<thead>
<tr>
<th>Ylid</th>
<th>pKa of conjugate acid</th>
<th>$\nu_{\text{nujol}}$ max for C=O</th>
</tr>
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<tr>
<td>$14a$</td>
<td>10.6</td>
<td>1626 cm$^{-1}$</td>
</tr>
<tr>
<td>$14b$</td>
<td>8.8</td>
<td>1615</td>
</tr>
<tr>
<td>$14c$</td>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>$14d$</td>
<td>6.4</td>
<td>1525</td>
</tr>
<tr>
<td>$14e$</td>
<td>6.0</td>
<td>1590</td>
</tr>
</tbody>
</table>

The basicities of ylids $14a-e$ reported as the pKa value of the conjugate acid, ranged from 6.0 to 10.6. The comparable pKa values for the conjugate acid of $5$ and $6$ are 7.1 and 6.5 respectively. Thus these ylids have a spread of basicities both above and below those of ylids $5$ and $6$.

Preparation of the Aldehydo Carbohydrates

The preparation of the aldehydo carbohydrates followed literature procedures. The first step in the preparation of $2,3,4,5,6$-penta-$O$-acetyl-aldehydo-$D$-glucose ($17$) was the mercaptalation of $D$-glucose using ethyl mercaptan in concentrated hydrochloric acid. The resulting mercaptal ($15$) was then acetylated yielding $16$ which was demercaptalated to give the desired aldehydo glucose derivative ($17$).
The preparation of 2,4,3,5-di-O-benzylidene-aldehyde-D-ribose (20) was accomplished via its di-n-propyl mercaptal (18). The OH groups in 18 were protected by the formation of benzylidene acetals to give compound 19. This compound was demercaptalated using mercuric chloride, mercuric oxide and water to yield the desired aldehyde ribose derivative (20).
The attempted preparation of 2-acetamido-2-deoxy-3,4,5,6-tetra-
O-acetyl-aldehyde-D-glucose is discussed later in this paper.

The Results of the Wittig Reactions

The Wittig reactions of ylids 14a-e with the aldehyde carbohy-
drates (17) and (20) were carried out in refluxing tetrahydrofuran
(THF) to give the products 21-30. This solvent was chosen because
ylid 14a decomposed in hot protonic solvents and it was desired to
use the same solvent for all of the reactions. The yields of these
reactions are recorded in Table 2.
21 and 26, R=NH₂
22 and 27, R=OEt
23 and 28, R=CN (where R replaces O⁻)
24 and 29, R=CH₃
25 and 30, R=Phenyl

21-25

26-30
Table 2

Percent Yields of the Wittig Reactions with Carbohydrates

<table>
<thead>
<tr>
<th>Ylid</th>
<th>Product from 17</th>
<th>Yield</th>
<th>Product from 20</th>
<th>Yield</th>
</tr>
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<tr>
<td>14a</td>
<td>21</td>
<td>55%</td>
<td>26</td>
<td>64%</td>
</tr>
<tr>
<td>14b</td>
<td>22</td>
<td>80</td>
<td>27</td>
<td>75</td>
</tr>
<tr>
<td>14c</td>
<td>23</td>
<td>48</td>
<td>28</td>
<td>60</td>
</tr>
<tr>
<td>14d</td>
<td>24</td>
<td>73*</td>
<td>29</td>
<td>82</td>
</tr>
<tr>
<td>14e</td>
<td>25</td>
<td>57</td>
<td>30</td>
<td>63</td>
</tr>
</tbody>
</table>

*6 hours in refluxing THF, all others for 2 hours in refluxing THF.

The reactions were run for 2 hr except for the reaction of ylid 14d with 2,3,4,5,6-penta-O-acetyl-aldehydo-D-glucose (17). In this case the reaction required 6 hr for completion. The reactions were followed using thin-layer chromatography (tlc). The yields recorded in Table 2 are based on actual recovery after purification and do not reflect upon the rate of the various reactions.

The Attempted Preparation of 2-Acetamido-2-deoxy-3,4,5,6-tetra-O-acetyl-aldehydo-D-glucose

The preparation of 2-acetamido-2-deoxy-3,4,5,6-tetra-O-acetyl-aldehydo-D-glucose was first reported by Kent in 1950. The synthetic route was similar to that reported for the preparation of other aldehydo sugars.
N-Acetyl-D-glucosamine (31) was prepared by selective N-acetylation of D-glucosamine hydrochloride using silver acetate and acetic anhydride in methanol. The melting point of this product agreed closely with that reported by White, but the specific rotation was lower ($\alpha$D = +33.7 (c 1, H2O)) compared to +41.2 reported by White. The nmr and ir spectral characteristics were consistent with the proposed structure and it gave a satisfactory C and H elemental analysis.

Compound 31 was converted to 32 by the procedure of Wolfrom and Anno. Its physical constants agreed with those reported by them and also those reported by Kent et al. Wolfrom, Lemieux and Olin first reported the preparation of 32 in 1949. However, this was
retracted in 1952 when they showed that the original compound obtained was a tetraacetyl rather than a pentaacetyl derivative. They also reported the correct physical constants for compound 33 in that paper: mp 75-77°; $\alpha_D^{28} +1$ (c 4, CHCl$_3$). In between Wolfrom's papers, Kent reported in 1950 that he had obtained compound 33 which was used as an intermediate in the preparation of the desired aldehydo glucosamine (34). The physical constants reported for 33 were: mp 160-161°; $\alpha_D +2$ (c 1, CHCl$_3$). Whitehouse, Kent and Pasternak reported in 1954 the full paper corresponding to Kent's 1950 preliminary communication. They noted in this paper that Wolfrom had disputed some of their earlier work and then gave complete experimental details for the preparation of 32, 33 and 34. In this paper, however, they give different constants yet for 33 which were: mp 177°; $\alpha_D -36.5$ (c 0.5, CHCl$_3$). They make no mention of the discrepancy in their own constants for 33.

In this work, the conversion of 32 to 33 was accomplished by the procedure of Wolfrom et al. Following this procedure, a syrup was obtained which could not be crystallized. The specific rotation, $\alpha_D^{25} -2.5$ (c 3.8, CHCl$_3$), agreed most closely with that reported by Wolfrom et al. The nmr and ir spectral data were in complete agreement with the proposed structure of 33. Furthermore, it gave satisfactory C, H, N and S elemental analyses. Therefore despite the disparity in physical constants previously reported and those obtained in this work, the product obtained from 32 was believed to be 33.

Kent et al reported the demercaptalation of 33 to 34 using CdCO$_3$ and HgCl$_2$ in aqueous acetone followed by chromatography over
cellulose. The product \( 3^4 \) was apparently obtained from \( 3^3 \) from re-
actions reported in both papers although as noted above, the reported
constants for \( 3^3 \) varied significantly in the two papers. The reported
yield, given in the 1954 paper only, was 7%. The constants for this
product were essentially the same in both papers: mp 156°; \([\alpha]_D^0 +36 \)
(\( c 1 \), CHCl\(_3\)). In a personal communication, Paul Kent was unable to
offer any suggestions nor could he provide a sample of his material.\(^{33} \)

Following the procedure of Kent, the conversion of \( 3^3 \) to \( 3^4 \) was
tried. The reaction was followed by tlc and it was observed that there
were two new spots, A and B, formed during the reaction. At the end of
the reaction only spot B remained. Spot A appeared to be an interme-
diate in the formation of B since its concentration appeared to build
up as the starting material was consumed and eventually diminished as
the concentration of B was increasing.

The final product in this reaction, corresponding to spot B,
was isolated. It was an aldehyde but the physical constants, mp
105-107°, \([\alpha]_D^{25} = -49 \) (\( c 1 \), CHCl\(_3\)), did not agree with those reported
by Kent\(^{18,22}\) for \( 3^4 \). Furthermore, the elemental analysis (C, H, and N)
suggested the empirical formula \( C_{14}H_{19}O_5N \) while that of \( 3^4 \) was
\( C_{16}H_{23}O_10N \). The difference in these formulas shows the loss of
\( C_2H_4O_2 \), or acetic acid. The infrared spectrum showed a peak at 1680
cm\(^{-1}\) suggesting the presence of an \( \alpha,\beta \) unsaturated aldehyde. The ir
spectrum also showed two other carbonyl peaks which was consistent with
the presence of O-acetate and N-acetate groups. The compound was as-
signed structure \( 3^5 \) based on the assumption of trans elimination of
acetic acid from \( 3^4 \). The same product was obtained when HgO was

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substituted for CdCO₃.

\[
\text{AcHN}\quad \text{CHO}
\]

The NMR spectrum of 35 revealed some unusual features. It was apparent from the spectrum that the rotation about some of the bonds in the molecule was hindered since the two protons on the terminal carbon were coupled with different J values to the other protons. The spectrum, a portion of which is shown in Figure 1, was interpreted by Dr. George Slomp of the Upjohn Company. Figure 2, also courtesy of Dr. Slomp, shows the 6th computer iterated simulated spectrum from which the chemical shifts and coupling constants are reported.

Since there apparently was an intermediate product (spot A) in the formation of 35, it was important to isolate and identify this other material. By interrupting the reaction before completion and chromatographing the mixture, it was possible to isolate this intermediate in low yield. This compound was not an aldehyde and its physical constants also did not agree with those reported by Kent for 34. It was characterized by its elemental analysis and spectral data as the oxazoline(36).
It was obtained in two crystalline forms which at first were felt to be the two diastereomers made possible by the creation of a new asymmetric center at carbon 1. However, both the forms had the same rotation (within experimental error) and could be intraconverted by carefully controlling the crystallization conditions. This clearly demonstrated that they were not diastereomers.

The assignment of the oxazoline structure (36) rather than some alternate structure such as an acetylated aziridine (36a) was based on two arguments. First, examples of anchimeric assistance of this type have been previously reported to involve oxazolines which were isolated.\textsuperscript{23,24} Secondly, in the nmr spectrum of 36, the methyl group of the oxazoline appeared as a doublet (\(J = 1.2\) Hz) at 1.95 \(\delta\). This was consistent with the nmr data reported for other oxazolines. For instance, Weinberger and Greenbalgh\textsuperscript{25} have reported that the methyl group of a series of methyl oxazolines (37) resonates at 1.95 \(\delta\) and is coupled to the protons on carbon 2 with a coupling constant of 1.4 Hz.
EXPERIMENTAL

General Procedures

The melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the infrared (ir) spectra. Ultraviolet spectra (uv) were obtained using a Cary 14 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60 instrument with solvents as noted. Tetramethylsilane (TMS) was used as the internal reference with all chemical shifts reported in $\delta$ units downfield from TMS. Elemental analyses were performed by Midwest Microlab Ltd. of Indianapolis, Indiana. Optical rotations were measured with a Beckman DU-2 fitted with a Keston polarimeter. Thin-layer chromatography (tlc) was done on glass microscope slides coated with Silica Gel G (acc. to Stahl) purchased from EM reagents, division of Brinkman, Westbury, New York. The slides were developed with solvents as noted. The spots were detected using iodine vapor and/or by sulfuric acid charring. Column chromatography was done on a 3X60 cm column using Baker's 60-200 mesh silica gel. The physical constants and spectral data reported are for analytical samples of the compounds in question unless otherwise stated.
Preparation of Compounds

Preparation of carbamoylmethylenetriphenylphosphorane (14a)

Chloroacetamide (9.4 g, 0.10 m) was added to a solution of triphenylphosphine (16.2 g, 0.10 m) in 200 ml of benzene. The solution was refluxed for 48 hr and the precipitate collected by filtration. The precipitate was dissolved in a small amount of hot 50% ethanol-water and the solution cooled to 0°. After cooling, 6N NaOH was added rapidly with vigorous stirring while maintaining the temperature at 0° until the solution was just basic. The precipitate was then collected quickly, washed with cold water, and dried under reduced pressure to yield 24 g (76%) of 14a, mp 175-177° (lit.26 mp 177-178°). Prior to use, this compound was pulverized and washed with cold ether to remove triphenylphosphine oxide.

Preparation of carboxethoxymethylenetriphenylphosphorane (14b)

Triphenylphosphine (15 g, 0.1 m) was added to a solution of ethyl bromoacetate (15 g, 0.1 m) in 500 ml of benzene. The solution was refluxed for 12 hr and the resulting precipitate collected and dissolved in a small amount of hot 30% ethanol-water. The solution was cooled to 5-10° and made alkaline by the addition of 6N NaOH. The mixture was set aside in a refrigerator to allow the oil to crystallize. The solid product was collected, washed with water, and twice recrystallized from ethyl acetate and petroleum ether (60-110°) to yield 16 g (75%) of 14b, mp 123-124°, (lit.28 mp 124°).

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Preparation of cyanomethylenetriphenylphosphorane (14c)

Triphenylphosphine (38 g, 0.15 m) was added to a solution of chloroacetonitrile (11 g, 0.15 m) in 500 ml of benzene and the resulting solution refluxed for 24 hr. After cooling, the precipitate was collected and dissolved in a small amount of hot 50% ethanol-water and this solution cooled to 5°. It was then made basic by the addition of 6N NaOH and the resulting mixture refrigerated for 12 hr. The precipitate was recrystallized twice from ethyl acetate-hexane to yield 19 g (45%) of 14c, mp 185-190° (lit.17 mp 190-192°). Before using this product in a reaction, it was pulverized and washed with cold ether to remove triphenylphosphine oxide.

Preparation of acetylmethylenetriphenylphosphorane (14d)

Triphenylphosphine (38 g, 0.15 m) was added to a solution of chloroacetone (12.5 g, 0.15 m) in 500 ml of benzene and the solution refluxed for 24 hr. The precipitate was collected by vacuum filtration and dissolved in a small amount of hot 50% ethanol-water. The resulting solution was then cooled to 10° and made basic by the addition of 6N NaOH with vigorous stirring. The resulting mixture was refrigerated for 10 hr and the precipitate collected and recrystallized from ethanol-water to yield 32 g (68%) of 14d, mp 205-210°, (lit.27 mp 205-206°).

Preparation of benzoylmethylenetriphenylphosphorane (14e)

Triphenylphosphine (38 g, 0.15 m) was added to a solution of
bromoacetophenone (30 g, 0.15 m) in 1000 ml of benzene. The solution was refluxed for 2 hr and the precipitate collected by vacuum filtration. This product was dissolved in 800 ml of ethanol, cooled to 10°, and made alkaline by the addition of 6N NaOH. The solution was allowed to crystallize in a refrigerator and the product collected was recrystallized from ethanol-water to yield 28 g (62%) of 14e, mp 182-185°, (lit.27 mp 178-180°).

Preparation of D-glucose diethyl dithioacetal (15)

Anhydrous D-glucose (100 g, 0.67 m) was dissolved in 85 ml of conc hydrochloric acid while the temperature of the solution was maintained near 0°. Ethyl mercaptan (100 ml) was then added to this solution with vigorous stirring and the stirring continued for 1 hr. The precipitate was collected and crystallized from an aqueous NaHCO₃ solution. The product was collected and washed with cold water and finally cold ethanol to yield 95 g (61%) of 15, mp 125-127°, (lit.31 mp 127°).

Preparation of 2,3,4,5,6-penta-O-acetyl-D-glucose diethyl dithioacetal (16)

D-Glucose diethyl dithioacetal (50 g, 0.17 m) was dissolved in 180 ml of dry pyridine and the solution cooled to 0°. The solution was stirred maintaining a temperature of 0-5° while 360 ml of acetic anhydride was added to it dropwise. The solution was allowed to stand overnight at room temperature, whereupon it was poured into 3 l of cold water. The water was decanted and the oil triturated with
several portions of cold water. The oil was then covered with water and placed in a refrigerator where it crystallized completely after 50 hr. The product was collected and recrystallized from methanol-water to yield 70 g (81%) of 16, mp 44-46°, (lit. mp 45-47°).

Preparation of 2,3,4,5,6-penta-O-acetyl-aldehydo-D-glucose (17)

Mercuric chloride (137 g, 0.5 m) was dissolved in 500 ml of acetone and the solution stirred vigorously while 200 g of dried cadmium carbonate was added. A solution of 2,3,4,5,6-penta-O-acetyl-D-glucose diethyl dithioacetal (50 g, 0.1 m) in 500 ml of acetone was added to it dropwise. The mixture was stirred for 24 hr at room temperature and finally filtered into a flask containing 150 g of cadmium carbonate. The residue was washed with 500 ml of acetone and the washings combined with the filtrate. The combined acetone solution was evaporated under reduced pressure yielding a residue which was extracted with 700 ml of warm chloroform. The chloroform solution was extracted with two 200 ml portions of 10% NaI, distilled water and finally dried using Na₂SO₄. The chloroform was evaporated under reduced pressure yielding a residue which was dissolved in 90 ml of hot acetone. Ether (40 ml) was added followed by the addition of sufficient hexane to cause opalescence. The dispersion was placed in a refrigerator and the crystalline product collected after 20 hr yielding 25 g (62%) of 17, mp 115-117°, (lit. mp 119.5-120.5°).
Preparation of D-ribose di-n-propyl dithioacetal (18)

D-Ribose (30 g, 0.20 m) was dissolved in 30 ml of conc hydrochloric acid and the solution cooled to 0°. To this cold solution, n-propyl mercaptan (25.4 g, 0.33 m) was added slowly with stirring. During this addition, the temperature was maintained at 0°. The mixture was stirred for 1 hr, poured into 300 ml of cold water, and allowed to stand overnight in a refrigerator. The solid product was then collected and recrystallized from an aqueous NaHCO₃ solution to yield 28 g (50%) of 18, mp 78-81°, (lit.²⁹ mp 85°).

Preparation of 2,4,3,5-di-O-benzylidene-D-ribose di-n-propyl dithioacetal (19)

One stick of fused ZnCl₂ (50 g) was stirred in a solution of 100 ml of benzaldehyde for 1-2 hr. D-Ribose di-n-propyl dithioacetal (8 g, 0.03 m) was added to it and the stirring continued for 1 hr. The solution was then poured, with vigorous stirring, into 1000 ml of hot petroleum ether (60-110°). The petroleum ether solution was decanted from the red oil and concentrated under reduced pressure. The crude product obtained in this way was recrystallized from 95% ethanol to yield 6.6 g (46%) of 19, mp 108-109°, (lit.³⁰ mp 110°).

Preparation of 2,4,3,5-di-O-benzylidene-aldehydo-D-ribose (20)

2,4,3,5-Di-O-benzylidene-D-ribose di-n-propyl dithioacetal (6 g, 0.013 m) was dissolved in a solution of 86 ml of acetone and 13 ml of water. Yellow mercuric oxide (8.2 g, 0.04 m) was added to it and the
mixture refluxed for 1 hr. Mercuric chloride (8.6 g, 0.04 m) in 43 ml of acetone was added dropwise in 10 min with vigorous stirring and the refluxing continued for 2 hr. The mixture was filtered using a Celite pad and the filtrate evaporated under reduced pressure. The residue was extracted with warm chloroform. The chloroform solution was extracted twice with a 10% aqueous solution of NaI followed by two portions of water. The chloroform solution was then dried (Na$_2$SO$_4$) and evaporated under reduced pressure to yield 3.7 g (95%) of 20, mp 97-99°, (lit.$^{30}$ mp 99-101°).

**General procedure for the Wittig reactions**

A solution of equimolar (0.006 m) amounts of the appropriate ylid and the aldehyde sugar in 100 ml of tetrahydrofuran was refluxed for 2 hr. The solvent was then removed by evaporation under reduced pressure. The resulting residue was recrystallized twice from ethanol or di-n-butyl ether to yield the products:

2,3-dideoxy-D-gluco-oct-2-enonamide 4,5,6,7,8-pentaacetate (21): mp 130-131°; ir (nujol mull) 3470, 3305, 3195 (NH, OH), 1755, 1690 and 1660 cm$^{-1}$ (C=O). Anal. Calcd for C$_{18}$H$_{25}$N$_2$O$_{11}$: C, 50.11; H, 5.84; N, 3.24. Found: C, 50.07; H, 5.60; N, 3.26.

ethyl 2,3-dideoxy-D-gluco-oct-2-enonate 4,5,6,7,8-pentaacetate (22): mp 133-135° (lit.$^{9}$ mp 133-134.5°).

2,3-dideoxy-D-gluco-oct-2-enonitrile 4,5,6,7,8-pentaacetate (23): mp 125-127°; ir (nujol mull) 2225 (C≡N), 1750 (C=O) and 1645 cm$^{-1}$ (C=C).
**1,3,4-trideoxy-D-gluco-non-3-ulose 5,6,7,8,9-pentaacetate (24):**

mp 123-124°C; ir (nujol mull) 1745, 1670 (C=O) and 1655 cm⁻¹ (C=C).

**2,3-dideoxy-l-G-phenyl-D-gluco-oct-2-enose 4,5,6,7,8-pentaacetate (25):**

mp 93-94°C; ir (nujol mull) 1740, 1675 (C=O) and 1635 cm⁻¹ (C=C).

**4,6,7-di-0-benzylidene-2,3-dideoxy-D-ribo-hept-2-enonamide (26):**

mp 260°C; ir (nujol mull) 3410, 3320, 3090 (NH, OH) and 1680 cm⁻¹ (C=O).

**Ethyl 4,6,7-di-0-benzylidene-2,3-dideoxy-D-ribo-hept-2-enonate (27):**

mp 160-161°C; ir (nujol mull) 1675 (C=O) and 1615 cm⁻¹ (C=C). Anal.

**4,6,7-di-0-benzylidene-2,3-dideoxy-D-ribo-hept-2-enonitrile (28):**

mp 169-171°C; ir (nujol mull) 2225 (C≡N) and 1645 cm⁻¹ (C=C). Anal.
Calcd for C₂₃H₁₉N₂O₄: C, 72.19; H, 5.48; N, 4.00. Found: C, 71.80; H, 5.55; N, 3.92.

**Anal. Calcd for C₂₄H₂₉O₁₁: C, 58.53; H, 5.73. Found: C, 58.27; H, 5.69.**

**Anal. Calcd for C₁₉H₂₆O₁₈: C, 53.02; H, 6.08. Found: C, 53.17; H, 6.05.**

**Anal. Calcd for C₂₃H₂ₖN₄O₅: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.80; H, 5.63; N, 3.79.**

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5,7-6,8-di-O-benzylidene-1,3,4-trideoxy-D-ribo-oct-3-enulose (2g):  
mp 196-197°; ir (nujol mull) 1685 (C=O) and 1645 cm⁻¹ (C=C). Anal.  
Calcd for C₂₂H₂₂O₅: C, 72.11; H, 6.05. Found: C, 71.89; H, 6.04.

4,6-5,7-di-O-benzylidene-2,3-dideoxy-1-C-phenyl-D-ribo-hept-2-enose (3g):  
mp 186-187°; ir (nujol mull) 1675 (C=O) and 1640 cm⁻¹ (C=C). Anal.  
Calcd for C₂₇H₂₄O₅: C, 75.68; H, 5.64. Found: C, 75.84; H, 5.69.

Preparation of N-acetyl-D-glucosamine (31)

D-Glucosamine hydrochloride (100 g, 0.465 m) and silver acetate  
(78 g, 0.465 m) were dissolved in 1000 ml of methanol. Acetic anhy­
dride (67.4 g, 0.660 m) was then added to the stirring mixture and  
stirring continued for 3 hr. The mixture was then refluxed for 5 min  
and filtered hot. The residue was washed with 250 ml of boiling  
water. The filtrate and wash were acidified with about 4 drops of  
conc hydrochloric acid and the solution filtered with the aid of a  
Celite pad after standing for 2 hr. The filtrate was concentrated un­  
der reduced pressure leaving a residue which was crystallized from 100  
ml of ethanol and 200 ml of ether. The product was recrystallized by  
dissolving in the minimum amount of hot water and adding a nine-fold  
excess of hot ethanol. Sufficient ether was then added to cause tur­  
bidity. The crystalline product was collected after 24 hr and yielded  
71 g (70%) of 31: mp 195° d (lit.¹⁹ mp 196° d); [α]²⁵ D +33.7 (c 1,  
H₂O) [lit.⁹ [α]²⁵ D +41.2 (c 1, H₂O)]. Repeated recrystallization  
from ethanol yielded an analytical sample of 31: mp 217-218° d; ir  
(nujol mull) 3460 and 3310 (OH and NH) and 1630 cm⁻¹ (amide C=O); nmr
Preparation of N-acetyl-D-glucosamine diethyl dithioacetal (32):

N-Acetyl-D-glucosamine (10 g, 0.045 m) was dissolved in 40 ml of conc hydrochloric acid and stirred mechanically with 40 ml of ethyl mercaptan for 24 hr at 0°. The reaction mixture was then slowly neutralized by the addition of basic lead carbonate \((\text{PbCO}_3)_2 \cdot \text{Pb(OH)}_2\) in portions with about 235 g required. Water (200 ml) was added to the mixture and the solids filtered off by vacuum filtration. The filtered solids were then extracted with two portions (300 ml) of hot water, and the mixture vacuum filtered again. The combined filtrate and washings were concentrated by vacuum evaporation to yield a residue. The residue was extracted with 100 ml of methanol, filtered and the solvent removed by vacuum evaporation. The resulting residue was recrystallized from methanol-ether to yield in two crops, 8.5 g (69%) of \(32\), mp 122-129° (lit.\(^20\) mp 129.5-130.5°). Recrystallization from methanol-chloroform-ether yielded \(32\): mp 126-128°; \([\alpha]^{25}_D -34 \text{ (c 1, H}_2\text{O)} \) [lit.\(^20\) \([\alpha]^{25}_D -35 \text{ (c 1, H}_2\text{O)} \) ]; ir (nujol mull) 3410, 3340 and 3090 (OH and NH) and 1660 cm\(^{-1}\) (amide \(\text{C}=\text{O}\)); nmr (\(\text{d}_6\text{DMSO}) \delta 7.48 \text{ (d, 1, NH)}\), 4.75-3.90 (m, 6), 3.44 (s, 5), 2.63 (q, 4, \(J = 6.5 \text{ Hz, SCH}_2\text{CH}_3\)), 1.88 (s, 3, COCH\(_3\)), and 1.19 ppm (t, 6, \(J = 6.5 \text{ Hz, SCH}_2\text{CH}_3\)).

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Preparation of 2,3,4,5,6-pentaacetyl-D-glucosamine diethyl dithioacetal (33)

N-Acetyl-D-glucosamine diethyl dithioacetal (9 g, 0.0275 M) was dissolved in 30 ml of dry pyridine. Acetic anhydride (30 ml) was added slowly to this solution at 0°C. The solution was warmed to room temperature and stirred an additional 24 hr. The solution was then poured into 800 ml of ice water and the water extracted with three portions (150 ml) of chloroform. The combined chloroform extract was extracted with a saturated solution of CdCl₂ until no further white precipitate formed. The precipitate was filtered and washed with chloroform. The washings and filtrate were combined and extracted with saturated NaHCO₃, water and finally dried (Na₂SO₄). The solvent was removed under reduced pressure to yield 11.6 g (85%) of the oily product 33. All attempts to crystallize this product failed. It was chromatographed over silica gel eluting with ethyl acetate to yield 9.4 g (80%) of 33 as a colorless glass: [α]²⁷ D -2.5 (c 3.8, CHCl₃); lit.²⁰ mp 75-77°C, [α]²⁸ D +1 (c 4, CHCl₃); lit.¹⁸ mp 160-161°C, [α]²⁵ D +2 (c 1, CHCl₃); lit.¹² mp 177°C, [α]²⁵ D -36.5 (c 0.5, CHCl₃); ir (neat) 3350 and 3270 (NH), 1740 (ester C=O) and 1670 cm⁻¹ (amide C=O); nmr (CDCl₃) 6.05-3.95 (m, 7), 3.20-2.40 (m, 4), 2.15, 2.07, 2.02 (s, total 15) and 1.66-1.07 ppm (m, 6). Anal. Calcd for C₉₀H₃₃N₀₉S₂: C, 48.47; H, 6.71; N, 2.83; S, 12.94. Found: C, 48.73; H, 6.58; N, 2.77; S, 12.68.

Preparation of (Z)-2-acetamido-2,3-dideoxy-D-erythro-hex-2-enose triacetate (35): Method A

Mercuric chloride (37 g, 0.157 M) was dissolved in 140 ml of
acetone. Water (8 ml) was added to this solution and the solution placed in a three neck flask. Cadmium carbonate (54 g, 0.31 m) was added to the rapidly stirring solution and the mixture stirred for an additional 15 min. A solution of 2,3,4,5,6-penta-acetyl-D-glucosamine diethyl dithioacetal (13.5 g, 0.027 m) in 140 ml of acetone was added dropwise to the stirring mixture. The mixture was stirred 24 hr and the mixture filtered into a flask containing 25 g of cadmium carbonate. The solvent was removed from this mixture and the residue extracted with three portions (150 ml) of chloroform. The combined chloroform extract was extracted with three portions (100 ml) of 10% NaI, saturated NaCl solution, and finally dried (Na₂SO₄). The solvent was removed under reduced pressure to yield 1.8 g (17%), mp 98-102° of a purified product. The mother liquor from the recrystallization was concentrated and chromatographed over silica gel eluting with hexane-ethyl acetate (3:7) yielding an additional 2.1 g (20%) of the product. An analytical sample of this material was obtained by repeated recrystallization from ethyl acetate hexane: mp 105-107°; $[\alpha]_{D}^{25} = -49$ (c 1, CHCl₃); ir (nujol mull) 3280 (N-H), 1735 (ester C=O) and 1680 cm⁻¹ (C=O). Anal. Calcd for C₁₄H₂₉NO₈: C, 51.06; H, 5.81; N, 4.25. Found: C, 51.05; H, 5.75; N, 4.27.

**Method B**

2,3,4,5,6-Pentaacetyl-D-glucosamine diethyl dithioacetal (5 g, 0.01 m) was dissolved in 75 ml of acetone and 10 ml of water. Yellow mercuric oxide (6.4 g, 0.074 m) was placed in the solution and the mixture stirred under reflux for 15 min. Mercuric chloride (8.1 g,
0.03 m) in 35 ml of acetone was then added dropwise. The refluxing was maintained for 2 hr. The mixture was then filtered with the aid of a Celite pad and the solids washed with two portions (50 ml) of acetone. The wash and filtrate were combined and the solvent removed under reduced pressure. The residue was extracted with hot chloroform and the chloroform solution extracted with two portions (50 ml) of 10% NaI. The chloroform layer was then washed with water and dried (Na₂SO₄). The solvent was removed under reduced pressure to yield 3.7 g of a crude yellow oil. This oil was chromatographed on silica gel, eluting with ether. Isolated first was 1.2 g (39%) of 35, followed by the isolation of 0.5 g (15%) of 36.

Preparation of D-arabino-1-C-[[4R]-5-(ethylthio)-2-methyl-2-oxazolin-4-yl] tetritol tetraacetate (36)

2,3,4,5,6-Pentaacetyl-D-glucosamine diethyl dithioacetal (2 g, 0.042 m) was dissolved in 100 ml of dry acetone. Yellow mercuric oxide (4 g, 0.185 m) was added to the solution and the resulting mixture refluxed with vigorous stirring. Mercuric chloride (4 g, 0.147 m) was added in portions and the stirring and refluxing maintained for 8 hr. The mixture was then filtered with the aid of a Celite pad and the solids washed with hot acetone. The filtrate and wash were combined and the solvent removed under reduced pressure. The residue was extracted with hot chloroform and the mixture filtered. The filtrate was extracted with two portions (50 ml) of 10% NaI solution, once with water, and finally with saturated NaCl solution. The chloroform solution was then dried (Na₂SO₄) and the solvent removed under reduced
pressure. The residue was extracted with hot petroleum ether (60-110°). This solution deposited a total of 0.5 g of \textsuperscript{26}. There were two crystalline forms which were mechanically separated. The low melting form, mp 88-89°, \([\alpha]^{25} = +204 \quad (c 0.5, \text{CHCl}_3)\), could be converted to the high melting form, mp 98-100°, \([\alpha]^{25} = +206 \quad (c 0.5, \text{CHCl}_3)\), by recrystallization from slowly cooling hexane. The high melting form could be converted to the low melting form by rapid cooling and scratching of the hexane solution. The following spectral constants and elemental analysis are for the high melting crystal: \textit{ir} (nujol mull) 1745 (ester C=O), 1740 (ester C=O) and 1675 cm\(^{-1}\) (C=N); \textit{nmr} (CDCl\(_3\)) \(8\) 2.70 (m, 2, \(J = 7\) Hz, CH\(_2\)-CH\(_3\)), 1.96 (d, 3, \(J = 1.2\) Hz, N=CO-CH\(_3\)), 1.32 (t, 3, \(J = 7\) Hz, CH\(_2\)-CH\(_3\)). \textit{Anal.} Calcd for C\(_{18}\)H\(_{27}\)NO\(_3\)S: C, 49.87; H, 6.28; N, 3.23; S, 7.40. Found: C, 49.63; H, 6.13; N, 3.08; S, 7.48.

**Measurement of relative pK\(_a\) values of the corresponding phosphonium salts of the ylids**

The method used was essentially that of Speziale and Ratts.\textsuperscript{17} Approximately 0.003 M of the desired ylid was dissolved in 50 ml of methanol and titrated with 0.06N hydrochloric acid. The observed pH of the solution (Beckman pH meter, mini electrode) at the half equivalence point was considered the observed pK\(_a\) value of the ylid conjugate acid. The values reported in Table 1 are the mean of four determinations in which the spread of values was within .2 pK\(_a\) units from the mean. While these pK\(_a\) values are not readily comparable to values determined at different concentrations or with different solvent
systems, the only significance given here to these values was the relative order of basicities of the ylids.
Figure 1: Partial NMR Spectrum and Coupling Constants for (Z)-2-Azetamido-2,3-dideoxy-\(\beta\)-erythro-hex-2-enose triacetate (35)

Coupling Constants

\[ J_{AB} = -12.2 \text{ Hz} \]
\[ J_{AC} = +7.6 \]
\[ J_{BC} = +3.2 \]
\[ J_{DC} = +1.5 \]
\[ J_{DE} = +8.8 \]
\[ J_{EC} = 0.4 \]

Solvent: CDCl\(_3\)
Peaks not shown: 9.35 (s, 1, CHO), 8.04 (s, 1, NHAc), 2.18, 2.12 and 2.05 ppm (acetate).
CONCLUSIONS

The Wittig reaction of stabilized phosphonium ylids with alde-hyde carbohydrates was shown to proceed normally in all of the investigated reactions. Even the very basic ylid 14a reacted cleanly to give the normal products. These examples plus those of other investigators lead to the conclusion that Wittig reactions using carbohydrate derivatives proceed as expected. Unsuccessful Wittig reactions which have been reported with carbohydrates apparently can neither be explained nor predicted from consideration of the ylid basicities alone.

The attempt to prepare 2-acetamido-2-deoxy-3,4,5,6-tetra-O-acetyl-\(\text{D}\)-glucose was unsuccessful. The products which were obtained in this reaction were unreported in the literature and were completely characterized by elemental analysis and spectral data. Because of the conflict regarding the physical constants of the intermediates in this synthesis, there remains more work to be done in this area.
PART II

THE ADDITION OF BENZENESULFONYL AZIDES TO INDOLES
The first addition of organic azides to olefins was reported by Wolff in a series of papers in 1912. The reaction is a 1,3 dipolar addition and has been investigated by many others since that time.

Buckley studied the reaction of phenyl azide (38) with styrene (39) in 1954. He demonstrated that the reaction was stereospecific. Phenyl azide added to 39 to give only the triazoline 41.

Gurvich and Terent’ev had shown earlier that the reaction of 38 with 40 was also stereospecific although the orientation of the product (42) was reversed.
It was known that the reaction proceeded most rapidly with strained or electron rich double bonds.\textsuperscript{37} Scheiner\textsuperscript{37} studied the reaction of norbornene with substituted phenyl azides in 1965. The rate of formation of the triazoline (45) was measured with respect to the R group of the phenyl azide. When R was an electron withdrawing group, the rate of the reaction was faster. Based on this and the rest of his kinetic evidence, Scheiner proposed that the transition state for the addition was best represented by structure 46.
In this transition state, the olefin nucleophilically attacks the azide with bond formation to the terminal nitrogen (bond a) ahead of bond formation to the other nitrogen (bond b). This mechanism is supported by the experimental facts that electron withdrawing groups on the azide as well as electron rich olefins increase the rate of addition.

Structure 46 can also be used to explain the orientation of the products. Recall that Buckley\textsuperscript{35} showed that phenyl azide (38) added stereospecifically to styrene (39) to give the triazoline 41. This is the product expected since the incipient carbonium ion would be formed on a benzylic carbon atom. It follows that the orientation for the addition of phenyl azide (38) to acrylonitrile (40) would be the opposite since the cyano group would be expected to destabilize a carbonium ion adjacent to it. Fusco et al.\textsuperscript{42} have used a similar argument to predict the stereochemistry of products from the addition of azides to enamines.

The fate of the triazolines depends on the other chemical features of the molecule. In the case of triazolines such as 47 formed from hydrocarbons, the triazolines are relatively stable and can be easily isolated.\textsuperscript{37} Electron withdrawing groups render the triazolines so unstable that they eliminate nitrogen rapidly to give the aziridine.\textsuperscript{40} The stable triazolines can on heating be thermally decomposed, the products being Schiff bases and/or aziridines.\textsuperscript{38} Baldwin and coworkers\textsuperscript{43} showed that the aziridines were not intermediates in the formation of the Schiff bases since the aziridines would not rearrange to the Schiff bases under the same reaction conditions. Decomposition under the influence of uv light gives the aziridines.
The Addition of Azides to Heterocyclic Systems

Rector and Harmon have studied the addition of substituted benzenesulfonyl azides (51) to dihydropyran (50). This reaction was also believed to proceed via a triazoline which could not be isolated. The products were imido lactones (52).
Similarly, Fusco has reported that the intermediate triazolines obtained by addition of sulfonyl azides to enamines could not be isolated. Generally the products obtained were analogous to 52 when the azides had sulfonyl, nitrophenyl, or other electron withdrawing groups attached to them.

The first report of the addition of azides to indoles was made by Bailey and Merer in 1966. They reported that picryl azide (53) reacted with 2-methylindole (54) to yield a 3,3' azoindole (55).

\[
\begin{align*}
\text{NO}_2 & \quad \text{NO}_2 \\
\text{NO}_2 & \quad \text{N}_3 \\
\text{NO}_2 & \quad \text{N}_3 \\
N & \quad \text{H} \\
\text{CH}_3 & \quad \text{N=N} \\
\text{CH}_3 & \quad \text{H}
\end{align*}
\]

Addition of tosyl (Ts) azide yielded a 3-sulfonamidoindoline product (56) as well as some 55.

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In 1968, Bailey and Churn\textsuperscript{45} reported the addition of tosyl azide to indole (57).

\[ \text{SnN}_3 \]

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The products were imino compound $58$, and its amino tautomer $59$. The presence of both tautomers was supported by the nmr spectral data.$^{45}$ The location of the sulfonamido group in structures $58$ and $59$ was not conclusively established but was consistent with Fusco's$^{42}$ observations regarding addition of azides to enamines.

Further evidence for the addition of azides to indoles to give 2-substituted products came in 1970 when Bailey$^{46}$ reported that the addition of picryl azide ($53$) to 1-methylindole ($60$) gave 1-methyl-2-picryliminoindoline ($61$). The structure of $61$ was conclusively established by X-ray crystallography.

In another 1970 paper, Bailey$^{47}$ reported the addition of tosyl azide to 1,3 dimethylindole ($62$). The products were characterized as the 2-sulfonamido derivatives $63$ and $64$. These tautomers and similar compounds in this paper are referred to as the imino ($63$) and amino ($64$) tautomers respectively. Bailey noted that the equilibrium between $63$ and $64$ was solvent dependent, the imino form ($63$) predominating in chloroform and the amino form ($64$) predominating in dimethyl sulfoxide (DMSO). In mixtures of the two solvents, both tautomers
were present.

\[
\begin{align*}
\text{62} & \xrightarrow{\text{TsN}_3} \text{CDCl}_3 \\
\text{63} & \xrightarrow{\text{DMSO}} \text{DMSO} \\
\text{64} &
\end{align*}
\]
DISCUSSION

The following study was undertaken to further examine the addition of benzenesulfonfonyl azides to indole systems. Since Bailey et al. had demonstrated solvent dependent imino-amino tautomerism in one case, it was desired to explore this tautomeric equilibrium as a function of substituents on the adding azide. It was found in the course of this work that 1-methylindole was more amenable to study than indole itself which Bailey had used.

Preparation of Starting Materials

The thirteen benzenesulfonfonyl azides (51a-m) chosen for this study are listed in Table 3. They were all prepared by the reaction of the corresponding benzenesulfonfonyl chloride with sodium azide in aqueous acetone according to the general procedure of Rector and Harmon. The physical constants are reported in Table 3. Compounds 51e and 51i were unreported in the literature and were characterized by their spectral characteristics (ir and nmr) and by satisfactory elemental analyses. A series of compounds with a wide range of electron withdrawing and donating groups on the benzene ring were chosen.
Table 3

Physical Properties of Some Substituted Benzenesulfonyl Azides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Benzene Substituent(s)</th>
<th>MP(BP) °C</th>
<th>Literature Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>51a</td>
<td>4-OC\textsubscript{H}\textsubscript{3}</td>
<td>49-50 d</td>
<td>48</td>
</tr>
<tr>
<td>51b</td>
<td>4-CH\textsubscript{3}</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>51c</td>
<td>4-NH\textsubscript{2}COCH\textsubscript{3}</td>
<td>107-109</td>
<td>49</td>
</tr>
<tr>
<td>51d</td>
<td>unsubstituted</td>
<td>(90, 15mm)</td>
<td>48</td>
</tr>
<tr>
<td>51e</td>
<td>2,4,6-trimethyl</td>
<td>&lt; -5</td>
<td>-</td>
</tr>
<tr>
<td>51f</td>
<td>4-Cl</td>
<td>37-39</td>
<td>48</td>
</tr>
<tr>
<td>51g</td>
<td>4-Br</td>
<td>53-54</td>
<td>41</td>
</tr>
<tr>
<td>51h</td>
<td>3,4-di Cl</td>
<td>60-61</td>
<td>41</td>
</tr>
<tr>
<td>51i</td>
<td>3-NO\textsubscript{2}-4-Cl</td>
<td>90-95</td>
<td>50</td>
</tr>
<tr>
<td>51j</td>
<td>2,4,6-triisopropyl</td>
<td>41-43</td>
<td>-</td>
</tr>
<tr>
<td>51k</td>
<td>4-NO\textsubscript{2}</td>
<td>100-102</td>
<td>41</td>
</tr>
<tr>
<td>51l</td>
<td>3-NO\textsubscript{2}</td>
<td>78-80</td>
<td>41</td>
</tr>
<tr>
<td>51m</td>
<td>2-NO\textsubscript{2}</td>
<td>71-73</td>
<td>41</td>
</tr>
</tbody>
</table>

The indole derivatives used in this study were indole (57) and 1-methylindole (60). 1-Methylindole was prepared by N-alkylation of indole using sodium amide and methyl iodide in liquid ammonia.

![Chemical reaction](image)

57 \[\text{NaNH}_2, \text{CH}_3\text{I}\] 60

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The Addition of Substituted Benzenesulfonyl Azides to Indole

Initially indole (57) was chosen for this study because of its simplicity, availability, and because it was reported to give the desired 2-sulfonamido derivatives upon reaction with benzenesulfonyl azides. The reaction of indole was done with three of the azides (51a, 51b and 51k) listed in Table 3 and the respective products were 65a, 65b and 65c. The reactions were run in p-dioxane or ethanol at 75-80° and gave yields of about 50%. All the products (65a, 65b and 65c) gave satisfactory C, H, N and S elemental analyses assuming the empirical formulas shown in Scheme 1 were correct.

Scheme 1

\[
\text{imino} \quad \text{amino}
\]

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The products were not soluble enough to allow their nmr spectra to be determined in chloroform. The spectra were obtained in d$_6$DMSO and it is assumed that Bailey also used this solvent although this was not stated.$^{45}$

The nmr spectra of the products from the addition of 51a, b and k to 57 were not completely consistent with Bailey’s conclusions. He assumed the presence of only the amino and imino tautomers as shown in Scheme 1. The nmr spectra of these compounds (65a-c) might better be explained by the inclusion of the third possible tautomer (pseudo-indole) as shown in Scheme 2.

Scheme 2

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The reasons for suspecting a third tautomer are based primarily on a peak near $\delta 3.55$ for 65a and b which cannot be explained assuming the presence of only the amino and imino tautomers of these compounds. In 65c, this peak is not visible but is possibly obscured by a large water peak (water was present in the d$_6$DMSO used as the solvent) in the same region. Consideration of the low field exchangeable peaks in the region of 10-12$\delta$ also raises some questions. For instance, in the spectrum of 65b, there were three peaks in this region with equal integrations which would be possible with a 2:1 ratio of amino to imino tautomers present. However the relative integrations of the protons in the 3 position of the indole nucleus of both the amino and imino tautomers suggested a ratio of 1:1. Complicating a complete understanding of the nmr spectra of 65a-c was the low solubility of the products in d$_6$DMSO. This resulted in nmr spectra of poor quality.

In order to avoid the two complications, namely the inconclusive nmr spectra and the low solubility in d$_6$DMSO, it was decided to try the reactions with 1-methylindole in place of indole itself. Substitution of a methyl group on the indole nitrogen eliminates the possibility of the third pseudo-indole tautomer. It also tended to make the resulting products more soluble allowing better nmr spectra to be obtained.

The Addition of Substituted Benzenesulfonyl Azides to 1-Methylindole

The additions of the substituted benzenesulfonyl azides to 1-methylindole were done in $p$-dioxane at 75° for 18-24 hr. The reactions were followed by tlc which showed the reactions were essentially
completed after that length of time. There were two new major spots as well as some minor colored components. The colored compounds were probably related in structure to the azoindole. The major product (66a-m) from each reaction was isolated by dilution of the reaction mixture with an appropriate solvent. The other product was isolated by column chromatography and will be discussed later.

Scheme 3

\[
\begin{align*}
\text{Compound} & \quad | \quad R \text{ Group(s)} \\
66a & \quad | \quad 4-\text{OCH}_3 \\
66b & \quad | \quad 4-\text{CH}_3 \\
66c & \quad | \quad 4-\text{NHCOCCH}_3 \\
66d & \quad | \quad \text{H} \\
66e & \quad | \quad 2,4,6-\text{trimethyl} \\
66f & \quad | \quad 4-\text{Cl} \\
66g & \quad | \quad 4-\text{Br} \\
66h & \quad | \quad 3,4-\text{di Cl} \\
66i & \quad | \quad 3-\text{NO}_2-4-\text{Cl} \\
66j & \quad | \quad 2,4,6-\text{triisopropyl} \\
66k & \quad | \quad 4-\text{NO}_2 \\
66l & \quad | \quad 3-\text{NO}_2 \\
66m & \quad | \quad 2-\text{NO}_2 
\end{align*}
\]
In the solid state, the major products were in the imino tautomeric form as shown in Scheme 3. The ir spectra (nujol mull) showed a characteristic C=N band at 1600 cm\(^{-1}\) and no absorption in the NH region.

Complete nmr data for 66a-m is given in Table 7. The spectra were consistent with a 2-substituted indole ring system. A further discussion regarding the expected location of the protons at the 2 and 3 position of the indole nucleus is included with the discussion on the model compounds.

The location of the sulfonamido group at the 2 position on the indole ring was established by acid hydrolysis. Hydrolysis of 66b yielded 1-methyloxindole (67) and p-chlorobenzenesulfonamide (68) in high yield.
Attempted Alternate Synthesis of 66d

The following attempt to synthesize 66d by an alternate route was unsuccessful. o-Nitrophenylpyruvic acid (69) was converted to o-nitrophenylacetonitrile (70). The literature procedure for this reaction specified the isolation of the oxime intermediate and required three days to complete. It gave an approximate overall yield of 70%.54

During the course of this work it was found that 70 could be obtained in 90% yield in 2-3 hrs by simply refluxing the reactants together in 25% ethanol-water.
Reduction of 70 using Pd/C gave o-aminophenylacetonitrile (71). The hydroiodide salt of 2-amino-1-methylindole (72) was obtained by treatment of 71 with methyl iodide in ethanol.

\[ \text{N} \quad \text{NH}_2 \quad \text{HI} \quad \text{CH}_3 \quad \text{N} \quad \text{NSO}_2 \quad \text{CH}_3 \]

1. Base
2. \( \text{C}_{6}\text{SO}_2\text{Cl} \)

Since the free aminoindoles are unstable and obtained only with great difficulty, the hydroiodide salt was treated in situ with a base and immediately treated with benzenesulfonyl chloride. A large variety of conditions were tried, none of which yielded the desired 66d. The reactions were followed by tlc which showed the products were mainly tarry materials with very low rf values. There was one faster moving material which was neither isolated nor identified. There were no spots having an rf value similar to 66d.

Tautomerism of the 2-Sulfonamido Products

The tautomerism of the products (66a-m) was studied by nmr spectroscopy using d6DMSO and 15% CDCl3-d6DMSO as solvents. Attempts to use other solvents such as pure CDCl3 were unsuccessful due to insufficient

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Table 4

Percentage of 2-Amino Tautomer in deDMSO and 15% CDCl₃-d₆DMSO

<table>
<thead>
<tr>
<th>Compound</th>
<th>R Group(s)</th>
<th>Solvent</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>4-OCH₃</td>
<td>A</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>66b</td>
<td>4-CH₃</td>
<td>B</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>66c</td>
<td>4-NHCOCH₃</td>
<td></td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>66d</td>
<td>H</td>
<td></td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>66e</td>
<td>2,4,6-trimethyl</td>
<td></td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>66f</td>
<td>4-Cl</td>
<td></td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>66g</td>
<td>4-Br</td>
<td></td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>66h</td>
<td>3,4-di Cl</td>
<td></td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>66i</td>
<td>3-NO₂-4-Cl</td>
<td></td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>66j</td>
<td>2,4,6-triisopropyl</td>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>66k</td>
<td>4-NO₂</td>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>66l</td>
<td>3-NO₂</td>
<td></td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>66m</td>
<td>2-NO₂</td>
<td></td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

± 2%

A=deDMSO, B=15% CDCl₃ in deDMSO
<table>
<thead>
<tr>
<th>Compound</th>
<th>MP °C</th>
<th>% Yield</th>
<th>Compound</th>
<th>MP °C</th>
<th>% Yield</th>
<th>Ratio 66:76</th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>189-191</td>
<td>47</td>
<td>76a</td>
<td>160-162</td>
<td>24</td>
<td>2:1</td>
</tr>
<tr>
<td>66b</td>
<td>197-199</td>
<td>44</td>
<td>76b</td>
<td>180-182</td>
<td>22</td>
<td>2:1</td>
</tr>
<tr>
<td>66c</td>
<td>260-262</td>
<td>67</td>
<td>76c</td>
<td>226-228</td>
<td>5</td>
<td>13:1</td>
</tr>
<tr>
<td>66d</td>
<td>143-144</td>
<td>54</td>
<td>76d</td>
<td>174-175</td>
<td>22</td>
<td>2.5:1</td>
</tr>
<tr>
<td>66e</td>
<td>209-210</td>
<td>34</td>
<td>76e</td>
<td>212-214</td>
<td>15</td>
<td>2.2:1</td>
</tr>
<tr>
<td>66f</td>
<td>189-191</td>
<td>60</td>
<td>76f</td>
<td>181-183</td>
<td>16</td>
<td>3.8:1</td>
</tr>
<tr>
<td>66g</td>
<td>202-203</td>
<td>49</td>
<td>76g</td>
<td>203-204</td>
<td>12</td>
<td>4:1</td>
</tr>
<tr>
<td>66h</td>
<td>208-209</td>
<td>63</td>
<td>76h</td>
<td>180-181</td>
<td>14</td>
<td>4.5:1</td>
</tr>
<tr>
<td>66i</td>
<td>212-214</td>
<td>82</td>
<td>76i</td>
<td>160-161</td>
<td>8</td>
<td>10:1</td>
</tr>
<tr>
<td>66j</td>
<td>172-174</td>
<td>32</td>
<td>76j</td>
<td>157-158</td>
<td>24</td>
<td>1.3:1</td>
</tr>
<tr>
<td>66k</td>
<td>243-244</td>
<td>72</td>
<td>76k</td>
<td>199-200</td>
<td>21</td>
<td>3.4:1</td>
</tr>
<tr>
<td>66l</td>
<td>194-195</td>
<td>74</td>
<td>76l</td>
<td>173-175</td>
<td>6</td>
<td>12:1</td>
</tr>
<tr>
<td>66m</td>
<td>208-210</td>
<td>75</td>
<td>76m</td>
<td>193-195</td>
<td>14</td>
<td>5.4:1</td>
</tr>
</tbody>
</table>

Table 5
Yields and Melting Points of Addition Products
<table>
<thead>
<tr>
<th>Compound</th>
<th>Empirical Formulas</th>
<th>Calcd %</th>
<th>Found %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C  H  N  S</td>
<td>C  H  N  S</td>
</tr>
<tr>
<td>66a</td>
<td>C₁₇H₁₈N₂O₃S</td>
<td>60.74  5.09  8.85  10.13</td>
<td>60.69  5.31  8.84  9.87</td>
</tr>
<tr>
<td>66b</td>
<td>C₁₇H₁₈N₂O₃S</td>
<td>67.98  5.36  9.32  10.67</td>
<td>64.07  5.56  9.24  10.48</td>
</tr>
<tr>
<td>66c</td>
<td>C₁₇H₁₇N₃O₃S</td>
<td>59.54  4.99  12.24 9.34</td>
<td>59.79  5.28  12.31 9.33</td>
</tr>
<tr>
<td>66d</td>
<td>C₁₇H₁₈N₂O₃S</td>
<td>62.96  4.92  9.78</td>
<td>63.38  4.98  9.83</td>
</tr>
<tr>
<td>66e</td>
<td>C₁₇H₂₀N₂O₃S</td>
<td>65.83  6.14  8.53  9.76</td>
<td>65.63  6.29  8.54  9.76</td>
</tr>
<tr>
<td>66f</td>
<td>C₁₇H₉ClN₂O₂S</td>
<td>56.16  4.08  8.73 11.05(C1)</td>
<td>55.89  4.31  8.77 11.28(C1)</td>
</tr>
<tr>
<td>66g</td>
<td>C₁₇H₉BrN₂O₂S</td>
<td>49.33  3.59  7.67  8.78</td>
<td>48.94  3.66  7.73  8.38</td>
</tr>
<tr>
<td>66h</td>
<td>C₁₇H₁₂Cl₂N₂O₂S</td>
<td>50.71  3.40  7.89  9.07</td>
<td>50.69  3.66  7.51  9.18</td>
</tr>
<tr>
<td>66i</td>
<td>C₁₇H₁₂ClN₃O₄S</td>
<td>49.25  3.31  11.49 8.76</td>
<td>49.03  3.42  11.41 8.79</td>
</tr>
<tr>
<td>66j</td>
<td>C₂₄H₂₆N₂O₆S</td>
<td>69.86  7.81  6.78</td>
<td>69.96  7.88  6.57</td>
</tr>
<tr>
<td>66k</td>
<td>C₁₇H₁₈N₃O₄S</td>
<td>54.37  3.95  12.68 9.67</td>
<td>54.47  3.95  12.75 9.52</td>
</tr>
<tr>
<td>66l</td>
<td>C₁₇H₁₈N₃O₄S</td>
<td>54.37  3.95  12.68 9.67</td>
<td>54.20  4.18  12.54 9.94</td>
</tr>
<tr>
<td>66m</td>
<td>C₁₇H₁₈N₉O₆S</td>
<td>54.37  3.95  12.68 9.67</td>
<td>54.57  4.14  12.88 9.73</td>
</tr>
</tbody>
</table>
Table 7
Nuclear Magnetic Resonance Spectral Data for Substituted 2-Sulfonamidoindolines (66a-66m)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ha</th>
<th>Hb</th>
<th>Hc</th>
<th>Hd</th>
<th>He</th>
<th>Others (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66a</td>
<td>4.24</td>
<td>3.36</td>
<td>7.17-8.35</td>
<td>3.64</td>
<td>6.00</td>
<td>3.93, s, OCH3</td>
</tr>
<tr>
<td>66b</td>
<td>4.24</td>
<td>3.40</td>
<td>7.19-8.17</td>
<td>3.60</td>
<td>6.00</td>
<td>2.44, s, CH3</td>
</tr>
<tr>
<td>66c</td>
<td>4.17</td>
<td>3.44</td>
<td>6.70-8.15</td>
<td>3.57</td>
<td>5.89</td>
<td>10.30, s, CH3CONH; 2.10, s, CH3CONH</td>
</tr>
<tr>
<td>66d</td>
<td>4.20</td>
<td>3.33</td>
<td>6.94-8.21</td>
<td>3.67</td>
<td>5.90</td>
<td></td>
</tr>
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</table>
Table 7
(continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>H_a</th>
<th>H_b</th>
<th>H_c</th>
<th>H_d</th>
<th>H_e</th>
</tr>
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<tbody>
<tr>
<td>66e</td>
<td>4.04</td>
<td>3.30</td>
<td>6.90-7.57</td>
<td>3.50</td>
<td>5.84</td>
</tr>
<tr>
<td>66f</td>
<td>4.20</td>
<td>3.44</td>
<td>6.90-8.21</td>
<td>3.60</td>
<td>5.90</td>
</tr>
<tr>
<td>66g</td>
<td>4.17</td>
<td>3.30</td>
<td>6.94-8.00</td>
<td>3.54</td>
<td>5.84</td>
</tr>
<tr>
<td>66h</td>
<td>4.24</td>
<td>3.34</td>
<td>7.00-8.34</td>
<td>3.64</td>
<td>not obs.</td>
</tr>
<tr>
<td>66i</td>
<td>4.27</td>
<td>3.40</td>
<td>7.06-8.60</td>
<td>3.67</td>
<td>not obs.</td>
</tr>
<tr>
<td>66i*</td>
<td>4.04</td>
<td>3.32</td>
<td>6.91-7.45</td>
<td>3.58</td>
<td>not obs.</td>
</tr>
<tr>
<td>66k</td>
<td>4.20</td>
<td>3.46</td>
<td>7.00-8.50</td>
<td>3.57</td>
<td>not obs.</td>
</tr>
<tr>
<td>66l</td>
<td>4.24</td>
<td>3.47</td>
<td>7.00-8.73</td>
<td>3.60</td>
<td>not obs.</td>
</tr>
<tr>
<td>66m</td>
<td>4.20</td>
<td>3.47</td>
<td>7.00-8.40</td>
<td>3.57</td>
<td>not obs.</td>
</tr>
</tbody>
</table>

* (CD$_3$CN)

** The solvent used in all cases was d$_6$DMSO except as noted for 66j. H$_c$ protons appeared as a multiplet, H$_a$, H$_b$, H$_d$ and H$_e$ as singlets and other protons as noted. Proton H$_f$ was not observed in any spectra. Proton H$_e$ was not observed when the amino tautomer concentration was less than about 10%.
solubility. The relative ratios of the peaks at 4.28 and 3.78 (see Table 7 for assignments) were used to determine the amounts of each tautomer in solution. It can be seen from Table 4 that in each case the imino tautomer predominates in deDMSO solution. This observation is quite surprising in light of Bailey's47 work with 1,3 dimethyl-indole. He observed that in DMSO, the amino tautomer was the major species present. The addition of CDCl₃ does shift the tautomeric ratio even more in favor of the imino tautomer which is consistent with Bailey's observation. This trend is the reverse of that reported for 2-aminoindoles.52,53

Examination of Table 4 also reveals another fact. Electron withdrawing substituents on the benzene ring of the benzenesulfora-
mido group reduce the percentage of amino tautomer in solution. Thus the amino tautomer concentration ranges from a high of 20% with a p-methoxy group to a low of about 3% with an o-nitro group. The balance of tautomer stability for this system is apparently close so that substituent effects can be readily observed.

It is known that compounds such as 1-methyloxindole exist primarily with an exocyclic double bond (67) rather than with an endo-
cyclic double bond (73). Presumably there is more resonance stabili-
ization of the amide structure than of the slightly aromatic indole system.51 Aminoindoles show the same type of tautomerism although the internally double bonded tautomer seems to predominate.52,53
This balance of resonance energies of the tautomers provides a key to the possible explanation of the observed trend in Table 4. Consider the most important resonance contributor to each of the tautomeric structures.
For the imino tautomer, the sulfonamide nitrogen must accept a negative charge while for the amino tautomer it must accept a positive charge. It follows from this that electron withdrawing groups stabilize the important resonance structure for the imino tautomer and simultaneously destabilize the important resonance structure of the amino tautomer. Electron donating groups should cause the reverse to be true. Thus it seems reasonable that the trend of increased amino tautomers with electron donating groups was observed.

One other interesting fact can be seen from Table 4. The percentage of amino tautomer was lower for the 2,4,6-trimethyl substituted compound 66e than it was for the p-methyl derivative (66b). The 2,4,6-triisopropyl amino derivative 66i was present in even smaller concentrations. Instead of the two added electron donating groups increasing the percentage of amino tautomer, the opposite was the result. This can be explained by consideration of the resonance structures. Donation via resonance from a para methyl requires a structure such as 74 to be drawn.
In order for there to be good π bonding between the carbon and sulfur, the sulfur must lie in the plane of the benzene ring. Large R groups would sterically hinder this structure, reducing its contribution to the resonance hybrid. Hence the two ortho isopropyl groups, and to a smaller extent the two ortho methyl groups, reduce the electron donating ability of the remaining para alkyl group.

This observed trend of increasing imino form with decreasing solvent polarity was the opposite of that observed by others for the tautomerism of 2-aminindoled 75a.52,53 Thus while their results

\[ \text{NH}_2 \quad \overset{\text{Polar Solvents}}{\leftrightarrow} \quad \text{NH} \quad \overset{\text{Nonpolar Solvents}}{\longleftrightarrow} \]

\[ \text{75a, R}=\text{H} \quad \text{75b, R}=\text{CH}_3 \]

might be explained by changes in hydrogen bonding with the solvent, this explanation does not seem reasonable in explaining the results of this work. The amino sulfonamido tautomer which has a hydrogen atom bonded to nitrogen might be stabilized by hydrogen bonding to the DMSO solvent. However, one would then expect that making the sulfonamido nitrogen effectively more electronegative (by way of electron withdrawing groups on the benzene ring) would make the hydrogen bonding to the solvent even better. Thus from the viewpoint of solvent

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hydrogen bonding interactions, it would seem that electron withdrawing groups would favor increased amino tautomer concentrations which was not observed.

**Anomalous 3-Sulfonamido Products**

The other major products isolated from these reactions were characterized as 3-sulfonamido derivatives 76a-m.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R Group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76a</td>
<td>4-CH₃</td>
</tr>
<tr>
<td>76b</td>
<td>4-CH₃</td>
</tr>
<tr>
<td>76c</td>
<td>4-NO₂CH₃</td>
</tr>
<tr>
<td>76d</td>
<td>H</td>
</tr>
<tr>
<td>76e</td>
<td>2,4,6-trimethyl</td>
</tr>
<tr>
<td>76f</td>
<td>4-Cl</td>
</tr>
<tr>
<td>76g</td>
<td>4-Br</td>
</tr>
<tr>
<td>76h</td>
<td>3,4-di Cl</td>
</tr>
<tr>
<td>76i</td>
<td>3-NO₂-4-Cl</td>
</tr>
<tr>
<td>76j</td>
<td>2,4,6-triisopropyl</td>
</tr>
<tr>
<td>76k</td>
<td>4-NO₂</td>
</tr>
<tr>
<td>76l</td>
<td>3-NO₂</td>
</tr>
<tr>
<td>76m</td>
<td>2-NO₂</td>
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Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Empirical Formulas</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>S</th>
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<tbody>
<tr>
<td>76a</td>
<td>C₁₆H₁₆N₂O₃S</td>
<td>60.74</td>
<td>5.09</td>
<td>8.85</td>
<td></td>
<td>60.53</td>
<td>4.98</td>
<td>8.62</td>
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<tr>
<td>76b</td>
<td>C₁₆H₁₆N₂O₂S</td>
<td>63.98</td>
<td>5.36</td>
<td>9.32</td>
<td></td>
<td>63.99</td>
<td>5.34</td>
<td>9.31</td>
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<tr>
<td>76c</td>
<td>C₁₇H₁₇N₃O₃S</td>
<td>59.54</td>
<td>4.99</td>
<td>12.24</td>
<td>9.34</td>
<td>59.38</td>
<td>5.07</td>
<td>12.15</td>
<td>9.23</td>
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<tr>
<td>76d</td>
<td>C₁₅H₁₅N₂O₃S</td>
<td>62.96</td>
<td>4.92</td>
<td>9.78</td>
<td></td>
<td>63.21</td>
<td>5.02</td>
<td>9.91</td>
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<tr>
<td>76e</td>
<td>C₁₈H₂₀N₂O₃S</td>
<td>65.83</td>
<td>6.14</td>
<td>8.53</td>
<td>9.76</td>
<td>65.61</td>
<td>6.14</td>
<td>8.74</td>
<td>9.78</td>
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<tr>
<td>76f</td>
<td>C₁₅H₁₃ClN₂O₂S</td>
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<td>55.90</td>
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<td>49.33</td>
<td>3.59</td>
<td>7.67</td>
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<td>49.11</td>
<td>3.43</td>
<td>7.59</td>
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<td>50.71</td>
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<td>50.94</td>
<td>3.14</td>
<td>7.80</td>
<td>8.92</td>
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<tr>
<td>76i</td>
<td>C₁₅H₁₂Cl₂N₃O₄S</td>
<td>49.25</td>
<td>3.31</td>
<td>11.49</td>
<td>8.76</td>
<td>49.39</td>
<td>3.25</td>
<td>11.39</td>
<td>8.74</td>
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<tr>
<td>76j</td>
<td>C₂₄H₃₂N₂O₂S</td>
<td>69.86</td>
<td>7.81</td>
<td>6.78</td>
<td>7.71</td>
<td>69.46</td>
<td>7.70</td>
<td>6.13</td>
<td>7.45</td>
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<td>C₁₅H₁₃N₃O₄S</td>
<td>54.37</td>
<td>3.95</td>
<td>12.68</td>
<td></td>
<td>54.18</td>
<td>4.02</td>
<td>12.70</td>
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<tr>
<td>76l</td>
<td>C₁₅H₁₃N₃O₄S</td>
<td>54.37</td>
<td>3.95</td>
<td>12.68</td>
<td>9.67</td>
<td>54.16</td>
<td>4.18</td>
<td>12.67</td>
<td>9.66</td>
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<tr>
<td>76m</td>
<td>C₁₅H₁₃N₃O₄S</td>
<td>54.37</td>
<td>3.95</td>
<td>12.68</td>
<td></td>
<td>54.24</td>
<td>4.06</td>
<td>12.73</td>
<td></td>
</tr>
</tbody>
</table>
Table 9

Nuclear Magnetic Resonance Spectral Data for Substituted 3-Sulfonamidoindoles (76a-76m)

\[
\begin{align*}
\text{NMR (}\delta\text{)}^* \\
\hline \\
\text{Compound} & H_a & H_b & H_c & \text{Others (R)} \\
76a & 9.54 & 6.73-7.91 & 3.67 & 3.77, s, OCH_3 \\
76b & 9.64 & 6.73-7.85 & 3.67 & 2.30, s, p-CH_3 \\
76c & 9.53 & 6.73-8.07 & 3.70 & 10.20, s, NHCOCH_3; 2.07, s, NHCOCH_3 \\
76d & 9.63 & 6.73-7.97 & 3.67 & \\
76e & 9.44 & 6.70-7.46 & 3.67 & 2.43, s, OCH_3; 2.17, s, p-CH_3 \\
76f & 9.84 & 6.73-7.90 & 3.67 & \\
76g & 9.84 & 6.73-7.90 & 3.70 & \\
76h & 9.93 & 6.73-8.00 & 3.73 & \\
76i & 10.10 & 6.73-8.43 & 3.73 & \\
76j & 6.34 & 6.84-7.37 & 3.67 & 4.00, m, o-CH(CH_3)_2; 2.87, m, p-CH(CH_3)_2; 1.20, d, p-CH(CH_3)_2; 1.07, d, o-CH(CH_3)_2 \\
76k & 10.10 & 6.50-8.54 & 3.70 & \\
76l & 10.00 & 6.73-8.60 & 3.72 & \\
76m & 10.00 & 6.73-8.00 & 3.67 & \\
\hline
\end{align*}
\]

* Solvent was d_6DMSO except for 76j (CDCl_3). Peaks from $H_a$ and $H_c$ were singlets, $H_b$ appeared as multiplets.

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In contrast to the results with the 2-sulfonamide derivatives, the 3-substituted products were all present in the crystalline form as the amino tautomer as shown. This was evidenced by their ir spectra (nujol mull) which showed N-H absorptions but no C=N absorptions. The nmr spectra also supported the proposed structures. There was one exchangeable low field signal (see Table 9) integrating for one proton. There was no signal near 6.1 which would have been expected were the products actually amino 2-sulfonamido derivatives. The presence of NH signals in the nmr spectra (d6DMSO) showed the compounds to be in the amino tautomeric form in solution.

The compounds were isolated by column chromatography. An effort was made to be as quantitative as possible regarding the isolation of both the 2 and 3-substituted isomers. Product isolation as a means of determining actual amounts of material formed does introduce possible substantial error. However, it was felt that one trend could be discerned from Table 5. Electron donating groups did seem to increase the proportion of 3-substituted product formed.

The apparent lack of stereospecificity for the addition of benzenesulfonyl azides to indoles or enamines has not been observed before. Recalling the work of Fusco et al, the results do not seem surprising. Fusco and coworkers showed that the reaction was stereospecific for the addition of benzenesulfonyl azides to enamines or phenyl olefins. 1-Methylindole has both structural features. Since the nitrogen and phenyl groups are bonded to opposite ends of the carbon-carbon double bond, it is perhaps not surprising that a mixture of products results. Still the reaction is stereoselective,
giving more 2- than 3-substituted product.

One possible mechanism for the formation of the 3-substituted products would be for the initial azide orientation to be the reverse (as shown in Scheme 4) of that giving the 2-substituted products.

Scheme 4

This mechanism does not offer a clear explanation for the fact that there seems to be a greater proportion of 3-substituted product formed when there are electron releasing groups on the azide. However, it is not inconsistent with those results.

Another way in which the 3-substituted products could be obtained is via a rearrangement of an initially formed adduct such as 77. Whether the rearrangement is stepwise with charge separated structures as shown, or whether a concerted aziridine type intermediate is involved is not important. In either case, the greater the electron density on the sulfonamide nitrogen, the greater the chance of rearrangement by this type of mechanism. This type of rearrangement therefore, offers an explanation for the fact that electron releasing groups on the benzene ring of the adding azide increased the proportion of
3-substituted product.

Two synthetic approaches were tried in order to offer further evidence for the structure of the 3-substituted isomers. Two attempts were made to prepare 3-amino-1-methylindole (78) which presumably could be sulfonylated with benzene sulfonyl chloride (79) to give one of the 3-substituted compounds, 76d, as shown in Scheme 5. Amino-indoles substituted in the 2 or 3 position are relatively unstable compounds, undergoing facile autooxidation. The desired 3-amino-1-methylindole (78) was not reported in the literature.
It was felt that 1-methyl-3-nitroindole which was a known compound might be reduced to the desired amino compound (78). The attempted preparation of 1-methyl-3-nitroindole by the literature procedure, however, produced only a small amount of a substance whose physical constants corresponded only roughly with those reported for the compound. The compound was obtained in a very small yield and was relatively unstable. Since it was known neither that it had the correct structure nor that it could be reduced to the desired 3-amino-1-methylindole, this route to 78 was abandoned.

The second approach to 3-amino-1-methylindole was the attempted preparation of 1-methyl-3-nitrosoidole. This compound was unreported in the literature. The nitrosation of 1-methylindole followed by the reduction of the nitroso function to the amino function seemed to be a feasible approach to 78. The nitrosation reaction, however, led to another product, 80. Similar results have been reported before for the nitrosation of indoles unsubstituted in the 2 position.
It was observed that the nitroso compound (60) could be readily reduced and sulfonylated to give 81. Thus the alternate synthetic route to 76d seems dependent only on a successful synthesis of 1-methyl-3-nitrosoindole.

Preparation of Model Compounds

Neither a 2-sulfonamido nor a 3-sulfonamido derivative could be prepared by the alternate synthetic routes tried. Therefore it was
decided to prepare model compounds in order to confirm the chemical shifts of the protons at the 2 and 3 position of the indole systems. Generally, the proton in the 3 position on an indole nucleus resonates around 6 ω. The proton at the 2 position resonates at a lower field, around 7 ω and is often obscured by aromatic protons in the region. \(^65\), \(^66\)

The model compounds chosen were carbobenzoxy 2- and 3-aminooindole (86 and 90 respectively). They were prepared via a Curtius Rearrangement of the corresponding indole 2- or 3-carbonyl azide in benzyl alcohol as shown in Schemes 6 and 7.

Scheme 6

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The NMR spectra of the model compounds (86 and 90) showed that both existed in solution (d$_6$DMSO) in the amino tautomeric form shown. Each compound had two low field (10-12 $\delta$) exchangeable peaks which integrated cleanly for one proton each. This rules out the other possible tautomers (imino or pseudo-indole) since they could only have one low field signal in this region. Therefore 88 should be a good model of 76a-m and 90 ought to be a good model for the amino tautomers of 66a-m.

The NMR spectra showed the expected characteristics. The proton in the 3 position of 90 showed as a doublet at 6 $\delta$. This is consistent
with Witkop et al.\textsuperscript{65,66} regarding the chemical shift of the protons at the 3 position of indole rings. Therefore it also supports the assigned structures of \textit{66a-m} since they also had a peak (assigned to the amino tautomer) in this region.

Likewise the nmr spectra of \textit{66} and \textit{76a-m} were very similar in the region around \(\delta 7\) and were also consistent with the observations of Witkop et al.\textsuperscript{65,66} Hence the structures of \textit{76a-m} are strongly supported.

The Addition of Substituted Benzenesulfonyl Azides to 1-Methylindole in Ethanol

The course of the addition of arylsulfonyl azides to 1-methylindole using ethanol as a solvent was different than when using \(p\)-dioxane as the solvent. A major product formed under these conditions using \textit{51b} or \textit{51f} is the diazo compound \textit{91a} or \textit{91b} respectively.

\[
\begin{align*}
\text{C}_6\text{H}_5\text{N} & \quad \text{51b and 51f} \quad \text{ethanol} \\
& \quad \text{91a} \quad \text{R=CH}_3 \\
& \quad \text{91b} \quad \text{R=Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{C}_6\text{H}_5\text{N} & \quad \text{92a} \quad \text{R=CH}_3 \\
& \quad \text{92b} \quad \text{R=Cl} \\
\end{align*}
\]
It was shown that 66b was probably an intermediate in the formation of the diazo derivative 91a since in ethanol, excess 51b converted 66b to 91a. This diazo product was not formed in p-dioxane in an isolable amount under similar conditions.

The diazo compounds 91a and 91b were light sensitive and difficult to separate from 66b and 66f respectively. Satisfactory elemental analyses of these compounds were not obtained. Stable triphenylphosphine derivatives 92a and 92b were readily prepared from 91a and 91b and satisfactory analyses obtained.64

This reaction is apparently analogous to the diazo transfer reactions reported by Regitz and others.63 Nearly all reported examples have involved the transfer of diazo groups to the $\alpha$ carbon of carbonyl compounds.63 There are no reported examples of transfer to an amidine system such as 66a and 66b. Generally, the transfer of diazo groups from sulfonyl azides required a base catalyst.63 However, 91a and 91b were formed without the aid of any added catalyst.
EXPERIMENTAL

General Procedures

The melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. A Beckman IR-8 spectrophotometer was used to determine the infrared (IR) spectra. Nuclear magnetic resonance spectra were obtained using a Varian A-60 instrument with solvents as noted. Tetramethylsilane (TMS) was used as the internal reference with all chemical shifts reported in ppm units downfield from TMS. Elemental analyses were performed by Midwest Microlab Ltd. of Indianapolis, Indiana. Thin-layer chromatography (TLC) was done on glass microscope slides coated with Silica Gel G (acc. to Stahl) purchased from EM Reagents, division of Brinkman, Westbury, New York. The spots were detected using iodine vapor. The slides were developed with solvents as noted. Column chromatography was done using a 3X60 cm column packed with SilicAR CC7 (200-325 mesh) brand of silica gel purchased from Mallinckrodt, St. Louis, Missouri. The physical constants and spectral data reported for all new compounds are values for an analytical sample of that compound unless otherwise stated.

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Preparation of Compounds

Preparation of substituted benzenesulfonyl azides (51a-51m)

All compounds were prepared according to the general procedure of Rector and Harmon. Physical data and literature references are given in Table 3. Compounds 51e and 51j were not reported in the literature.

Preparation of mesitylenesulfonyl azide (51e)

This compound was prepared according to the procedure of Rector and Harmon. It was obtained in 81% yield and used without further purification. An analytical sample was obtained by precipitation of the oil from ethanol-water yielding 51e as a colorless oil: mp less than -5°; \( \mu^2 \) 1.5548; ir (neat) 2120 (N\(_3\)) and 1164 cm\(^{-1}\) (S\(_2\)O); nmr (CDCl\(_3\)) \( \delta \) 7.00 (s, 2, ArH), 2.62 (s, 6, ortho CH\(_3\)) and 2.30 ppm (s, 3, para CH\(_3\)). Anal. Calcd for C\(_9\)H\(_{13}\)N\(_3\)O\(_2\)S: C, 57.99; H, 4.92; N, 18.65. Found: C, 58.00; H, 4.89; N, 18.40.

Preparation of 2,4,6-triisopropylbenzenesulfonyl azide (51j)

This compound was obtained by the procedure of Rector and Harmon. The crude product was recrystallized from ethanol-water to give an 80% yield of 51j: mp 41-43°; ir (nujol mull) 2120 (N\(_3\)) and 1164 cm\(^{-1}\) (S\(_2\)O); nmr (CDCl\(_3\)) \( \delta \) 7.25 (s, 2, ArH), 4.10 (m, 2, \( \tilde{j} = 6 \) Hz, ortho CH(CH\(_3\))\(_2\)), 2.97 (m, 1, \( \tilde{j} = 7 \) Hz, para CH(CH\(_3\))\(_2\)), 1.30 (d, 12, \( \tilde{j} = 6 \) Hz, ortho CH(CH\(_3\))\(_2\)) and 1.25 ppm (d, 6, \( \tilde{j} = 7 \) Hz, para CH(CH\(_3\))\(_2\)).
Found:  C, 58.21; H, 7.69; N, 13.42.

Preparation of 1-methylindole (60)

Ammonia (400 ml) was condensed into a three neck flask fitted with a mechanical stirrer.  Ferric nitrate nonahydrate (0.1 g) was added and clean metallic sodium (20 g, 0.44 m) was added in small portions at a rate just sufficient to maintain the blue color.  Indole (46 g, 0.39 m) was then added dropwise in 80 ml of absolute ether.  The solution was stirred 10 min and methyl iodide (62.5 g, 0.44 m) was added dropwise in 30 ml of absolute ether.  The solution was then allowed to warm to room temperature allowing the ammonia to evaporate.  Ether (100 ml) and water (150 ml) were carefully added and the aqueous layer separated and extracted twice with 75 ml of ether.  The ether layers were then combined, extracted twice with water, once with saturated sodium chloride solution, and finally dried over sodium sulfate. The ether was removed by vacuum evaporation yielding the oily crude product.  This material was refluxed (250°) over metallic sodium for 20 hr and finally vacuum distilled to yield 41 g (78%) of 60, bp 75° at 2.1 mm (lit.38 70-75° at 2 mm).

Preparation of p-methyl-N-(2-indolinyldene) benzenesulfonamide (65a)

Indole (0.9 g, 0.0077 m) and tosyl azide (2 g, 0.01 m) were heated at 75-80° for 48 hr in p-dioxane.  The solution was then diluted with 3 ml of ether and 3 ml of methanol giving 1.0 g (46%) of 65a:  
mp 234-236°; ir (nujol mull) 3150 (NH), 1580, 1610 (C=N) and 1140 cm⁻¹.
\[(\text{SO}_2)\text{; nmr (d}_6\text{DMSO}) \delta 11.50 (s, NH), 10.08 (s, NH), 8.00-6.65 (m, aromatic H), 5.80 (s), 4.10 (s), 3.57 (s, shoulder) and 2.37 ppm (s, CH}_3\]. Anal. Calcd for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_2\)S: C, 62.91; H, 4.92; N, 9.78; S, 11.19. Found: C, 62.85; H, 4.99; N, 9.81; S, 11.05.

**Preparation of \(p\)-methoxy-N-(2-indolylidene) benzenesulfonamide (65b)**

Indole (1 g, 0.0085 m) and \(p\)-methoxybenzenesulfonyl azide (2 g, 0.0094 m) were heated at 80° for 26 hr in p-dioxane. The solution was diluted with 5 ml of methanol giving 0.6 g (22%) of 65b: mp 224-226° d; ir (nujol mull) 1580 (C=N), 1145 and 1135 cm\(^{-1}\) (SO\(_2\)); nmr (d\(_6\)DMSO) \(\delta 11.40 (s, NH), 10.70 (s, NH), 10.30 (s, NH), 8.00-6.80 (m, aromatic H), 5.73 (s), 4.04 (s), 3.80 (s, OCH\(_3\)), 3.77 (s, OCH\(_3\)) and 3.53 ppm (s). Anal. Calcd for C\(_{15}\)H\(_{14}\)N\(_2\)O\(_3\)S: C, 59.58; H, 4.66; N, 9.26; S, 10.60. Found: C, 59.33; H, 4.94; N, 9.55; S, 10.62.

**Preparation of \(p\)-nitro-N-(2-indolylidene) benzenesulfonamide (65c)**

Indole (2 g, 0.017 m) and \(p\)-nitrobenzenesulfonyl azide (4 g, 0.017 m) were refluxed in 75 ml of ethanol for 6 hr. On cooling, the solution deposited 3.3 g (61%) of the product 65c: mp 240-260° d; ir (nujol mull) 1560 (C=N), 1150 and 1145 cm\(^{-1}\) (SO\(_2\)); nmr (d\(_6\)DMSO) \(\delta 12.21 (s, NH), 11.40 (s, NH), 8.87-8.17 (m, 4, sulfonamide aromatic H), 7.91-7.00 (m, 4, indole aromatic H), 6.07 (d, \(J = 2 \text{ Hz}\)) and 4.37 ppm (s). Anal. Calcd for C\(_{14}\)H\(_{11}\)N\(_3\)O\(_4\)S: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: C, 52.80; H, 3.62; N, 13.53; S, 10.16.

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General procedure for the addition of substituted benzenesulfonyl azides to 1-methylindole and isolation of products 66a-66m and 76a-76m

1-Methylindole (1.3 g, 0.01 m) was dissolved in 5 ml of dry p-dioxane. A 1.5 molar excess of the appropriate substituted benzene sulfonyl azide (51a-51m) was dissolved in this solution. The solution was heated (oil bath) and stirred at 75-80° for 18-24 hr. The solution was then cooled and diluted with about 25 ml of ethanol (heptane was used for 66j, 76j) causing the majority of each 2-substituted product (66a-66m) to crystallize from the solution. The filtrate was evaporated to dryness and chromatographed eluting with chloroform (2:8:10 ether-hexane-chloroform used for 66j, 76j; 9:1 ethyl acetate-heptane for 66c, 76c; 9:1 benzene-ethyl acetate for 66b, 76b; 20:1 chloroform-ethyl acetate for 66i, 76i; methylene chloride for 66m, 76m). The fractions containing the 2-sulfonamido products (66a-66m) were combined and evaporated to dryness. The residue obtained was recrystallized from butanone or ethanol and combined with the product obtained from dilution of the reaction mixture. This total yield is reported in Table 5. The fractions containing the 3-sulfonamido derivatives (76a-76m) were similarly treated and the yields of these products are also reported in Table 5. All other chromatographic fractions and all mother liquors from recrystallizations which showed a tlc detectable amount of either isomer were combined and evaporated to dryness. The weight of this residue was less than 0.2 g in all cases. All compounds gave satisfactory elemental analyses and these are reported in Tables 6 and 8. Melting points are reported in Table

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5. Spectral data (nmr) is reported in Tables 7 and 9.

**Nitration of 1-methylindole**

Benzoyl nitrate was prepared by adding benzoyl chloride (2.6 g, 0.0182 m) to silver nitrate (2.4 g, 0.02 m) in portions over a period of 20 min at 0° in 10 ml of acetonitrile. This solution was added with stirring at -5° to 1-methylindole (2 g, 0.016 m) in 15 ml of acetonitrile. The mixture was stirred 30 min and diluted with 500 ml of water. The solution was repeatedly extracted with benzene and the combined benzene extracts washed with aqueous sodium bicarbonate. The benzene solution was dried using saturated sodium chloride and finally using sodium sulfate. The benzene solution was divided in half. The first half was concentrated and chromatographed over silica gel eluting with chloroform. Four compounds were collected. The second fraction was an unstable yellow solid, mp 160° and weighed 0.1 g. This compound corresponded most closely to 1-methyl-3-nitroindole, mp 154-157° reported by Berti and coworkers. 58

The second half of the benzene solution was evaporated to dryness and dissolved in ethanol. It was then catalytically reduced using PtO/C at 50 psi for 12 hr. The solution was filtered to remove the reduced catalyst and treated with 1 g of benzenesulfonyl chloride. The tlc of this mixture showed a number of new spots, none of which corresponded to 66d.

**Hydrolysis of p-chloro-N-(1-methyl-2-indolylidene) benzenesulfonamide (66f)**

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p-Chloro-N-(1-methyl-2-indolinylidene) benzenesulfonamide (1 g, 0.0031 m) was refluxed in 100 ml of ethanol to which 3 ml of conc hydrochloric acid had been previously dissolved. The mixture was refluxed for 10 hr and evaporated to dryness under reduced pressure. Two 50 ml portions of ethanol were co-distilled from the residue. The resulting residue was chromatographed on silica gel eluting with ether. Obtained first was .55 g (92%) of p-chlorobenzenesulfonamide. It was recrystallized from ethanol-heptane giving .5 g (84%) of pure p-chlorobenzenesulfonamide, mp 144-145° (lit. 143-144°). Eluted next was 1-methyloxindole and it was obtained in 87% crude yield. Recrystallization from heptane gave 0.3 g (66%) of pure 1-methyloxindole, mp 84-87° (lit. 84-86°).

Preparation of o-nitrophenylacetonitrile (70)

o-Nitrophenylpyruvic acid (5 g, 0.024 m) was dissolved in 400 ml of 25% ethanol in water. Hydroxylamine hydrochloride (3 g, 0.043 m) was added and the solution refluxed for 3 hr. After cooling, the crystalline product was collected giving 3.45 g (89%) of 70; mp 81-83° (lit. 84°).

Preparation of o-aminophenylacetonitrile (71)

o-Nitrophenylacetonitrile (14 g, 0.088 m) was dissolved in 150 ml of tetrahydrofuran (THF). Added to the solution was .2 g of 10% Pd/C as catalyst. The mixture was reduced at 50 psi (Parr) for 8 hr. The mixture was filtered through a Celite pad and the filtrate concentrated to an oil by evaporation at reduced pressure yielding 11.3 g.
(99%) of 71. A pure sample could be obtained by chromatography over silica gel eluting with 2:1 ether-hexane followed by two recrystallizations from ethyl acetate-heptane, giving pure 71, mp 68-70° (lit. mp 70-72°).

--- Preparation of 2-amino-1-methylindole hydroiodide (72)

Crude o-aminophenylacetonitrile (11.3 g, 0.86 m) was dissolved in 20 ml of ethanol. Methyl iodide (20 ml) was added and the solution allowed to stand for 7 days. The black crystals were collected and recrystallized from water-isopropanol to yield 1.5 g of 72. The filtrate was evaporated to dryness and the residue triturated with methylene chloride. The tan precipitate of 72 weighed 2 g. The combined yield of 72 was 3.5 g (16%), mp 250-260° d (lit. mp 260° d).

Attempted preparation of N-(1-methyl-2-indolinylidene) benzenesulfonamide (66d) via sulfonylation of 2-amino-1-methylindole hydroiodide (72)

In dry pyridine, 2-amino-1-methylindole hydroiodide (.1 g) was dissolved and cooled to 0°. Benzenesulfonyl chloride (1 ml) was added causing the solution to turn black. The tlc of this solution showed a spot with low (~.1) rf value (developed with chloroform) and one with a higher (.7) rf value. Neither spot corresponded to 66d or 76d. Also tried as solvent with the same results in the above procedure were ethanol, benzene and THF. Triethyl amine (2 ml) was added in these cases to free the 2-amino-1-methylindole from its hydroiodide salt.
Attempted hydrolysis of \( p\)-chloro-\( N\)-(1-methylindol-3-yl) benzenesulfonamide (76f)

\( p\)-Chloro-\( N\)-(1-methylindol-3-yl) benzenesulfonamide (0.1 g, 0.00031 m) was dissolved in 15 ml of ethanol containing 1 ml of conc hydrochloric acid. The solution was refluxed for 4 days. The tlc after this time was unchanged and 0.085 g (85%) of 76f was recovered unchanged.

Preparation of 1-methyl-2-(1-methylindol-3-yl)-3-nitrosoindole (80)

1-Methylindole (14.5 g, 0.123 m) was dissolved in 500 ml of glacial acetic acid and stirred vigorously while sodium nitrite (10 g, 0.162 m) in 14 ml of water was added dropwise. The temperature was maintained at less than 15° throughout the addition. The solution was then diluted with 500 ml of ether and again with 500 ml of hexane. The mixture was cooled to 5° and after 1 hr, the mother liquor was decanted from a black precipitated oil. The oil was triturated with ether and the brown-yellow solid collected. The solid was washed with acetone giving a green solid, mp 220°. The green solid was recrystalized from acetonitrile yielding green crystals, 3 g (20%) of 82: mp 243-244°; ir (nujol mull) 1560 cm\(^{-1}\) (\(\text{N=O}\)); nmr (\(d_6\text{DMSO}\)) \(\delta\) 7.10-8.30 (m, 9, aromatic \(H\)), 4.00 (s, 3, N-\(CH_3\)) and 3.94 ppm (s, 3, N-\(CH_3\)).

Anal. Calcd for C\(_{18}\)H\(_{15}\)N\(_3\)O: C, 74.72; H, 5.22; N, 14.53. Found: C, 74.59; H, 5.72; N, 14.86.
Preparation of N-[1-methyl-2-(1-methylindol-3-yl)]-2-benzenesulfonamide (83)

1-Methyl-2-(1-methylindol-3-yl)-3-nitrosoindole (1 g, 0.00345 m) was dissolved in 50 ml of ethanol. Adam's catalyst (.2 g) was added and the mixture reduced (Parr) at 50 psi for 10 hr. The solvent was removed under reduced pressure and the oil dissolved in 20 ml of dry pyridine. Benzenesulfonyl chloride (2 ml) was added and the solution allowed to stand 1 hr. It was then poured into water and extracted with chloroform. The chloroform layer was separated and dried (Na2SO4) and the solvent removed under reduced pressure leaving a yellow-green oil. The oil was crystallized from ethyl acetate-heptane yielding 0.85 g (60%) of 83: mp 176-177°; ir (nujol mull) 3270 (NH) and 1158 cm⁻¹ (SO2); nmr (d6DMSO) δ 9.64 (s, 1, NH), 3.77 (s, 3, N-CH₃) and 3.50 ppm (s, 3, N-CH₃). Anal. Calcd for C₁₅H₁₁N₂O₅: C, 69.37; H, 5.09; N, 10.11; S, 7.71. Found: C, 69.17; H, 5.17; N, 10.17; S, 8.04.

Preparation of methyl indole-3-carboxylate (83)

Indole-3-carboxylic acid (City Chemical or K and K, 7 g, 0.044 m) was dissolved in 300 ml of methanol and the solution saturated with hydrochloric acid at 0°. The solution was allowed to stand for 24 hr at room temperature and the solvent removed by evaporation at reduced pressure. Water (100 ml) was added to the residue and the mixture extracted with 200 ml of ether. The ether layer was separated and washed with an aqueous NaHCO₃ solution, dried by extraction with saturated aqueous NaCl and finally with Na₂SO₄. The ether was removed by
evaporation at reduced pressure to yield 4.9 g (65%) of crude 83, mp 142-145°. Recrystallization from ethanol-water yielded 3.5 g of 83, mp 146-148° (lit.57 mp 147-148°).

Preparation of indole-3-carboxylic acid hydrazide (84)

Methyl indole-3-carboxylate (2 g, 0.0114 m) was refluxed in a solution of 25 ml of ethanol and 20 ml of 95% hydrazine for 36 hr. The solution was diluted with 25 ml of water and scratched to start crystallization. Collection of the product by vacuum filtration yielded 1.8 g (90%) of 84, mp 231-234° (lit.58 mp 232-234°).

Preparation of indole-3-carbonyl azide (85)

Indole-3-carboxylic acid hydrazide (1 g, 0.0057 m) was dissolved in 10 ml of glacial acetic acid. Sodium nitrite (1.2 g, 0.0175 m) was dissolved in 5 ml of water and the solution added portionwise to the acetic acid solution. Hydrochloric acid (5%), 50 ml, was added and the resulting mixture poured into 500 ml of water and stirred for 20 min. The product was collected by vacuum filtration yielding 1.05 g (100%) of 85: mp 144° d; ir (nujol mull) 3250 (NH), 2145 (N₃), 2120 (N₃) and 1650 cm⁻¹ (C=O); nmr (d₄DMSO) δ 12.12 (s, 1, NH) and 7.00-8.33 ppm (m, 5, aromatic H). Anal. Calcd for C₉H₆N₄O: C, 58.06 H, 3.25; N, 30.09. Found: C, 57.50; H, 3.26; N, 29.79.

Preparation of carbobenzoxy-3-aminoindole (86)

Indole-3-carbonyl azide (1 g, 0.0054 m) was added portionwise to
a refluxing solution of 30 ml of toluene and 2 ml of benzyl alcohol. The solvent was removed by evaporation at reduced pressure and the residue recrystallized from benzene-heptane to yield 1.1 g (79%) of 86, mp 148-155°. Repeated recrystallization from benzene-heptane yielded a white analytical sample: mp 164-165°; nmr (dDMSO) δ 10.69 (s, 1, NH), 9.41 (s, 1, NH), 7.88-6.79 (m, 10, aromatic and 2-indole H) and 5.18 ppm (s, 2, OCH2O). Anal. Calcd for C16H14N2O2: C, 72.17; H, 5.29; N, 10.52. Found: C, 72.57; H, 5.57; N, 10.76.

**Preparation of indole-2-carboxylic acid hydrazide (88)**

Ethyl indole-2-carboxylate (Aldrich, 10 g, 0.053 m) was dissolved in 120 ml of ethanol. Hydrazine (95%, 13 g, 0.27 m) was added and the resulting solution refluxed for 4 hr. The solution was diluted with 50 ml of hexane and the solution deposited crystals after cooling. The product was collected by vacuum filtration yielding 8.5 g (90%) of 88, mp 247-251° (lit.56 mp 247°).

**Preparation of indole-2-carbonyl azide (89)**

Indole-2-carboxylic acid hydrazide (4 g, 0.023 m) was dissolved in 200 ml of glacial acetic acid. Sodium nitrite (4.8 g, 0.07 m) was dissolved in 100 ml of water and the resulting solution added dropwise to the acetic acid solution. The temperature was maintained at 10°. Following the addition of the sodium nitrite solution, 200 ml of 5% aqueous hydrochloric acid was added and the solution stirred an additional 30 min. The resulting precipitate was collected, washed with

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water and vacuum dried to yield 3.3 g (78%) of 89, mp 138-139° d (lit. 55 mp 139° d).

**Preparation of carbobenzoxy-2-aminoindole (90)**

Indole-2-carbonyl azide (3 g, 0.016 m) was added portionwise to a refluxing solution of 40 ml of toluene containing 6 g of benzyl alcohol. The reaction mixture was refluxed for an additional 2 hr and the toluene removed by evaporation at reduced pressure. The black residue was extracted with two portions (250 ml) of hot heptane and the heptane then removed by vacuum evaporation to yield an oil. The oil which consisted mainly of benzyl alcohol and 90 was vacuum distilled at 80° (1 mm) to dryness. The residue was chromatographed over silica gel eluting with methylene chloride yielding 1.4 g of impure 90. The black residue from the extraction was also chromatographed to give an additional 1.5 g of 90. The combined product 1.9 g (45%) was recrystallized repeatedly from benzene-heptane to give white crystals of 90: mp 138-139° (lit. 55 mp 139-140°); nmr (d6DMSO) δ 10.65 (s, 1, NH), 10.29 (s, 1, NH), 7.57-6.80 (m, 9, aromatic H), 6.00 (d, 2, J = 4 Hz, 3 indole H) and 5.20 ppm (s, 2, OCH2C).

**Addition of tosyl azide to 1-methylindole in ethanol: The preparation of p-methyl-N-(3-diazo-1-methyl-2-indolinylidene) benzenesulfonamide (91a)**

A solution of 1-methylindole (1.3 g, 0.01 m) in 100 ml of ethanol was refluxed with tosyl azide (2.5 g, 0.0127 m) for 20 hr. The solution deposited 1.0 g (33%) of 66b which was collected. The filtrate

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was refluxed an additional 20 hr after more tosyl azide (1.0 g, 0.0051 m) had been added. Upon cooling, the solution deposited 1.0 g of another product believed to be \( p \)-methyl-\( N \)-(3-diazo-1-methyl-2-indolinyldene) benzenesulfonamide (91a), mp 161-163°C. The same product could be obtained in 61% yield by treating \( \text{66b} \) with a three-fold excess of tosyl azide in refluxing ethanol for 1-2 days. This product was not obtained under the same conditions using \( p \)-dioxane as a solvent instead of ethanol. Subsequent recrystallization from butanone gave 91a: mp 165-166°C; ir (nujol mull) 2100 cm\(^{-1}\) (N\(_2\)). Anal. Calcd for \( \text{C}_{16}\text{H}_{14}\text{N}_{4}\text{S}_{02} \): C, 58.88; H, 4.32; N, 17.17. Found: C, 59.42; H, 4.47; N, 16.26.

Preparation of \( p \)-methyl-\( N \)-(1-methyl-3-[(triphenylphosphoranylidene) hydrazono]-2-indolinyldene] benzenesulfonamide (92a)

\( p \)-Methyl-\( N \)-(3-diazo-1-methyl-2-indolinyldene) benzenesulfonamide (1 g, 0.000306 m) was refluxed with triphenylphosphine (1 g, 0.00035 m) in 25 ml of ethanol for 2 hr. The solution deposited 0.11 g and was concentrated to give an additional 0.01 g (total yield 67%) of 92a: mp 206-207°C; ir (nujol mull) 1575 and 1510 cm\(^{-1}\). Anal. Calcd for \( \text{C}_{34}\text{H}_{29}\text{N}_{4}\text{O}_{2}\text{PS} \): C, 69.37; H, 4.97; N, 9.52; P, 5.26. Found: C, 69.19; H, 4.85; N, 9.45; P, 5.50.

Preparation of \( p \)-chloro-\( N \)-(1-methyl-3-[(triphenylphosphoranylidene) hydrazono]-2-indolinyldene] benzenesulfonamide (92b)

\( p \)-Chloro-\( N \)-(1-methyl-2-indolinyldene) benzenesulfonamide (1.5 g, 0.0046 m) was refluxed with \( p \)-chlorobenzenesulfonfyl azide (2 g, 0.0092 m)
in 125 ml of ethanol for 66 hr. After cooling, 1.1 g (68%) of the intermediate p-chloro-N-(3-diazo-1-methyl-2-indolinylidene) benzene-

sulfonamide was collected. This material was recrystallized from ethanol and .3 g (0.00029 m) of the purified material was refluxed with triphenylphosphine (.3 g, 0.00095 m) for 3 hr in ethanol. The solution deposited in two crops a total of 0.48 g (84% calcd from intermediate) of 2b: mp 223-224° d; ir (nujol mull) 1510 and 1580 cm⁻¹. Anal. Calcd for C₃₃H₂₆C₁N₄O₂PS: C, 65.07; H, 4.30; N, 9.20; Cl, 5.82; P, 5.09. Found: C, 65.01; H, 4.33; N, 9.45; Cl, 5.81; P, 5.10.
CONCLUSIONS

It has been shown that substituted benzenesulfonyl azides add to 1-methylindole in $d_1$-dioxane to give two isolable isomers. The 2-substituted indole isomers exhibit an imino-amino tautomeric equilibrium which is substituent and solvent dependent. The structures of these 2-substituted derivatives were determined from chemical and spectral data. Also obtained in these reactions were 3-substituted products which did not show a tautomeric equilibrium. The structure of these products was based on spectral evidence. Synthesis of model compounds aided in the interpretation of the nmr spectra of both the 2- and 3-substituted isomers.

The addition of benzenesulfonyl azides to 1-methylindole in ethanol led to the formation of another product which involved transfer of a diazo group from the benzenesulfonyl azide to the indole nucleus. The resulting diazo products could not be characterized and it was necessary to prepare triphenylphosphine derivatives which were readily purified and characterized.
REFERENCES

4. loc. cit., p 52.
5. loc. cit., p 154.
6. loc. cit., p 140.


