PART I THE UNH REARRANGEMENT IN THE REACTIONS OF BENZIMIDAZOLES AND DINITROANILINES
PART II THE THREE-AXIAL ALKYL EFFECT

JOHN LAWRENCE LAMATTINA

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Keywords
Chemistry, Organic
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University of New Hampshire, Ph.D., 1975
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PART I.
THE UNH REARRANGEMENT IN THE REACTIONS
OF BENZIMIDAZOLES AND DINITROANILINES

PART II.
THE THREE-AXIAL ALKYL EFFECT

by

JOHN LAWRENCE LaMATTINA
B.S., Boston College, 1971

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Thesis director, Robert E. Lyle
Professor of Chemistry

James D. Morrison
Professor of Chemistry

Kenneth K. Andersen
Professor of Chemistry

James H. Weber
Associate Professor of Chemistry

Miyoshi Ikawa
Professor of Biochemistry

Date

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The author is especially grateful to his parents and sisters whose encouragement was always a source of strength. Most important of all, the author is indebted to his wife, Mary, whose personal sacrifices, understanding, and love, made it all possible, as well as worthwhile.
THIS THESIS IS DEDICATED TO MY WIFE MARY
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ABSTRACT

PART I.
THE UNH REARRANGEMENT IN THE REACTIONS
OF BENZIMIDAZOLES AND DINITROANILINES

PART II.
THE THREE-AXIAL ALKYL EFFECT

by

JOHN LAWRENCE LaMATTINA

Part I
An investigation into the preparation of 7-nitro and 7-amino benzimidazoles is reported. Specific syntheses of isomeric benzimidazoles have been developed and a correlation of structure with nmr spectra is presented.

The mono- and di-reduction of 2,6-dinitroanilines has also been studied. Of particular importance is the discovery of a unique unsymmetrical nitrogen hop (UNH rearrangement) of an alkyl group when a 1-alkyl-2,6-dinitroaniline is reduced with tin and hydrochloric acid. A second type of rearrangement was uncovered which also involves migration of an alkyl group when a 1-alkylamino-2,6-diaminobenzene is treated with an acylating agent. The possible mechanisms for these novel rearrangements, as well as the resulting impact on the use of these compounds as herbicides is discussed.
Part II

In order to elucidate the parameters governing the "Three-Axial Alkyl Effect", a series of 1-benzyl-3,4-disubstituted piperidines have been prepared and their respective nmr spectra analyzed. It has been found that the greater the contribution of a conformer containing a 3-axial (or 3-pseudoaxial) group, the greater the observable magnetic non-equivalence of the N-benzyl methylene protons. The use of the "Three-Axial Alkyl Effect" as a stereochemical probe is also discussed.
PART I
THE UNH REARRANGEMENT IN THE REACTIONS
OF BENZIMIDAZOLES AND DINITROANILINES
INTRODUCTION

The Twentieth Century has seen man take great strides in science and technology. Yet for all the progress that has been made, there are still great potential problems ahead, including the threat of famine. Efforts are being made to combat this threat by increased crop yield, and toward this end potent herbicides are being developed. The importance of weed control is obvious. However, these compounds must be ecologically safe, otherwise their use will be self-defeating. Researchers, then, must not only establish the safety of these compounds but also must be sure that the degradation products and metabolites of the herbicide are also harmless to man.

In the past few years, a large number of N-substituted-2,6-dinitroanilines have been developed as herbicides. A typical example is Trifluralin (1), which has been quite effective. In 1970, 241,000 pounds of this material was used in California alone. Another compound currently showing great promise is Profluralin (2). Research has shown that these compounds are converted by either bacterial metabolism or photochemical degradation into benzimidazoles. In particular, it is believed that 2-methyl-7-nitrobenzimidazole-5-carboxylic acid (3), 2-methyl-7-nitro-5-trifluoromethylbenzimidazole (4), and 2-methyl-7-nitro-1-propyl-5-trifluoromethylbenzimidazole (5) are reasonable metabolites of 2.
The purpose of this research was to develop a synthetic method by which large amounts of 3, 4, and 5 could be prepared. Once available, the synthetic material could be compared with the natural metabolites to identify conclusively their structure; also, the toxicities of these compounds could readily be determined. Additionally, various aspects of the chemical behavior of benzimidazoles were to be studied, as well as the application of spectroscopic techniques for structural elucidation. Finally, it was hoped that some fundamental information could be obtained concerning the mechanism of the metabolic (or photochemical) conversion of 2,6-dinitroanilines into benzimidazoles. Such data could be of value to the chemist, especially when the polyfunctional nature of these molecules is considered.

The general method for the synthesis of benzimidazoles such as 3, 4, and 5, suggested that the synthetic problem would largely involve the preparation of substituted o-phenylenediamines. The preparation of these o-phenylene-
diamines in turn required the synthesis of o-nitroanilines which on reduction would provide the desired compounds. The particular benzimidazoles that were required contained a nitro substituent, and thus the intermediate dinitroaniline must undergo selective reduction in order to provide the desired intermediates 6, 7, and 8. A number of selective reduction procedures are known and this synthetic route thus appeared to feasible.

\[
\begin{align*}
\text{o-nitroaniline} & \quad \rightarrow \quad \text{dinitroaniline} \\
\begin{array}{c}
\text{NHR} \\
\text{O}_2\text{N} \\
\text{X} \\
\text{NO}_2
\end{array} & \quad \rightarrow \quad \\
\begin{array}{c}
\text{NHR} \\
\text{O}_2\text{N} \\
\text{X} \\
\text{NH}_2
\end{array} & \quad \rightarrow \quad \\
\text{6} & \quad \text{7} & \quad \text{8}
\end{align*}
\]

\[
\begin{align*}
9 & \quad R = H, \; X = \text{CO}_2\text{H} \\
21a & \quad R = H, \; X = \text{CF}_3 \\
21c & \quad R = \text{C}_3\text{H}_7-\text{n}, \; X = \text{CF}_3
\end{align*}
\]
RESULTS AND DISCUSSION

I. Preparation of 2-Methyl-7-nitrobenzimidazole-5-carboxylic Acid (3), 2-Methyl-7-nitro-5-trifluoromethylbenzimidazole (4), and 2-Methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (5)

A. The Syntheses of the Dinitroanilines

The preparation of the 2,6-dinitroanilines can be approached in either of two ways. The first method involves the nitration of amino-protected anilines using strenuous conditions needed to effect dinitration. The second method involves the displacement of halogen in a nucleophilic aromatic substitution. Ordinarily, nitro functions are introduced into aromatic rings via electrophilic substitution; however, electrophilic substitution becomes increasingly difficult each time an electron-withdrawing substituent is added to the substrate. On the other hand, an aromatic ring which contains electron-withdrawing functions properly situated can undergo attack by a nucleophile resulting in an intermediate Meisenheimer complex. In the case of 2,6-dinitrohalobenzenes, a nucleophile such as ammonia can add at the one position thereby generating the complex. Loss of halide results in the regeneration of the aromatic ring and the ultimate formation of the 2,6-dinitroanilines.
The original approach to the synthesis of 4-amino-3,5-dinitrobenzoic acid (9) was the dinitration of p-amino-benzoic acid (10). The protection of the amino group in 10 was attempted using acetic anhydride to form the N-acyl compound 11. The acylation in refluxing acetic anhydride gave a mixture of mono and diacylated p-aminobenzoic acid (11 and 12); however, this mixture was difficult to separate. Refluxing 10 in acetic acid did, however, give 11 in good yield with no trace of diacylated product. On nitration 11 gave 46% of 4-acetamido-3-nitrobenzoic acid (13) and 18% of 4-amino-3-nitrobenzoic acid (14). No matter how vigorous the reaction conditions, dinitration could not be accomplished. Apparently, the steric effect of the acetamide function interferes with the approach of the nitronium ion, thus preventing the further reaction.
A better synthesis for the intermediate dinitroanilines proved to be the displacement by ammonia of the chlorine of a substituted 2,6-dinitrochlorobenzene via an aromatic nucleophilic substitution mechanism. Thus, p-chlorobenzoic acid \((\text{15})\) could be readily dinitrated to give 4-chloro-3,5-dinitrobenzoic acid \((\text{16})\) and the chlorine could easily be substituted by \(\text{NH}_2\) to give 4-amino-3,5-dinitrobenzoic acid \((\text{9})\) using ammonia as the nucleophile. All attempts to acylate \(\text{9}\) using acetyl chloride or acetic anhydride failed to give the N-acetyl group indicating the low basicity of the amino group due to the strong electron withdrawing effects of the ring substituents.
Attempts to dinitrate p-chlorobenzotrifluoride (18) using the same conditions employed for the synthesis of 16 were unsuccessful due to hydrolysis of the trifluoromethyl group. However, 4-chloro-3,5-dinitrobenzotrifluoride (19) was prepared using Giam's method\(^4\) for the nitration of 4-chloro-3-nitrobenzotrifluoride (20). The chlorine of 19 could be substituted by ammonia or primary amines to form the corresponding anilines 21(a-i) in excellent yields, as listed in Table 1.

Although this work satisfied the immediate need for the 2,6-dinitroanilines necessary for the preparation of benzimidazoles 3, 4, and 5, further studies on the chemistry of benzimidazoles in general required the preparation of
### TABLE 1
SYNTHESSES OF DINITROANILINES 21(a-i)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>% Yield</th>
<th>mp (°C)</th>
<th>Literature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>74</td>
<td>144-145°</td>
<td>142-144°</td>
</tr>
<tr>
<td>b</td>
<td>C₂H₅</td>
<td>86</td>
<td>73-74°</td>
<td>69-73°</td>
</tr>
<tr>
<td>c</td>
<td>n-C₃H₇</td>
<td>82</td>
<td>63-64°</td>
<td>A</td>
</tr>
<tr>
<td>d</td>
<td>n-C₄H₉</td>
<td>86</td>
<td>39-40°</td>
<td>39-40°</td>
</tr>
<tr>
<td>e</td>
<td>C₂H₅CHCH₃</td>
<td>85</td>
<td>72.5-73°</td>
<td>69.5-70.5°</td>
</tr>
<tr>
<td>f</td>
<td>(CH₃)₃C</td>
<td>89</td>
<td>55-56°</td>
<td>54-55°</td>
</tr>
<tr>
<td>g</td>
<td>C₆H₅</td>
<td>80</td>
<td>121-122°</td>
<td>119-121°</td>
</tr>
<tr>
<td>h</td>
<td>(+)-C₆H₅CHCH₃</td>
<td>98</td>
<td>oil</td>
<td>C</td>
</tr>
<tr>
<td>i</td>
<td>(+)-C₂H₅CHCH₃</td>
<td>85</td>
<td>77-77.5°</td>
<td>D</td>
</tr>
</tbody>
</table>

---

A - Calcd for C₁₀H₁₀F₃N₃O₄: C, 40.96; H, 3.44; N, 14.33.
Found: C, 41.18; H, 3.47; N, 14.32

B - Boiling Point 128° at 0.04 mm of Hg; [α]D = (+) 124.9°

C - Calcd for C₁₅H₁₂F₃N₃O₄: C, 50.11; H, 3.41; N, 11.83.
Found: C, 50.82; H, 3.57; N, 11.53.

D - [α]D = (+) 22.0°; Calcd for C₁₁H₁₂F₃N₃O₄: C, 43.00; H, 3.94; N, 13.68. Found: C, 43.20; H, 4.20; N, 13.50.
other 2,6-dinitroanilines, specifically 4-amino-3,5-dinitrotoluene (22a), 4-n-propylamino-3,5-dinitrotoluene (22b), 4-amino-3,5-dinitrochlorobenzene (23a) and 4-n-propylamino-3,5-dinitrochlorobenzene (23b). The syntheses of these compounds involved both methods of dinitroaniline synthesis outlined at the start of this section.

p-Toluidine (24) is easily acylated in refluxing acetic acid to afford N-acetyl p-toluidine (25) in excellent yield. Treatment of 25 with a nitric acid-acetic anhydride mixture, followed by hydrolysis afforded 35% of 22a. It is interesting to note that the same conditions used to prepare 22a were unsuccessful for the preparation of 4-amino-3,5-dinitrobenzoic acid (9). Obviously the carboxylic acid function strongly deactivates the ring thus allowing for only mononitration; the methyl function in 25, however, exerts the opposite effect and thus dinitration does occur, albeit in poor yield.
The preparation of 4-n-propylamino-3,5-dinitrotoluene (22b) involved the initial conversion of 22a to 4-chloro-3,5-dinitrotoluene (26) by means of a Sandmeyer reaction. Displacement of the halide of 26 by n-propylamine readily afforded 22b.

4-Amino-3,5-dinitrochlorobenzene 23a was prepared by the mononitration of 4-amino-3-nitrochlorobenzene (27) as described by Elderfield. Conversion of 27 to 2,5-dichloro-1,3-dinitrobenzene (28) was also accomplished by a Sandmeyer reaction, and the resulting 28 was converted to 4-n-propylamino-3,5-dinitrochlorobenzene (23b) by nucleophilic aromatic substitution using n-propylamine (as previously described).
The above results indicate that one's approach to the preparation of 2,6-dinitroanilines is dependent upon the nature of the substituents on the aromatic ring. Dinitration can be effected directly if electron-donating groups are present to activate the ring for electrophilic substitution. On the other hand, the presence of electron withdrawing substituents necessitates either a step-wise approach, or the formation of an intermediate 2,6-dinitrochlorobenzene from which the desired anilines can be obtained via aromatic nucleophilic substitution.

B. The Syntheses of o-Phenylenediamines

The selective reduction of m-dinitrobenzenes to m-aminonitrobenzenes has been described using sodium hydrosulfide and ammonium polysulfide under a variety of conditions. The selectivity of these reductions has proved valuable to the synthetic chemist since the standard methods employed for the reduction of nitro groups (tin-hydrochloric acid, catalytic hydrogenation) are rapid and non-specific, thus resulting in reduction of both nitro functions. The use of these sulfides does have its limitations, however, since the desired products are obtained in only fair yields and are difficult to purify.

The next step in the proposed benzimidazole syntheses involved the reduction of just one nitro function of the 2,6-dinitroanilines to give the corresponding 1,2-diamino-3-nitrobenzenes (o-phenylenediamines). The most promising
reaction conditions utilized hydrated sodium sulfide in methanol as the solvent following a procedure described by Idoux. This reaction with 4-amino-3,5-dinitrobenzoic acid (9), however, failed to give a product because of the low solubility of the sodium salt of the starting material. For this reason, the acid was converted to the methyl ester (29a), but reduction of this material gave only a 21% yield of the desired methyl 3,4-diamino-5-nitrobenzoate (30a). Since the monoreduction of 4-amino-3,5-dinitrobenzotrifluoride (21a) was reported to proceed in only fair yield with ammonium polysulfide, an alternative method of monoreduction was sought.

Catalytic hydrogenation had not been successfully applied to specific monoreductions of this type; however, this method would make this a viable technique. A procedure outlined by Secrist and Logue which converted nitrobenzenes to the hydrochloride of the corresponding anilines seemed particularly worthwhile. Thus, reduction of 21a over 10% palladium on carbon in 10:1 ethanol-chloroform as solvent at room temperature and three atm. gave complete reduction and 3,4,5-triaminobenzotrifluoride (31) was isolated after basic work-up. However, moderation of hydrogenation was achieved by using 1,2-dimethoxyethane in place of ethanol in the solvent mixture. Thus, 21a was converted to 3,4-diamino-5-nitrobenzotrifluoride (7) in good yield. Obviously, the substitution of an aprotic solvent for ethanol sufficiently slowed reduction to allow for isolation of the o-phenylene-
diamine. This procedure was also successful for the preparation of 3,4-diamino-5-nitrobenzoic acid (6), 3,4-diamino-5-nitrotoluene (32), and ethyl 3,4-diamino-5-nitrobenzoate (30b). Furthermore, all of these compounds were obtained in yields superior to those using the basic sulfides. These results are outlined in Table 2.

Unfortunately, some of the other o-phenylenediamines that were needed were not accessible by catalytic hydrogenation. Reduction of 4-amino-3,5-dinitrochlorobenzene (23a) using the above conditions gave a moderate yield of 3,4-diamino-5-nitrochlorobenzene (33). However, a small amount of cleavage of the chlorine atom also took place resulting in the formation of 1,2-diamino-3-nitrobenzene (34). These results were confirmed by both combustion analyses, and the nuclear magnetic resonance (nmr) spectrum of the product. Although this impure sample of 33 could be used to obtain products further along in the synthetic sequence, these products were obtained in poor yields and were difficult to purify.
### TABLE 2

**SELECTIVE HYDROGENATIONS OF 2,6-DINITROANILINES**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>Reaction Time</th>
<th>mp</th>
<th>lit. mp</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1 hr</td>
<td>123.5-125°</td>
<td>121-123°</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;H</td>
<td>3 hr</td>
<td>275°</td>
<td>275°&lt;sup&gt;15&lt;/sup&gt;</td>
<td>89</td>
</tr>
<tr>
<td>32</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5 hr</td>
<td>152-154°</td>
<td>152-154°&lt;sup&gt;16&lt;/sup&gt;</td>
<td>81</td>
</tr>
<tr>
<td>30b</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>1.5 hr</td>
<td>199-200°</td>
<td>A</td>
<td>63</td>
</tr>
</tbody>
</table>

A - Calcd for C<sub>9</sub>H<sub>11</sub>N<sub>3</sub>O<sub>4</sub>: C, 48.00; H, 4.92; N, 18.66.

Found: C, 48.22; H, 4.90; N, 18.30
Even more disappointing was the catalytic reduction of 4-n-propylamino-3,5-dinitrobenzotrifluoride (21c). Although the infrared (ir) spectrum of the product, a dark viscous oil, indicated that monoreduction of the dinitroaniline had occurred (NH$_2$, 3450 cm$^{-1}$; NO$_2$, 1540 and 1330 cm$^{-1}$), the nmr spectrum of the product showed it to be a mixture of two isomers with small amounts of other side products as well. The nmr spectrum of the product showed it to be a mixture of two isomers of the desired material 8 and the isomer resulting from alkyl rearrangement, 35. Attempts were made to convert this viscous oil to the corresponding mixture of benzimidazoles in order to facilitate separation and purification. However, cyclization of this mixture by reaction with acetic anhydride, or any other method$^2$ (such as acetyl chloride or acetic acid under a variety of conditions) failed to afford an isolable product. This difficulty in forming the benzimidazole was not limited to the diamine from catalytic hydrogenation of 21c for similar results were obtained using the product of monoreduction of 21d as well.
These difficulties led to a reconsideration of the use of sulfides for the syntheses of 8 and 33. Using a modification of the procedure of Crosby and Leitis\(^1\), dinitroaniline 21c was treated with a sodium sulfide-sodium bicarbonate solution to afford 3-amino-4-\(\text{\textregistered}\)-propylamino-5-nitrobenzotrifluoride (8) in good yield. This material did not contain any significant amount of product of rearrangement. These reaction conditions were also successfully employed for the conversion of 4-amino-3,5-dinitrochlorobenzene (23a) to 3,4-diamino-5-nitrochlorobenzene (33), and of 4-ethylamino-3,5-dinitrobenzotrifluoride (21b) to 3-amino-4-ethylamino-5-nitrobenzotrifluoride (36) although the yields of both 33 and 36 were low.

In summary, therefore, it seems evident that catalytic hydrogenation, using 10% palladium on carbon as catalyst and 10:1 dimethoxyethane-chloroform as solvent, is a useful method for the synthesis of 3-nitro-o-phenylenediamines. However, certain o-phenylenediamines cannot be isolated in pure form by this method, and so chemical reductions employing basic sulfides are more suitable for these cases.

C. The Syntheses of Benzimidazoles

The reaction of o-phenylenediamines with various acetic acid derivatives has been shown to produce the corresponding 2-methylbenzimidazoles.\(^2\) Since the reaction with acetic anhydride and hydrochloric acid was previously found
to be satisfactory for the preparation of 2,5-dimethyl-7-nitrobenzimidazole (37), this was the method of choice for the general preparation of benzimidazoles. 16

Some problems were anticipated in the preparation of 2-methyl-7-nitrobenzimidazole-5-carboxylic acid (3) since this material is an amino acid and thus amphoteric. Treatment of 3,4-diamino-5-nitrobenzoic acid (6) with acetic anhydride followed by boiling in 3N hydrochloric acid gave 3 as a mixture of the hydrochloride and free amino acid, as indicated by carbon, hydrogen, nitrogen (C,H,N) analysis. Recrystallization of this material from aqueous hydrochloric acid provided a purer product but analyses still indicated the presence of some free amino acid. As a consequence the compound was characterized as the methyl ester, methyl 2-methyl-7-nitrobenzimidazole-5-carboxylate (3a), which was purified and then hydrolyzed to 3. A work-up procedure, consisting of complete evaporation of solvent, trituration with water, and further evaporation, led to the isolation of 3 as the free amino acid. This material showed no trace of the hydrochloride in the ir spectrum. The fact that 3

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{NH}_2 \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{32} & \quad \text{37}
\end{align*}
\]
loses hydrogen chloride from the salt indicates that the imidazole portion of this molecule is a very poor base, thus making the hydrochloride unstable.

The remaining conversions of the 3-nitro-o-phenylene diamines into their respective benzimidazoles was straightforward using the cyclization procedure of treatment with acetic anhydride followed by hydrolysis in 3N hydrochloric acid. The results are summarized in Table 3.

In conclusion, a general scheme for the large scale preparation of various benzimidazoles, in particular, 3, 4, and 5, the suspected metabolites, has been realized.

II. Reactions of Benzimidazoles

A. Alkylation

During the syntheses of the target benzimidazoles 3, 4, and 5, a number of alternative routes of syntheses were explored. One such study concerned the alkylation of the N-benzimidazoles as a method of introducing a nitrogen substituent. The purpose of this work was three-fold: first, as a class of compounds little work has been reported using benzimidazoles as substrates since most research on these compounds has centered on their preparation; second, the preparation and comparison of isomeric benzimidazoles would make future work on the identification of plant metabolites of dinitroanilines much easier; finally, it was hoped that alternative methods for the synthesis of substituted benzimidazoles could be developed which would be superior to those described in Section I.
TABLE 3
SYNTHESSES OF BENZIMIDAZOLES FROM o-PHENYLENEDIAMINES \textsuperscript{A}

\[
\begin{align*}
\text{Product} & \quad \text{X} & \quad \text{R} & \quad \text{mp} & \quad \text{Yield} \\
4 & \text{CF}_3 & \text{H} & 207.5-208^\circ & 84 \\
5 & \text{CF}_3 & \text{C}_3\text{H}_7-n & 82-83.5^\circ & 70 \\
38 & \text{CF}_3 & \text{R}_2\text{H}_5 & 81-84^\circ & 70 \\
37 & \text{CH}_3 & \text{H} & 238-240^\circ & 56 \\
& & & & (\text{lit}^{16} 238-240^\circ) \\
39 & \text{Cl} & \text{H} & 236-237^\circ & 79
\end{align*}
\]

\textsuperscript{A} - Other pertinent data for these compounds are given in the Experimental Section.
In considering the structure of a 7-nitrobenzimidazole, it is interesting to note that removal of the nitrogen proton would generate an anion which is capable of delocalization of the charge between the two nitrogens in the ring. Thus, alkylation of the anion could take place at either site. The steric effect of the nitro function at the 4-position, however, could hinder attack at the proximate nitrogen and thus direct alkylation to the 1-position.

The anion of 2-methyl-7-nitro-5-trifluoromethylbenzimidazole (4) was generated by reaction of 2 with sodium hydride, and treatment with n-propylbromide afforded 2-methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40) in high yield. No trace of the other possible isomer 2-methyl-7-nitro-1-propyl-5-trifluoromethylbenzimidazole (5) was detected. The difference between isomers 5 and 40 was substantiated by the nmr spectra of these compounds. In 5 the aromatic hydrogens appear at 8.56 and 8.48 ppm; those for 40 appear at 7.88 and 8.40 ppm. The large upfield shift (8.56 - 7.88 ppm) for an aromatic hydrogen in 4 must result from shielding, by the propyl group, of the hydrogen para to the nitro group, since only this hydrogen

\[
\begin{align*}
\text{NO}_2 & \quad \text{H} \\
& \quad \text{N} \\
\text{CF}_3 & \quad \text{CH}_3 \\
\end{align*}
\]
is able to feel the effects of the alkyl substituent in either isomer.

In the same manner the anion of 4 was alkylated with ethyl iodide, n-butyl bromide, and sec-butyl bromide and in each case the only product isolated was the 1-alkyl-4-nitrobenzimidazole. Thus, 1-ethyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (41), 1-n-butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (42), and 1-sec-butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (43), were prepared in reasonable yields. Similarly, 2,5-dimethyl-7-nitrobenzimidazole (37) afforded 2,6-dimethyl-1-propyl-4-nitrobenzimidazole (44) and 5-chloro-2-methyl-7-nitrobenzimidazole (39) afforded 6-chloro-2-methyl-4-nitro-1-propylbenzimidazole (45) on alkylation with n-propylbromide. It seems quite apparent, therefore, that the nitro group exerts a strong steric effect. Thus alkylation is preferential at the nitrogen which is further removed. These results are summarized in Table 4.

B. Acylation

Since alkylation of 7-nitrobenzimidazoles occurs exclusively at the nitrogen distant from the nitro group, acylation probably would be selective as well. Furthermore, it seemed feasible that once the less hindered nitrogen was acylated, alkylation could be directed to the hindered nitrogen. Thus, the acyl group would act as a protecting group. After alkylation has occurred, the acyl group could then be
TABLE 4
PHYSICAL DATA FOR ALKYL NITROBENZIMIDAZOLES

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>mp</th>
<th>Yield (%)</th>
<th>NMR Chemical Shifts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>CF₃</td>
<td>C₃H₇-n</td>
<td>82-83.5°</td>
<td>--</td>
<td>Hₐ: 8.48 Hₖ: 8.56</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>CF₃</td>
<td>C₂H₅</td>
<td>81.84°</td>
<td>--</td>
<td>Hₐ: 8.48 Hₖ: 8.55</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>CF₃</td>
<td>----</td>
<td>131.5-132°</td>
<td>80</td>
<td>Hₐ: 8.40 Hₖ: 7.88</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>CF₃</td>
<td>----</td>
<td>152-153°</td>
<td>70</td>
<td>Hₐ: 8.58 Hₖ: 8.08</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>CF₃</td>
<td>----</td>
<td>102-103°</td>
<td>45</td>
<td>Hₐ: 8.60 Hₖ: 8.12</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>CF₃</td>
<td>----</td>
<td>115-117°</td>
<td>30</td>
<td>Hₐ: 8.56 Hₖ: 8.21</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>CH₃</td>
<td>----</td>
<td>135-136°</td>
<td>66</td>
<td>Hₐ: 7.90 Hₖ: 7.25</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>Cl</td>
<td>----</td>
<td>115-116.5°</td>
<td>42</td>
<td>Hₐ: 7.87 Hₖ: 7.48</td>
</tr>
</tbody>
</table>
removed to give the 1-alkyl-7-nitrobenzimidazole. Such a technique would nicely complement the direct alkylation method in that specific alkylation of either nitrogen would then be available.

Treatment of 2-methyl-7-nitro-5-trifluoromethylbenzimidazole (4) with acetyl chloride afforded only one product, 1-acetyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (46) in 73% yield. The site of acylation was again determined by nmr. Thus, the hydrogen para to the nitro group of 4 was shifted upfield in 46 indicating that acylation had occurred on the neighboring nitrogen and that the hydrogen in the 7-position is being affected by the shielding cone of the carbonyl.

Attempts were made to alkylate 46 using n-butyl bromide and sodium iodide under a variety of conditions. Unfortunately no reaction was successful and, depending upon the conditions, either deacylation or decomposition resulted. It seems evident, therefore, that the steric effect of the nitro group is even greater than anticipated and that additions to the proximate nitrogen may not be possible.
C. Reduction of the Nitro Function

As was previously discussed, it has been reported that the photochemical and microbiological treatment of substituted 2,6-dinitroanilines gives reductive cyclization to nitrobenzimidazoles.\(^1\) It seems plausible, therefore, that perhaps these nitrobenzimidazoles can be further reduced to the corresponding aminobenzimidazoles under these same conditions. Thus, it was desirable to have authentic samples of various aminobenzimidazoles for comparison and for toxicity data.

Reduction of 2-methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40) using mossy tin and concentrated hydrochloric acid afforded the corresponding 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47) in excellent yield. In fact, this method of reduction was highly successful for all 1-alkyl-4-nitrobenzimidazoles.

\[\text{NO}_2 \quad \text{CH}_3 \quad \text{N} \quad \text{R} \quad \rightarrow \quad \text{NH}_2 \quad \text{N} \quad \text{R} \quad \text{CH}_3\]

\[
\begin{array}{ll}
40 & \text{X}=\text{CF}_3, \text{R}=\text{C}_3\text{H}_7-n \\
41 & \text{X}=\text{CF}_3, \text{R}=\text{C}_2\text{H}_5 \\
42 & \text{X}=\text{CF}_3, \text{R}=\text{C}_4\text{H}_9-n \\
43 & \text{X}=\text{CF}_3, \text{R}=\text{C}_4\text{H}_9-\text{sec} \\
44 & \text{X}=\text{CH}_3, \text{R}=\text{C}_3\text{H}_7-n \\
45 & \text{X}=\text{Cl}, \text{R}=\text{C}_3\text{H}_7-n \\
47 & \text{X}=\text{CF}_3, \text{R}=\text{C}_3\text{H}_7-n \\
48 & \text{X}=\text{CF}_3, \text{R}=\text{C}_2\text{H}_5 \\
49 & \text{X}=\text{CF}_3, \text{R}=\text{C}_4\text{H}_9-n \\
50 & \text{X}=\text{CF}_3, \text{R}=\text{C}_4\text{H}_9-\text{sec} \\
51 & \text{X}=\text{CH}_3, \text{R}=\text{C}_3\text{H}_7-n \\
52 & \text{X}=\text{Cl}, \text{R}=\text{C}_3\text{H}_7-n
\end{array}\]
However, the results were more complex when 1-alkyl-7-nitrobenzimidazoles were reduced. Treatment of 2-methyl-7-nitro-1-propyl-5-trifluoromethylbenzimidazole (5) with tin and hydrochloric acid afforded a mixture which contained the expected 7-amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53) along with an unidentified substance, 54. That two components were present in the mixture was confirmed by thin layer chromatography (tlc), and by the nmr spectrum which showed two sets of signals for the aromatic protons.

\[
\begin{array}{c}
\text{NO}_2 \quad \text{C}_3\text{H}_7-n \quad \text{CH}_3 \\
\text{CF}_3 \\ \\
\text{N} \\ \\
\text{5} \\
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{NH}_2 \quad \text{C}_3\text{H}_7-n \quad \text{CH}_3 \\
\text{CF}_3 \\ \\
\text{N} \\ \\
\text{53} \\
\end{array}
\]

In order to develop a synthesis which would yield only 53, other methods of reduction were investigated. Catalytic hydrogenation of 5 over platinum oxide in 95% ethanol also gave a mixture similar to that obtained by the tin-hydrochloric acid method. The use of a sodium sulfide-sodium bicarbonate medium (the same conditions used for the conversion of dinitroanilines to nitrophenylenediamines) was also tried, but no reduction occurred. A quantitative yield of starting material was recovered. Success in the synthesis of 53 was finally achieved using catalytic hydrogenation over platinum oxide with glacial acetic acid as solvent. Thus, 5 was converted to 53 in 92% yield, and 1-ethyl-2-methyl-7-nitro-5-trifluoromethylbenzimidazole (38) was reduced to 7-amino-1-
ethyl-2-methyl-5-trifluoromethylbenzimidazole (55) in 78% yield using these conditions.

It was clear that unknown 54 possessed a structure similar to 53 by spectral data and by tlc. Since 54 also differed from 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47), it was thought that perhaps 54 might be 2-methyl-7-n-propylamino-5-trifluoromethylbenzimidazole (56), an isomer of 53 and 47. Thus, 56 was independently synthesized for comparison.

Complete reduction of 4-amino-3,5-dinitrobenzotri fluoride (21a) using tin and hydrochloric acid afforded 3,4,5-triaminobenzotrifluoride (57). Conversion of 57 to 7-amino-2-methyl-5-trifluoromethylbenzimidazole (58) was achieved with triethylorthoacetate. Refluxing 58 in propionic acid resulted in the exclusive propionylation of the primary amino function to give 2-methyl-7-propionamido-5-trifluoromethylbenzimidazole (59). Reduction of the amide group of 59 could be effected with lithium aluminum hydride. However, C,H,N analysis of the product indicated that some reduction of the trifluoromethyl group was also occurring. Brown's method of amide reduction\textsuperscript{17} using diborane avoided this side reaction and 2-methyl-7-n-propylamino-5-trifluoromethylbenzimidazole (56) was obtained in good yield. This four-step sequence proved successful for the 5-methylbenzimidazole series as well.
TLC and nmr clearly showed that 56 was not identical with the unknown 54. Thus, 54 is not one of the three isomeric N-propylbenzimidazoles. Since it is clear that the unknown substance is a product of reduction similar to 53 and 56, perhaps it results from reductive cyclization to give 54X. It should be noted, however, that although such a product is consistent with the experimental data, no conclusive evidence for such a structure is currently available.
D. Comparison of the NMR Spectra of the N-n-Propyl Isomers of 7-Aminobenzimidazoles

The work outlined in the previous section resulted in the preparation of the three N-n-propyl isomers of 7-amino-2-methyl-5-trifluoromethylbenzimidazole (54, 53, and 56) and the corresponding isomers of 7-amino-2,6-dimethylbenzimidazole (51, 63, and 64; the synthesis of 7-amino-2,5-dimethyl-l-propylbenzimidazole, 64, is discussed in Section IV). The nmr spectra of these compounds were studied in order to relate the location of the propyl substituent with the proton resonance signals.

The nmr data for these compounds is found in Table 5. Comparing 7-amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53) with 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47), and 7-amino-2,5-dimethyl-1-propylbenzimidazole (64) with 4-amino-2,6-dimethyl-1-propylbenzimidazole (51), it is worthwhile to compare the aromatic protons (H_A and H_B) and the N-methylene protons of each. When the propyl group is on the ring nitrogen closer to the amino group (R_2) both aromatic protons are similar and un-
TABLE 5A

NMR SPECTRA OF N-n-PROPILBENZIMIDAZOLES

![Diagram of benzimidazole structure]

<table>
<thead>
<tr>
<th>Compound</th>
<th>X</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>H₁ (s)</th>
<th>H₂ (s)</th>
<th>CH₃ (s)</th>
<th>NCH₂ (t)</th>
<th>CH₂ (h)</th>
<th>CH₃ (t)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>CF₃</td>
<td>H</td>
<td>nC₃H₇</td>
<td>--</td>
<td>7.01</td>
<td>7.75</td>
<td>2.66</td>
<td>4.36</td>
<td>1.90</td>
<td>1.00</td>
</tr>
<tr>
<td>47</td>
<td>CF₃</td>
<td>H</td>
<td>--</td>
<td>nC₃H₇</td>
<td>7.01</td>
<td>6.76</td>
<td>2.76</td>
<td>4.05</td>
<td>1.84</td>
<td>0.96</td>
</tr>
<tr>
<td>56</td>
<td>CF₃</td>
<td>nC₃H₇</td>
<td>(H)</td>
<td>(H)</td>
<td>6.42</td>
<td>6.82</td>
<td>2.54</td>
<td>3.16</td>
<td>1.64</td>
<td>0.96</td>
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<tr>
<td>64</td>
<td>CH₃</td>
<td>H</td>
<td>nC₃H₇</td>
<td>--</td>
<td>6.37</td>
<td>7.01</td>
<td>2.52</td>
<td>4.12</td>
<td>1.84</td>
<td>0.96</td>
</tr>
<tr>
<td>51</td>
<td>CH₃</td>
<td>H</td>
<td>--</td>
<td>nC₃H₇</td>
<td>6.37</td>
<td>6.52</td>
<td>2.55</td>
<td>3.96</td>
<td>1.81</td>
<td>0.95</td>
</tr>
<tr>
<td>63</td>
<td>CH₃</td>
<td>nC₃H₇</td>
<td>(H)</td>
<td>(H)</td>
<td>6.12</td>
<td>6.41</td>
<td>2.41</td>
<td>3.12</td>
<td>1.58</td>
<td>0.91</td>
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</tbody>
</table>

A - All spectra were determined in CDCl₃ and chemical shifts are reported in parts per million relative to TMS.
affected by the alkyl group. However, when the propyl group is on the other ring nitrogen (R₃), H₇ should feel a shielding effect. As can be seen from the nmr data, this is the case. Thus, H₇ is shifted 0.99 ppm upfield comparing 5₃ with 4₇, and 0.49 ppm in 6₄ as compared with 5₁. The chemical shift of the NCH₂ group has also changed. This is presumably due to the fact that this group in the R₂ position is deshielded by the adjacent amino function. Thus, there are upfield shifts of 0.31 ppm in comparing 5₃ with 4₇ and 0.16 ppm in comparing 6₄ with 5₁.

As one might expect, there is a large difference in the chemical shifts of 2-methyl-7-n-propylamino-5-trifluoromethylbenzimidazole (5₆) and 2,5-dimethyl-7-n-propylamino-benzimidazole (6₃) (which both have the propyl group on the amino nitrogen) relative to the other isomers (5₃, 4₇, 6₄, and 5₁) that have the propyl group on the ring nitrogen. The methylene protons of the NCH₂ in 5₆ and 6₃ are shifted 0.8-1.2 ppm upfield since the propyl group no longer feels the deshielding effects of either the electron-poor imidazole ring or the aromatic ring current. The aromatic protons of 5₆ and 6₃ are shifted upfield due to the inductive effect of the propyl group.

These results, therefore, indicate that the location of a propyl (and probably other alkyl groups as well) group can be determined within a series of 7-aminobenzimidazoles.
III. Complete Reductions of Dinitroanilines

A. Reductions Using Mossy Tin and Hydrochloric Acid: The UNH Rearrangement

The monoreduction of 2,6-dinitroanilines (see Section I.B.) can be accomplished using various conditions provided the reduction process proceeds sufficiently slowly to allow for selectivity. Obviously, therefore, more vigorous conditions should result in the reduction of both nitro groups of a 2,6-dinitroaniline. The resulting 1,2,3-triaminobenzenes were of interest for the following reasons. First, it is possible that compounds of this type could be formed by the bacterial reduction of 2,6-dinitroanilines. Second, these triaminobenzenes should be easily converted to 7-aminobenzimidazoles, which, in turn, could be converted to 7-nitrobenzimidazoles by oxidation\textsuperscript{18} or by a Sandmeyer reaction.\textsuperscript{19} Thus, the 1,2,3-triaminobenzenes could be valuable synthetic intermediates.

\[
\text{O}_2\text{N} \quad \text{NO}_2 \quad \text{H}_2\text{N} \quad \text{NH}_2
\]

\[
\text{NHR} \quad \text{NHR} \quad \text{NH}_2 \quad \text{R} \quad \text{CH}_3
\]
Addition of 4-sec-butylamino-3,5-dinitrobenzotrifluoride (2le) to a mixture of mossy tin and concentrated hydrochloric acid followed by heating on a steam bath for one hour, afforded, after basic work-up, a quantitative yield of a viscous oil. Although both the ir spectrum and elemental analyses were as expected for the reduction of both nitro groups, the nmr spectrum indicated that this product was 3-sec-butylamino-4,5-diaminobenzotrifluoride (65e). The unsymmetrical structure of 65e was evident from the non-identity of the aromatic hydrogens (two singlets at 6.76 ppm and 6.72 ppm, each integrating for one proton). Obviously, during the reduction the alkyl group had migrated from the central nitrogen to a peripheral one. The structure of 65e was confirmed by conversion to the corresponding benzimidazole using acetic anhydride. Thus, 65e afforded 4-amino-1-sec-butyl-2-methyl-6-trifluoromethylbenzimidazole (50) which was identical to 50 prepared by an independent route (see section II.C.).

![Chemical Structures](image)
This unsymmetrical nitrogen hop (referred to as the UNH rearrangement) of an alkyl group from one ortho nitrogen to another proved to be somewhat general. Thus, the rearrangement was observed during the reduction of the 2,6-dinitroanilines 21b (R=C\textsubscript{2}H\textsubscript{5}), 21c (R=n-C\textsubscript{3}H\textsubscript{7}), and 21d (R=n-C\textsubscript{4}H\textsubscript{9}). These results are summarized in Table 6. As can be seen, the amount of rearrangement observed varies with the alkyl group. Thus, 21b and 21c give substantial amounts of the corresponding symmetrical triamines 66b and 66c. For those 2,6-dinitroanilines containing N-alkyl groups which are easily eliminated, such as t-butyl (21f) or \(\alpha\)-phenethyl (21e), reduction gave 3,4,5-triaminobenzotrifluoride (57). When the substituent was phenyl (21g) no rearrangement or elimination was observed, and the product was 4-anilino-3,5-diaminobenzotrifluoride (66g). The reduction was also studied on 2,6-dinitroanilines having groups other than trifluoromethyl para to the substituted amino function. Thus, 4-n-propylamino-3,5-dinitrochlorobenzene (23b) on reduction gave a 50-50 mixture of the symmetrical (66j) and unsymmetrical (65j) triamines, while 4-n-propylamino-3,5-dinitrotoluene (22b) afforded only the symmetrical product (66k).

In order to determine whether the migration occurred by an internal nucleophilic displacement or some other intermediate, optically active 4-sec-butylamino-3,5-dinitrobenzotrifluoride (21i) was prepared using chiral 2-butylamine to give 21i ([\(\alpha\])\textsubscript{D}\textsuperscript{20} = +22.0\textdegree). Reduction of 21i gave 3-sec-butylamino-4,5-diaminobenzotrifluoride (65e) with no optical
TABLE 6

TIN/HCl REDUCTIONS OF N-SUBSTITUTED-2,6-DINITROANILINES

<table>
<thead>
<tr>
<th>2,6-Dinitroaniline</th>
<th>Relative Yields of Products (%)&lt;sup&gt;A&lt;/sup&gt;</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21b X=CF&lt;sub&gt;3&lt;/sub&gt;, R=C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>b 50 b 50 ---</td>
<td>82</td>
</tr>
<tr>
<td>21c X=CF&lt;sub&gt;3&lt;/sub&gt;, R=nC&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>c 33 c 67 ---</td>
<td>50</td>
</tr>
<tr>
<td>21d X=CF&lt;sub&gt;3&lt;/sub&gt;, R=nC&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>d 5 d 95 ---</td>
<td>100</td>
</tr>
<tr>
<td>21e X=CF&lt;sub&gt;3&lt;/sub&gt;, R=sC&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>e 100 ---</td>
<td>100</td>
</tr>
<tr>
<td>21b X=CF&lt;sub&gt;3&lt;/sub&gt;, R=(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;C</td>
<td>0 0 100</td>
<td>74</td>
</tr>
<tr>
<td>21g X=CF&lt;sub&gt;3&lt;/sub&gt;, R=C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>g 100 0 ---</td>
<td>71</td>
</tr>
<tr>
<td>21h X=CF&lt;sub&gt;3&lt;/sub&gt;, R=(+)-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CHCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0 0 100</td>
<td>73</td>
</tr>
<tr>
<td>21i X=CF&lt;sub&gt;3&lt;/sub&gt;, R+(+)-sec-C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>0 i 100 ---</td>
<td>100</td>
</tr>
<tr>
<td>23b X=Cl, R=nC&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>j 50 j 50 ---</td>
<td>81</td>
</tr>
<tr>
<td>22b X=CH&lt;sub&gt;3&lt;/sub&gt;, R=nC&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;7&lt;/sub&gt;</td>
<td>k 100 0 ---</td>
<td>74</td>
</tr>
</tbody>
</table>

<sup>A</sup> Determined by NMR.
activity. For comparison, the reduction of 21i was accomplished with catalytic hydrogenation over platinum to give 4-sec-butylamino-3,5-diaminobenzotrifluoride, 66i, ([α]_D^{19} = -25.3°). These data suggested that the chiral carbon was converted to a radical during the tin/hydrochloric acid reduction.

There are reported rearrangements in which a group appears to have migrated from one ortho nitrogen to another. However, in these cases the rearrangement does not involve migration of the substituent; rather a molecular rearrangement, either through an intermediate heterocycle or else an opening-reclosing of the ring is occurring.²⁰ An example of the latter mechanism is the Dimroth rearrangement ²¹, the net result of which is the shifting of an aryl group from a ring nitrogen to an exocyclic amino group.

\[
\begin{align*}
\text{H}_2\text{N} & \text{-C} \equiv \text{CCO}_2\text{C}_2\text{H}_5 \\
\text{Ar-N} & \text{N} \quad \rightarrow \quad \text{+NH}_2 \\
\text{ArN-C} & \equiv \text{C-N=N} \\
\text{ArNH-C} & \equiv \text{CCO}_2\text{C}_2\text{H}_5 \\
\text{HN} & \text{-N} \\
\end{align*}
\]
It is postulated that the UNH rearrangement proceeds via a radical intermediate for two reasons: first, the migrating carbon atom undergoes racemization; second, tin-hydrochloric acid reductions are reported to proceed by a free-radical process.\textsuperscript{22} The proposed mechanism for the rearrangement is outlined in Scheme 1. The initial step of the reduction results in the conversion of a nitro function to a nitroso group (I) which in turn is reduced to a radical species, II. An intramolecular abstraction of hydrogen from the N-alkyl group then generates the alkyl radical, III, which is further reduced to the dihydrobenzimidazole IV. Reduction of this intermediate occurs with C-N bond cleavage thus forming the unsymmetrically substituted triamine.

Similar mechanisms have been proposed for the formation of benzimidazoles by the reductive photolysis of dinitroanilines; however, no rearrangement of the alkyl group has been reported. It is probable, however, that such rearrangement products are present in the weathered pesticide but have not been detected.

It is of value to compare this mechanism with that proposed for the "t-Amino Effect".\textsuperscript{23} This remarkable reaction involves treatment of N,N-dialkyl-2-nitroanilines with stannous chloride in hydrochloric acid to yield the expected phenylenediamine along with the unexpected 1,2-dialkylbenzimidazole.
Scheme I
The mechanism proposed for the formation of the benzimidazole involves reduction of the nitro group to a nitroso function, followed by intramolecular abstraction of a proton to generate an iminium intermediate. Intramolecular cyclization, followed by dehydration affords the benzimidazole, as shown in Scheme II.
The question arises as to why the UNH rearrangement and the "t-Amino Effect" ultimately lead to different products despite the fact that the substrates and reaction conditions in each case are strikingly similar. Although a conclusive answer cannot be given at this time, two points can be made: first, the mechanism for the UNH rearrangement cannot include an N-hydroxydihydrobenzimidazole intermediate since no trace of benzimidazole is formed in the reaction; second, since the two reactions do differ, the other nitro substituent of the 2,6-dinitroaniline may be playing a key role in the rearrangement.

In light of the "t-Amino Effect", one may argue that the UNH rearrangement, though different, may also involve a heterolytic rather than homolytic mechanism. Clearly, either pathway would convert an optically active 2,6-dinitroaniline into a racemic triaminobenzene. However, since tin reductions are known to proceed via a homolytic mechanism, and since similar 2,6-dinitroaniline radicals are reported to be generated in reductive photolysis, the homolytic mechanism currently seems more plausible.

The discovery of the UNH rearrangement is of particular importance when one considers its effect on the identification of the various metabolites of herbicidal 2,6-dinitroanilines. Since benzimidazoles are products in the bacterial reduction process, it is entirely possible that some of these products might result from rearrangement. Thus, it is of importance that the metabolites of the 2,6-dinitroanilines be investigated for any evidence of rearrangement.
products, and, if any rearranged products are detected, these compounds should be tested for toxicity.

B. Catalytic Hydrogenation

The catalytic hydrogenation of (+)-4-sec-butylamino-3,5-dinitrobenzotrifluoride (21i) over platinum in 95% ethanol afforded predominantly the corresponding optically active symmetrical triamine, 4-sec-butylamino-3,5-diaminobenzotrifluoride (66i). The nmr spectrum of the crude product indicated that it consisted of approximately 15% of the rearranged isomer (65e). It was found, however, that the symmetrical isomer could be easily separated by recrystallization.

Since catalytic hydrogenation was successful for the synthesis of 66i, it was decided to investigate this type of reduction as a general method for the preparation of symmetric triamines such as 66.

As expected, the hydrogenation of racemic 4-sec-butylamino-3,5-dinitrobenzotrifluoride (21e), using the conditions described above, afforded symmetric (66e) and unsymmetric (65e) products in the same ratio as was obtained
for the optically active isomer. However, reduction of 4-ethylamino-3,5-dinitrobenzotrifluoride (21b) under these conditions afforded not only the symmetric (66b) and unsymmetric (65b) isomers, but also a significant amount of 7-amino-2-methyl-5-trifluoromethylbenzimidazole (58). The formation of 58 was surprising, especially since no trace of benzimidazole product was detected in the reduction of 21e under the same conditions.

It seems reasonable that the benzimidazole is formed heterolytically via a mechanism somewhat similar to that postulated for the "t-Amino Effect" (see Section III.A.). For the benzimidazole to form, the corresponding N-hydroxydihydrobenzimidazole must be an intermediate. This intermediate can be generated by abstraction of a proton by a nitroso function, followed by cyclization. Subsequent dehydration would yield 58. Such a mechanism is consistent with that of the "t-Amino Effect".
In 21e, the alkyl group is a sec-butyl moiety. In this case, the nitroso function is probably reduced before it has the chance to abstract the alkyl proton. This seems reasonable when one considers that the sec-butyl group is larger than the ethyl group and thus, less likely to cyclize. The difference in the size of the alkyl groups, therefore, accounts for the different products.

Since it was believed that a rapid reduction would lead to only symmetric triamines as products, the reduction was carried out in the presence of three milliliters of concentrated hydrochloric acid, keeping the remainder of the conditions the same. Surprisingly, more complex product mixtures resulted. Thus, 21e gave both symmetric and unsymmetric triamines (66e and 65e) in equal amounts, along with unidentified side products. The same results occurred when
4-n-propylamino-3,5-dinitrobenzotrifluoride (21c) was reduced under the same conditions. Obviously, the acid is playing an important role in these two reactions, and perhaps the reaction pathway is dependent upon pH.

Therefore, because of the number of products generated, catalytic hydrogenation was abandoned as a method for the exclusive synthesis of the symmetric triamines.

IV. Conversion of the Triaminobenzenes to Benzimidazoles

A. Cyclization to 7-Aminobenzimidazole

One of the initial purposes for the preparation of the triaminobenzenes was to investigate the feasibility of using these compounds as precursors to 7-aminobenzimidazoles, which, in turn, could be converted to the corresponding 7-nitrobenzimidazoles. Since various triaminobenzenes were available (see Sections III.A. and III.B.), this alternate route to benzimidazoles was examined.
Treatment of 3-n-butylamino-4,5-diaminobenzotri fluoride (65d) with an excess of acetic anhydride, followed by refluxing in 3N hydrochloric acid afforded a viscous oil. The ir spectrum of this material contained an absorption at 1690 cm\(^{-1}\), indicating that the 4-amino function was acylated. By refluxing this material in 6N hydrochloric acid, the free amine, 4-amino-1-n-butyl-6-trifluoromethylbenzimidazole (49) was isolated. This material was identical in all respects to 49 prepared by the butylation of 2-methyl-7-nitro-5-trifluoromethylbenzimidazole (4), followed by reduction of the nitro group (see Section II.C.). Similarly, 3-sec-butylamino-4,5-diaminobenzotri fluoride (65e) could be converted to 4-amino-1-sec-butyl-6-trifluoromethylbenzimidazole (50), also identical to that 50 which had previously been prepared.
This method was also used to convert some of the symmetric triamines to the 7-aminobenzimidazoles. Thus, 4-sec-butylamino-3,5-diaminobenzotrifluoride (66e) afforded 7-amino-1-sec-butyl-2-methyl-5-trifluoromethylbenzimidazole (67) which was clearly isomeric with 49. Likewise, 4-anilino-3,5-diaminobenzotrifluoride (66g) afforded 7-amino-2-methyl-1-phenyl-5-trifluoromethylbenzimidazole (68). All of these aminobenzimidazoles were isolated in yields of greater than 80%.

\[
\begin{align*}
66e & \quad R = C_4H_9-sec \\
66g & \quad R = C_6H_5 \\
67 & \quad R = \text{sec-C}_4H_9 \\
68 & \quad R = C_6H_5
\end{align*}
\]

In view of the results with 66d and 66e, it was quite surprising that when 4-n-propylamino-3,5-diaminobenzotrifluoride (66c) was treated under identical conditions 7-amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53) was not the product. Rather, the isomeric 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47) was isolated in excellent yield. The starting material, 66c, was clearly the symmetric triamine as shown by the appearance of a two-proton singlet in its nmr spectrum. That 47 was the product was apparent by its physical properties, identical with those of 47 made by an alternate method (see Section II.C.).
To test the generality of this novel rearrangement, other symmetric propyl triamines were subjected to these same conditions. Interestingly, 4-n-propylamino-3,5-diaminotoluene (66k) gave the expected 7-amino-2,5-dimethyl-1-propylbenzimidazole (64), and 4-n-propylamino-3,5-diaminochlorobenzene (66j) gave the expected 7-amino-5-chloro-2-methyl-1-propylbenzimidazole (69). In both cases no trace of the rearranged products were observed.
It was thought that the strongly acidic conditions, coupled with the large excess of acetic anhydride might be necessary for the migration of the propyl group of 66c and, therefore, a different acylating agent, triethylorthoacetate was used. Treatment of 66c with a molar equivalent of triethylorthoacetate in refluxing benzene gave a 50-50 mixture of 47 and 7-n-propylamino-2-methyl-5-trifluoromethylbenzimidazole (56). The identity of these products was confirmed by nmr and tlc analysis. Thus other reagents also result in rearrangement.

From the above experimental evidence, the following points seem clear: first, since the propyl group migrates, and the phenyl and sec-butyl groups do not, the mechanism of rearrangement is dependent on the nature of the substituent. Second, since the triaminotoluene (66k) and the triaminochlorobenzene (66j) give the non-rearranged products, the migration of the propyl group is dependent upon having a strong electron-withdrawing moiety para to the n-propylamino function. Third, since 4-n-propylamino-3,5-diaminobenzotrifluoride (66c) does not undergo rearrangement by only refluxing in 3N hydrochloric acid, the acylated intermediate
must play an important role in causing the rearrangement.

A mechanism consistent with these observations is depicted in Scheme III. A large amount of steric interference results from each acylation of an amino group. Thus, a diacylated species such as A could be somewhat unstable. Consideration of a possible resonance structure A' shows that, by an intramolecular nucleophilic displacement, this steric strain can be released if migration of the n-propyl group occurs to give structure B. Subsequent rearomatization and tautomerism would give the product of diacylation and rearrangement, structure C, which on cyclization affords the benzimidazole resulting from rearrangement.

A strong electron-attracting group para to the alkylated nitrogen increases the electrophilicity of the α-carbon of the alkyl group and facilitates the nucleophilic displacement on that carbon. Thus the trifluoromethyl group would assist this internal displacement while the methyl and chloro substituents would not. A nucleophilic displacement would not be expected to occur with a phenyl or a sec-butyl group. The ease of rearrangement of the nitrogen substituents and the effect of the aromatic ring substituents on the rearrangement are consistent with this mechanism.

Although this mechanism has not been confirmed, it is clear that this rearrangement is distinctly different from the previously described UNH rearrangement, and therefore, this rearrangement represents another type of N to N' alkyl migration. Furthermore, although somewhat limited in scope,
SCHEME III
the discovery of this rearrangement greatly adds to the possibility that products of rearrangement can result from 2,6-dinitroanilines in nature.

B. Conversion of Aminobenzimidazoles to Nitrobenzimidazoles

To complete the synthetic sequence, the successful conversion of the aminobenzimidazoles to nitrobenzimidazoles remained to be investigated. Of the procedures available, the Sandmeyer reaction seemed to be the method of choice. 19

Initial conversion of 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47) to the corresponding diazonium salt, followed by decomposition of the salt in an aqueous solution of sodium nitrite and copper sulfites, afforded 2-methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40) in 43% yield. This compound was identical with the 40 prepared by alkylation of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4). Similarly, 1-n-butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole and 1-sec-butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (43) were prepared in 25% and 32% yields, respectively. These products were also identical with the compounds prepared previously by alkylation.
The conversion of 7-amino-2,5-dimethyl-1-propylbenzimidazole (64) to the corresponding 7-nitrobenzimidazole failed to give an isolable product. Apparently reduction and phenol formation occurred. This failure suggested that severe steric interaction between a 1-alkyl group and a 7-substituent provides unfavorable interference in the transition state for the Sandmeyer reaction thereby preventing the formation of a nitrobenzimidazole. The attempted oxidation of the amino group of 64 with peracids\textsuperscript{18} also was unsuccessful for extensive decomposition occurred. Furthermore, these problems were not unique for 64. Similar attempts to convert 7-amino-2-methyl-1-phenyl-5-trifluoromethylbenzimidazole (68) to the 7-nitroderivative using peracids also failed.

Thus the alternate route for the preparation of 1-alkyl-7-nitrobenzimidazoles by either the Sandmeyer reaction or by oxidation was unsuccessful. The Sandmeyer reaction
was moderately successful, however, for the preparation of 1-alkyl-4-nitrobenzimidazoles.

V. Applications of the Novel Rearrangements

A. Attempted Preparation of 2-Oxoindoles

The treatment of 4-N-$n$-propylamino-3,5-diaminobenzotrifluoride (66c) with acetic anhydride, followed by boiling in acid, resulted not only in the formation of a benzimidazole, but also caused a rearrangement of the propyl group (see Section IV.A.). The mechanism postulated for this rearrangement required that the lone pair of electrons on the 4-nitrogen be delocalized within the aromatic ring. It seemed reasonable, therefore, that an anion at the 4-nitrogen would be more stable if the aromatic ring contained electron-withdrawing groups.
Consideration of the possible resonance forms for such an anion shows that the charge is delocalized at the ortho and para positions. Assuming that the substituent on the 4-nitrogen contained a good leaving group, it appeared possible that the delocalized anion could cyclize via an intramolecular nucleophilic displacement to generate a bicyclic ring system. In particular it was hoped that by treating 4-(a-chloroacetamido)-3-nitrobenzotrifluoride (70) with a poorly nucleophilic base, the anion would be generated, displace the chlorine, and ultimately result in the formation of a 2-oxoindole. The realization of such a synthetic scheme would be of interest since it would represent a new method of synthesis of these compounds via a cyclization to an electron-deficient ring.
Initial attempts to prepare 70 involved treatment of 4-amino-3-nitrobenzotrifluoride (71) with α-chloroacetylchloride (72) in refluxing benzene in the presence of triethylamine (1 molar equiv.). Using these conditions a mixture of 70 and 71 resulted after 2 1/2 hr, and also after 8 hr. In order to obtain complete reaction, a neat solution of 71 in 72 was heated under reflux for 8 hr. This led to a pure product which was not the amide (70) but rather the imide (73) as indicated by spectral data and elemental analyses. The amide (70) was finally prepared by heating a mixture of 71 and 72 (1:1 ratio) in toluene under reflux for 18 hr.

Once available, 70 was treated with a variety of bases, such as lithium diisopropylamide, potassium t-butoxide, and sodium hydride, in dry tetrahydrofuran. In each case no trace of the 2-oxoindole was formed. Instead, a large amount of cleavage of the amide resulted. It seemed reasonable, therefore, that similar treatment of the imide (73) would also result in cleavage of one of the carbon-nitrogen bonds, thus producing the key anionic intermediate.
When 73 was treated with lithium diisopropylamide, however, the only product detected was the amide, 70, rather than the 2-oxoindole. It seems clear, therefore, that although the anion was formed it did not produce the 2-oxoindoles. Work in this area was therefore discontinued.

B. Attempted Preparation of Optically Active Deuterated Ethyl Benzene

The tin-hydrochloric acid reduction of (+)-4-(α-methylbenzylamino)-3,5-dinitrobenzotrifluoride (21h) was shown to result in the formation of 3,4,5-triaminobenzotrifluoride (57) (see Section III.A.). It was apparent that ethyl benzene was the other cleavage product formed, since small amounts of the hydrocarbon were detected by nmr. By using a deuterium source as the solvent for the reaction, information about the mechanism of the reaction could be obtained and perhaps a stereospecific synthesis of deuterated ethyl benzene could be obtained. The results could be important in demonstrating the nature of the intermediate in the cleavage reaction.
Unfortunately, the exact conditions for the duplication of the tin-hydrochloric acid reduction were difficult to achieve for a deuterated medium. Initially a solution of stannous chloride and CF₃CO₂D (prepared by treatment of D₂O with trifluoroacetic anhydride) was used but the reaction afforded a tarry residue which proved uncharacterizable. Another attempt using thionyl chloride and D₂O (as a source of DC1) along with mossy tin was also unsuccessful. A final attempt using 20% DC1 in D₂O as solvent with mossy tin was moderately successful in that some 57 was isolated. However, no ethyl benzene was detected.

The reduction appears to be highly dependent on the reaction conditions and the acid concentration. No further attempts to prepare deuterated ethyl benzene were made.
EXPERIMENTAL

General

Melting Points. Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus and were not corrected.

Boiling Points. Boiling points were measured at the pressure indicated in parentheses and are uncorrected.

Elemental Analyses. Elemental analyses were determined at the University of New Hampshire with an F and M Model 185 carbon, hydrogen, and nitrogen analyzer. Mrs. Deanna Cardin performed the analyses for which the author expresses appreciation.

Infrared Spectra. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating infrared spectrometer and were calibrated with polystyrene at 1601.4 and 1029 cm\(^{-1}\). Solid samples were recorded as potassium bromide pellets while liquid or noncrystalline samples were recorded as neat films between sodium chloride plates.

Nuclear Magnetic Resonance Spectra. All nuclear magnetic resonance spectra were recorded on a JEOL Model MH-100 spectrometer and chemical shifts are reported in parts per million (\(\delta\)) downfield from tetramethylsilane (TMS) as an internal standard. The chemical shifts represent the center of multiplets, and abbreviations used are, \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(q\) = quartet, \(h\) = sextet, and \(m\) = multiplet.
Optical Rotations. Optical rotations were measured on a Carl Zeiss Photoelectric Precision Polarimeter, 0.005°, equipped with a deuterium light source and filtered to give readings at 578, 546, 435, 405, and 365 nm. Rotations are reported at the sodium-D line (589 nm) and were calculated from the Drude equation. Unless otherwise noted the rotations were determined using methanol as solvent, with solution concentrations of 0.200 g/10 ml.

\[
[a]_D = \left[ \frac{[\alpha]_{578}}{[\alpha]_{546} - [\alpha]_{578}} \frac{[\alpha]_{578}}{[\alpha]_{578} + 1.3727} \right]
\]

\[ [\alpha]_{546} \]
SECTION A. SYNTHESIS OF THE METABOLITES

**p-Acetamidobenzoic Acid (11).** A mixture of 5.0 g (36.5 mmol) of p-aminobenzoic acid (10) and 40 ml of glacial acetic acid was heated under reflux for 7 hrs. On cooling a solid precipitated and was removed by filtration, washed well with water, and dried under reduced pressure. The product was isolated as 4.6 g (70.4%) of a white crystalline solid, mp 257-258° (lit. 24 259-260°).

**Attempted Synthesis of 11 Using Acetic Anhydride.** A mixture of 20.0 g (0.146 m) of p-aminobenzoic acid (10) and 110 ml of acetic anhydride was heated under reflux for 2 hr. The mixture was cooled, poured into ice-water, and allowed to stand overnight. The resulting white precipitate was removed by filtration and dried under vacuum. The amount of product that was recovered was 17.1 g (mp 265°d). Analysis of the nmr spectrum of the product indicated that although a large amount of 11 was present, approximately 30% consisted of 4-diacetimidobenzoic acid (12), as shown by the appearance of two sets of AB quartets for the aromatic protons.

**Nitration of p-Acetamidobenzoic Acid (11).** A mixture of 50 ml of fuming nitric acid and 12 ml of acetic anhydride was stirred in a 250 ml round-bottom flask, and cooled to 5° with an ice bath. Pure p-acetamidobenzoic acid (11) was added, and the mixture was allowed to warm to room temperature. After stirring for an hour, the mixture was poured into 200 ml of ice water. The resulting yellow
precipitate was removed by filtration and allowed to dry. The amount of this product that was isolated was 3.0 g (46%) which was identified as 4-acetamido-3-nitrobenzoic acid (13), mp 218-221° (lit.25 220-221°). After 12 hr a further orange precipitate had formed in the mother liquor, and 0.9 g (18%) of this product was isolated by filtration. Spectral data indicated that this product was 4-amino-3-nitrobenzoic acid (14), mp 280-283° (lit.25 284°).

4-Chloro-3,5-dinitrobenzoic Acid (16). A three-necked, round-bottom flask, fitted with an overhead stirrer, condenser, and thermometer, was charged with 1 kg of H₂SO₄ and 5.0 g (0.320 m) of p-chlorobenzoic acid (15). The mixture was heated by means of an oil bath to 70° and 165.0 g of KNO₃ was added all at once. The temperature of the mixture rose to 120° and was kept between 120-140° for 1.5 hr. The heating was halted, and the mixture was cooled to 15° with an ice bath. The mixture was then poured into a 2 l Erlenmeyer containing 1 l of ice water. A solid precipitated and was removed by filtration, washed vigorously with cold water, and allowed to dry to give 73.7 g (93.4%) of 16, mp 157-160° (lit.26 159°). The material was used without further purification.

4-Amino-3,5-dinitrobenzoic Acid (9). A 1 l Erlenmeyer flask was charged with 600 ml of concentrated ammonium hydroxide and 40.0 g (0.162 m) of 4-chloro-3,5-dinitrobenzoic acid (16) was added. The mixture was stirred for 15 min, during which time the color of the reaction changed to bright red and a brown precipitate formed. The solid was removed by
filtration and the filtrate was added with stirring to 400 ml of 3N HCl in a 1 l Erlenmeyer flask. The solid which had formed during 15 min stirring was removed by filtration and dried. The solid was recrystallized from 95% ethanol to give 22.6 g (61%) of 9 as bright yellow needles, mp 269-271° (lit. 27 mp 269-271°).

4-Chloro-3,5-dinitrobenzotrifluoride (19). A mixture of 160 ml of fuming sulfuric acid and 140 ml of fuming nitric acid was heated to 60° in a three-necked, one liter round-bottom flask, fitted with an overhead stirrer, addition funnel, and condenser. At 60°, 4-chloro-3-nitrobenzotrifluoride (20) (42.5 g, 0.19 m) was added dropwise over a 30 min period. The mixture was kept at 60° for an additional 30 min then the temperature was slowly raised to 100-105° over a 45 min period. The reaction was kept at this temperature for 1.5 hr, and after cooling with an ice bath, was poured over ice and allowed to stand for 1 hr. The precipitate was removed by filtration, washed with a large volume of water, and dried. The amount of 19 recovered was 40.8 g (79.4%) mp 54-56° (lit. 4 55°). This material was used without further purification.

4-Amino-3,5-dinitrobenzotrifluoride (21a). A mixture of 20.0 g (0.074 m) of 4-chloro-3,5-dinitrobenzotrifluoride (19) was added to 150 ml of concentrated ammonium hydroxide in a 500 ml Erlenmeyer flask, and the mixture was stirred vigorously for 1 hr. The yellow solid which formed was removed by filtration and allowed to dry. Recrystalli-
zation of the crude 21a from CCl₄ gave 13.8 g (74.2%) of 21a as bright yellow prisms, mp 144-145° (lit. 142-144°).

General Procedure for the Preparation of 4-N-Alkyl-amino-3,5-dinitrobenzotrifluoride (21b-i). A mixture of 5.4 g (20 mmol) of 4-chloro-3,5-dinitrobenzotrifluoride (19), 6.0 g of triethylamine, and 100 ml of benzene was stirred in a 250 ml round-bottom flask, and to this mixture was added the appropriate amine. The mixture was heated under reflux for 2 hr and then the solvent was removed by evaporation to give a mixture of solid and oil. This mixture was triturated with 200 ml of hot hexane, and the insoluble triethylamine hydrochloride was removed by filtration. The filtrate was heated on a steam bath until all but 60 ml of hexane had evaporated. On cooling the dinitroanilines precipitated as bright orange or yellow needles. These results are summarized in Table 1.

N-Acetyl-p-Toluidine (25). A mixture of 107 g (1.00 m) of p-toluidine (24) and 300 ml of glacial acetic acid was heated under reflux for 2 hr in a 1 l round-bottom flask. After cooling, the mixture was poured into 1.5 l of ice water. The solid which precipitated was removed by filtration, washed with water, then dried under reduced pressure. The amount of 25 recovered was 130 g (87.2%), mp 147-150° (lit. 150-151°). This material was used without further purification.

2,6-Dinitro-p-toluidine (22a). A mixture of 1 l of fuming nitric acid and 240 ml of acetic anhydride was placed in a 2 l Erlenmeyer flask and cooled to 5-8° with an
ice bath. N-acetyl-\(\text{p}\)-toluidine (25) (67.3 g, 0.45 m) was added in portions over 1.5 hr, while the temperature was maintained between 5-8°. The mixture was allowed to warm to room temperature, and then poured into 2 l of water. The resulting yellow precipitate was removed by filtration, washed copiously with water, and dried under reduced pressure. The solid was then added to 500 ml of 50% aqueous sulfuric acid. This was heated at 100° for 1 hr. After cooling, the mixture was poured into 2 l of ice water. The orange precipitate was removed by filtration and allowed to dry. Recrystallization from ethanol afforded 27.8 g (31.4%) of 22a as orange needles, mp 169-170° (lit.\(^29\) 168°).

4-Chloro-3,5-dinitrotoluene (26). A solution of 5.6 g (0.081 m) of sodium nitrite in 120 ml of concentrated sulfuric acid was cooled to 20° and a slurry of 14.7 g (0.075 m) of 4-amino-3,5-dinitrotoluene (22a) in 150 ml of warm glacial acetic acid was added at such a rate to keep the temperature below 40°. After stirring for 0.5 hr at 40°, the solution was added in portions to 15.8 g (0.16 m) of cuprous chloride in 150 ml of concentrated hydrochloric acid. After the addition was finished, the reaction mixture was heated at 80° for 0.5 hr. The yellow solid which had separated was removed by filtration. The solid was boiled in 500 ml of benzene, and the solution was decanted from the inorganic solids. Evaporation of the benzene gave 12.4 g (76.5%) of 4-chloro-3,5-dinitrotoluene (26) as a yellow solid, mp 112-114° (lit.\(^30\) mp 113-114°).
4-N-Propylamino-3,5-dinitrotoluene (22b). A solution of 5.0 g (0.023 m) of 26 in 40 ml of benzene and 5 ml of triethylamine was placed in a 250 ml round-bottomed flask and 7.4 g (0.125 m) of n-propylamine was added. The mixture was heated under reflux for 2 hr and the solvent was evaporated to give a mixture of solid and oil. This mixture was triturated with 70 ml of hot pentane and the insoluble material was removed by filtration. The filtrate was evaporated in a hood, leaving 4-N-propylamino-3,5-dinitrotoluene (22b) as an orange solid. Recrystallization of the solid from hexane afforded 5.5 g (100%) of 22b, mp 65-66° (lit. 31 55°).

Anal. Calcd for C_{10}H_{13}N_{3}O_{4}: C, 50.21; H, 5.48; N, 17.57. Found: C, 49.90; H, 5.54; N, 17.33.

4-Amino-3,5-dinitrochlorobenzene (23a). A mixture of 200 g (1.16 mol) of 4-chloro-2-nitroaniline (21) in 900 g of concentrated nitric acid was stirred at 35° for 1 hr, during which time orange needles precipitated. The mixture was cooled with an ice bath, and then was filtered. The product was washed with 1 l of 50% aqueous nitric acid, then with 2 l of water. After drying under reduced pressure, 127 g (50.4%) of 23a was obtained as orange needles, mp 145-146° (lit. 9 147-148°). This material was used without further purification.

2,5-Dichloro-1,3-dinitrobenzene (28). Concentrated sulfuric acid (200 ml) was placed in a 500 ml three-necked flask fitted with an overhead stirrer and thermometer, and
11.2 g (0.16 m) of solid sodium nitrite was added over a period of 10-15 min with stirring. After the addition was completed, the temperature of the reaction was raised to 60° and stirring was continued until all the sodium nitrite had dissolved. The solution was cooled to 25-30° with an ice bath, and a solution of 32.6 g (0.15 m) of 4-amino-3,5-dinitrochlorobenzene (23a) in 200 ml of hot glacial acetic acid was added slowly, with stirring, at such a rate that the temperature remained below 40°. After the addition was complete, the solution was stirred at 40° for 0.5 hr. A solution of 31.6 g (0.32 m) of cuprous chloride in 300 ml of concentrated hydrochloric acid was prepared in a 2 l beaker and cooled in an ice bath, and the solution of the diazonium salt was added in portions over a period of about 5 min, with manual stirring, at a rate which minimized effervescence. The mixture was heated on a steam bath, with occasional stirring, until the temperature reached 80°. After 1.5 hr at this temperature, 500 ml of water was added, and the mixture was cooled in an ice bath for 0.5 hr. The yellow precipitate was collected on a suction filter and dried. The solid was then taken up in benzene, and the solution was filtered to remove insoluble inorganics. Evaporation of the benzene afforded 24.2 g (68.0%) of 28 as a yellow solid, mp 104-105° (lit.32 104-105°). This compound was used without further purification.
4-n-Propylamino-3,5-dinitrochlorobenzene (23b). A solution of 4.74 g (20.0 mmol) of 2,5-dichloro-1,3-dinitrobenzene (28) in 80 ml of benzene and 10 ml of triethylamine was placed in a 250 ml round-bottom flask, and 5.9 g (0.10 m) of n-propylamine was added. The mixture was heated under reflux for 2 hr and the solvent was evaporated to give a mixture of solid and oil. This mixture was triturated with 150 ml of hot pentane, and the insoluble triethylamine hydrochloride was removed by filtration. The filtrate was evaporated leaving 5.1 g (98.1%) of 23b as orange needles, mp 50-51° (lit.7 46-48°).

Methyl 4-Amino-3,5-dinitrobenzoate (29a). A mixture of 17.8 g (0.0784 m) of 4-amino-3,5-dinitrobenzoic acid (9) and 150 ml of methanol in a 250 ml round-bottom flask fitted with a condenser was saturated with gaseous HCl and heated under reflux for 12 hr. On cooling the mixture a precipitate formed and was removed by filtration. After drying, the solid was recrystallized from 95% ethanol to give 11.5 g (60.0%) of 29a as bright yellow needles, mp 146.5-147.5° (lit.36 144°).

Ethyl 4-Amino-3,5-dinitrobenzoate (29b) was prepared by exactly the same method using ethanol instead of methanol. The product was isolated as brilliant yellow needles, mp 115-116° (lit.15 114°) in 83% yield.

Methyl 3,4-Diamino-5-nitrobenzoate (30a). A mixture of 2.134 g (8.85 mmol) of methyl 4-amino-3,5-dinitrobenzoate (29a), 50 ml of methanol, and 5 ml of toluene in a
standard 250 ml 3-necked set-up was heated to boiling, and a solution of 1.293 g of NaHS·xH₂O in 50 ml of methanol was added dropwise. After the addition was completed, the mixture was heated under reflux for 12 hr. The warm mixture was filtered and the filtrate was evaporated under reduced pressure to give a black solid residue. The residue was partitioned between 100 ml of ether and 100 ml of 3N HCl. The aqueous layer was separated, and the ether layer was extracted four times with 125 ml portions of 3N HCl. The aqueous extracts were combined, made basic with 10% NaOH, and extracted five times with 30 ml portions of CHCl₃. The CHCl₃ extracts were combined, dried over anhydrous Na₂SO₄, filtered, and evaporated leaving 0.390 g (21%) of a red solid as residue. Recrystallization of the residue from benzene gave (30a) as bright red prisms, mp 214-215.5°.

Anal. Calcd for C₈H₉N₃O₄: C, 45.50; H, 4.29; N, 19.90. Found: C, 45.93; H, 4.35; N, 20.05.

Attempted Monoreduction of 4-Amino-3,5-dinitrobenzotrifluoride (21a) Using Catalytic Hydrogenation with Ethanol as Solvent. A solution of 2.5 g (10 mmol) of 4-amino-3,5-dinitrobenzotrifluoride (21a) in 50 ml of absolute ethanol and 5 ml of chloroform was hydrogenated over 10% palladium on charcoal at low pressure (3 atm) and ambient temperature. The mixture was allowed to absorb the theoretical amount of hydrogen required to reduce one nitro group to an amino function (3 molar equiv.). The reaction was stopped and the catalyst was removed by filtration through a Celite pad.
Evaporation of the filtrate afforded a dark viscous residue which formed a solid when triturated with ether. The solid was dissolved in water, and the solution was made basic with 10% sodium hydroxide solution. The aqueous solution was extracted three times with a total of 60 ml of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered and evaporated leaving 0.45 g (24%) of 3,4,5-triaminobenzotrifluoride (31). Recrystallization from CCl₄ afforded 31 as white needles, mp 91-92°. Further investigation of the initial ether solution was unfruitful and only intractable products were isolated.

General Procedure for the Syntheses of 3,4-Diamino-5-nitrobenzotrifluoride (7), 3,4-Diamino-5-nitrotoluene (32), and Ethyl 3,4-Diamino-5-nitrobenzoate (30b). A solution of 60.0 mmol of the 2,6-dinitroaniline in 150 ml of 1,2-dimethoxyethane and 15 ml of chloroform was hydrogenated over 600 mg of 10% palladium on charcoal at low pressure (3 atm) and ambient temperature. The mixture was allowed to absorb the theoretical amount of hydrogen required to reduce one nitro group to an amino function (3 molar equiv.). The reaction was stopped and the catalyst was removed by filtration through a Celite pad. The filtrate was poured into an evaporating dish, and the solvent was allowed to evaporate in a hood. Recrystallization afforded the phenylenediamines as indicated in Table 2. Thus, 7 was recrystallized from CCl₄; 32 was recrystallized from H₂O; and 30b was recrystallized from benzene-hexane. The product, 6, was obtained by pouring the
reaction mixture into a large volume of chloroform and removing the solid product by filtration.

**Attempted Monoreduction by Catalytic Hydrogenation of 4-\(n\)-Propylamino-3,5-dinitrobenzotrifluoride (21c).** A solution of 2.93 g (10.0 mmol) of 21c in 50 ml of 1,2-dimethoxyethane and 5 ml of chloroform was hydrogenated over 100 mg of 10% palladium on charcoal at low pressure (3 atm) and ambient temperature. The mixture was allowed to absorb the theoretical amount of hydrogen required to reduce one nitro group to an amino function (3 molar equiv.). The reaction was stopped, and the catalyst was removed by filtration through a Celite pad. The filtrate was evaporated and the dark red oil residue was taken up into 100 ml of 3N hydrochloric acid. The aqueous solution was washed three times with a total of 60 ml of chloroform. The aqueous solution was made basic with 100% sodium hydroxide and extracted three times with a total of 75 ml of chloroform. The combined extracts were dried over sodium sulfate, filtered, and evaporated leaving 1.3 g (50%) of a dark viscous oil. The ir spectrum of this material indicated that monoreduction had occurred \((\text{NH}_2, 3400 \text{ cm}^{-1}; \text{NO}_2, 1530 \text{ and } 1360 \text{ cm}^{-1})\) and the nmr spectrum clearly showed the presence of two distinct isomers (two sets of triplets for the terminal methyl protons at 1.05 ppm and 1.28 ppm and four one proton signals for the aromatic protons at 8.12 ppm, 7.60 ppm, 7.16 ppm, and 6.84 ppm). On this basis the products were assigned as 3-amino-5-nitro-4-\(n\)-propylaminobenzotrifluoride (8) and its isomer 4-
Amino-5-nitro-3-n-propylaminobenzotrifluoride (35).

3-Amino-5-nitro-4-n-propylaminobenzotrifluoride (8).

A solution of sodium sulfide nonahydrate (75 g, 0.30 m) and sodium bicarbonate (25.2 g, 0.30 m) in 150 ml of water was added dropwise to a stirred solution of 26.4 g (0.09 m) of 4-n-propylamino-3,5-dinitrobenzotrifluoride (21c) in 900 ml of methanol at room temperature over 0.25 hr. The mixture was stirred at room temperature for 3 hr then poured into 3 l of water. After standing for 4 hr, the mixture was filtered and the solid residue was washed vigorously with water. After drying under reduced pressure, 8 was isolated as 17.7 g (74%) of a dark reddish-brown solid, mp 79-81° (lit. 1 82-83°).

3,4-Diamino-5-nitrochlorobenzene (33). A mixture of sodium sulfide nonahydrate (75 g, 0.30 m) and sodium bicarbonate (25.2 g, 0.30 m) in 150 ml of water was added dropwise to a stirred solution of 26.4 g (0.09 m) of 4-amino-3,5-dinitrochlorobenzene (23a) in a 750 ml - 250 ml mixture of methanol-acetone at room temperature over 0.25 hr. The mixture was stirred at room temperature for 3 hr, and then poured into 6 l of water. After stirring 7 hr, the mixture was filtered and the product was washed with a large volume of water. After drying under reduced pressure, 4.3 g (26%) of 33 was isolated as a reddish-brown solid, mp 157-158°. This material was used without further purification.
3-Amino-4-ethylamino-5-nitrobenzotrifluoride (36).
A solution of sodium sulfide nonahydrate (25 g, 0.10 m) and
sodium bicarbonate (8.4 g, 0.10 m) in 50 ml of water was
added dropwise to a stirred solution of 8.4 g (0.03 m) of
4-ethylamino-3,5-dinitrobenzotrifluoride (21b) in 300 ml of
methanol at room temperature over 10 min. The mixture was
stirred at room temperature for 3 hr and then was poured
into 1 l of water. After standing for 2 hr, the mixture
was filtered and the product was washed with water. After
drying under reduced pressure, 36 was isolated as 2.0 g
(27%) of a reddish-brown solid, mp 63.5°. This material was
used without further purification.

2-Methyl-7-nitrobenzimidazole-5-carboxylic Acid (3).
A solution of 10.02 g (50.8 mmol) of 3,4-diamino-5-nitrobenzoic
acid (6) in 90 ml of acetic anhydride was heated on a steam
bath for 0.5 hr. The reaction was cooled, and 120 ml of 3N
HCl was carefully added. The reaction vessel was fitted with
a condenser, and the mixture was heated under reflux for 6
hr. While hot, the mixture was diluted with 120 ml of hot
H₂O, boiled briefly with Norit, and filtered through Celite.
The filtrate was evaporated under reduced pressure leaving a
solid residue which was triturated thoroughly with H₂O, and
then evaporated once again. The insoluble residue was dried
under reduced pressure and recrystallized from methanol-
ether to give 5.82 g (50.2%) of 3 as an off-white solid, mp
314-315°. IR (in cm⁻¹): 2900 (broad), 1705 (s), 1605 (m),
1545 (s), 1405 (s), 1355 (s), 1320 (m), 1240 (s), 1190 (s),
1050 (w), 1030 (m), 855 (s), 765 (m), 720 (w). nmr (TFA): 9.04δ (s-1H); 8.82δ (s-1H); 2.76δ (s-3H).

The methyl ester of 3 was prepared by Fischer esterification using anhydrous HCl to give 3.5 g (54%) of 3a, mp 237-238°.

Anal. Calcd for C_{10}H_{9}N_{3}O_{4}: C, 51.06; H, 3.86; N, 17.87. Found: C, 51.07; H, 3.90; N, 17.56.

2-Methyl-7-nitro-5-trifluoromethylbenzimidazole (4). A solution of 13.25 g (0.0600 m) of 3,4-diamino-5-nitrobenzotrifluoride (7) and 90 ml of acetic anhydride was heated to a 500 ml round-bottomed flask on a steam bath for 0.5 hr. The flask was fitted with a condenser, and 120 ml of 3N HCl was added to the cooled reaction mixture. The mixture was heated under reflux for 3 hr and 120 ml of H_{2}O was added. The solution was boiled briefly with Norit and then filtered through a Celite pad. The cooled filtrate was made basic by addition of concentrated NH_{4}OH. The precipitate which formed was removed by filtration and dried. Recrystallization of the solid from 30% EtOH-H_{2}O gave 10.4 g (84.4%) of 4 as tan platlets, mp 207.5-208°.

Anal. Calcd for C_{9}H_{6}F_{3}O_{2}: C, 44.09; H, 2.47; N, 17.14. Found: C, 44.07; H, 2.65; N, 17.34.

2-Methyl-7-nitro-1-n-propyl-5-trifluoromethylbenzimidazole (5). A mixture of 17.7 g (67 mmol) of 3-amino-4-n-propylamino-5-nitrobenzotrifluoride (8) and 100 ml of acetic anhydride was heated in a 1 l round-bottom flask on
a steam bath for 10 min. After cooling the reaction mixture in an ice bath, 300 ml of 3N hydrochloric acid was added, and the mixture was heated under reflux for 2.5 hr. The hot mixture was diluted with 300 ml of water, boiled briefly with Norit, and filtered while hot. The cooled mixture was made basic with concentrated NH$_4$OH, and the resulting precipitate was removed by filtration and allowed to dry. Recrystallization of this material from hexane afforded 13.4 g (70%) of 5 as a pale yellow solid, mp 82-84°.

Anal. Calcd for C$_{12}$H$_{12}$F$_3$N$_3$O$_2$: C, 50.18; H, 4.21; N, 14.63. Found: C, 49.85; H, 4.15; N, 14.65.

2-Methyl-7-nitro-1-ethyl-5-trifluoromethylbenzimidazole (38). A mixture of 2.0 g (8.0 mmol) of 3-amino-4-ethylamino-5-nitrobenzotrifluoride (36) and 12 ml of acetic anhydride was heated in a 100 ml round-bottom flask on a steam bath for 10 min. After cooling the mixture in an ice bath, 35 ml of 3N hydrochloric acid was added, and the mixture was heated under reflux for 2.5 hr. The hot mixture was diluted with 35 ml of water, boiled briefly with Norit, and filtered while hot. The cooled mixture was made basic with concentrated NH$_4$OH, and the resulting precipitate was removed by filtration and allowed to dry. Recrystallization of the material from hexane afforded 1.5 g (70%) of 38 as a pale yellow powder, mp 81-84°.

2,6-Dimethyl-4-nitrobenzimidazole (37). A solution of 7.5 g (0.045 m of 3,4-diamino-5-nitrotoluene (32) and 25 ml of acetic anhydride was heated in a 500 ml round-bottomed flask on a steam bath for 0.5 hr. The flask was fitted with a condenser, and 80 ml of 3N hydrochloric acid was added to the cooled reaction mixture. The mixture was heated under reflux 1 hr and diluted with 100 ml of H₂O. The solution was boiled briefly with Norit and then was filtered through a Celite pad. The cooled filtrate was made basic by addition of concentrated NH₄OH. The precipitate which formed was removed by filtration and dried. Recrystallization of the solid from 35% aqueous EtOH gave 4.8 g (56%) of 37 as a tan solid, mp 238-240° (lit. 16 238-240°).

5-Chloro-2-methyl-7-nitrobenzimidazole (39). A mixture of 4.0 g (21 mmol) of 3,4-diamino-5-nitrochlorobenzene (33) and 40 ml of acetic anhydride was heated in a 500 ml round-bottom flask on a steam bath for 10 min. The reaction was cooled in an ice bath, 100 ml of 3N hydrochloric acid was added, and the mixture was heated under reflux for 2.5 hr. The hot mixture was diluted with 100 ml of water, boiled briefly with Norit, and filtered while hot. The cooled mixture was made basic with concentrated NH₄OH, and the resulting precipitate was removed by filtration and allowed to dry. Recrystallization of the material from 35% aqueous ethanol afforded 3.3 g (75%) of 39 as a white solid, mp 236-237°.
Anal. Calcd for $\text{C}_8\text{H}_6\text{ClN}_3\text{O}_2$: C, 45.41; H, 2.86; N, 19.86. Found: C, 45.42; H, 3.03; N, 19.69.
SECTION B. REACTIONS OF BENZIMIDAZOLES

2-Methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40). A mixture of 13.1 g (53.5 mmol) of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4), 2.26 g (53.5 mmol) of a 57% NaH-paraffin oil dispersion, and 170 ml of dry 1,2-dimethoxyethane was heated under reflux under nitrogen for 3 hr. The cooled mixture was treated with 31.8 g (0.25 m) of 1-bromopropane, and the mixture was again heated under reflux, this time for 42 hr. The cooled mixture was diluted with 350 ml of water and then was extracted three times with a total of 150 ml of chloroform. The combined chloroform layers were dried over sodium sulfate, filtered, and evaporated leaving a crude solid residue. Recrystallization of the residue from 40% aqueous-ethanol and decolorization with Norit gave 12.4 g (80.5%) of 40 as white needles, mp 131.5-132°.

Anal. Calcd for C_{12}H_{12}F_{3}N_{3}O_{2}: C, 50.18; H, 4.21; N, 14.63. Found: C, 50.22; H, 4.24; N, 14.42.

1-n-Butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (42). A mixture of 2.45 g (10.0 mmol) of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4), 421 mg (10.0 mmol) of a 57% NaH-paraffin oil dispersion, and 35 ml of dry dimethoxyethane was heated under reflux for 2 hr. To the cooled solution was added 4.11 g (30.0 mmol) of n-butyl bromide, and the mixture was heated under reflux for 24 hr. The mixture was cooled and 50 ml H$_2$O was added. The aqueous
solution was extracted three times with 20 ml portions of CHCl₃, and the combined CHCl₃ layers were dried (K₂CO₃), filtered, and evaporated, leaving a brown solid residue. Recrystallization of the solid and decolorization (Norit) of the solution in 40% aqueous EtOH gave 1.1 g (37%) of 42 as white needles, mp 102-102.5°.


1-Ethyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (41). A mixture of 2.45 g (10.0 mmol) of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4), 421 mg (10.0 mmol) of a 57% NaH-paraffin oil dispersion, and 40 ml of dry 1,2-dimethoxyethane was heated under reflux for 2 hr. To the cooled solution was added 7.8 g (50.0 mmol) of ethyl iodide, and the mixture was heated under reflux for 38 hr. The mixture was cooled and 100 ml of H₂O was added. The aqueous solution was extracted three times with 20 ml portions of CHCl₃, and the combined CHCl₃ layers were dried (K₂CO₃), filtered, and evaporated, leaving behind a dark brown solid. Recrystallization of the solid and decolorization (Norit) of the solution in 40% aqueous ethanol gave 1.9 g (70.4%) of 41 as a tan solid, mp 152-153°.

Anal. Calcd for C₁₁H₁₀F₃N₃O₂: C, 48.36; H, 3.69; N, 15.38. Found: C, 48.64; H, 4.06; N, 15.00.

1-sec-Butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (43). A mixture of 2.45 g (10.0 mmol) of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4), 421 mg (10.0 mmol)
of a 57% NaH-paraffin oil dispersion and 40 ml of dry 1,2-dimethoxyethane was heated under reflux under nitrogen for 3 hr. To the cooled solution was added 6.85 g (50.0 mmol) of sec-butylbromide, and the mixture was heated under reflux for 51 hr. The mixture was cooled and 100 ml of water was added. The aqueous solution was extracted three times with 20 ml portions of CHCl₃, and the combined CHCl₃ layers were dried (K₂CO₃), filtered, and evaporated, leaving behind 2.0 g of a crude solid, whose nmr spectrum indicated that it was a mixture of product and starting material. The material was boiled briefly in hexane and filtered. Evaporation of the filtrate gave a solid which was mostly the alkylated product. Recrystallization of the mixture from hexane (three times) afforded 660 mg (22%) of tan needles, mp 115-117°.


2,6-Dimethyl-5-nitro-1-propylbenzimidazole (44).

A mixture of 4.78 g (25.0 mmol) 2,5-dimethyl-7-nitrobenzimidazole (37), 1.06 g (25.0 mmol) of a 57% NaH-paraffin oil dispersion and 100 ml of dry tetrahydrofuran was heated under reflux for 3 hr. To the cooled solution was added 12.3 g (0.100 m) of n-propyl bromide, and the mixture was heated under reflux for 36 hr. The mixture was cooled and 200 ml of H₂O was added. The aqueous solution was extracted four times with 30 ml portions of CHCl₃, and the combined CHCl₃ layers were dried (K₂CO₃), filtered, and evaporated, leaving 3.8 g (66%) of a brown solid, the nmr of which showed
the presence of only 44. Recrystallization from 40% aqueous EtOH afforded 44 as gold needles, mp 135.5-136°.

Anal. Calcd for C_{12}H_{15}N_{3}O_{2}: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.53; H, 6.48; N, 17.63.

6-Chloro-2-methyl-4-nitro-1-propylbenzimidazole (45).

A mixture of 3.36 g (16.0 mmol) of 6-chloro-2-methyl-4-nitrobenzimidazole (39), 674 mg of a 57% NaH-paraffin oil dispersion, and 100 ml of dry 1,2-dimethoxyethane was heated under reflux under nitrogen for 2.5 hr. To the cooled mixture was added 9.8 g (80 mmol) of n-propyl bromide, and the mixture was heated under reflux for 34 hr. The mixture was cooled and 150 ml of H_{2}O was added. The aqueous solution was extracted three times with a total of 90 ml of chloroform, and the combined chloroform layers were dried (K_{2}CO_{3}), filtered, and evaporated, leaving a crude solid. Recrystallization from 40% aqueous ethanol afforded 1.6 g (40%) of 45 as pale yellow crystals, mp 115-116°.

Anal. Calcd for C_{11}H_{12}ClN_{3}O_{2}: C, 52.08; H, 4.77; N, 16.56. Found: C, 52.33; H, 4.79; N, 16.39.

1-Acetyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (46). A solution of 4.90 g (20.0 mmol) of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4) in 2.02 g (20.0 mmol) of triethylamine and 50 ml of acetone was treated with 1.59 g (20.0 mmol) of acetyl chloride, and the mixture was stirred at room temperature for 1 hr. The mixture was poured into 100 ml of ether, and the triethylamine hydrochloride was removed by filtration. Evaporation of the filtrate gave
4.20 g (73.2%) of 46 as tan needles, mp 108-110°. ir (in cm\textsuperscript{-1}): 1740 (s), 1620 (w), 1525 (s), 1445 (w), 1420 (w), 1365 (m), 1330 (s), 1280 (s), 1250 (s), 1220 (w), 1165 (s), 1130 (s), 1085 (w), 1055 (m), 965 (m), 905 (m), 850 (w), 775 (m). nmr (acetone, D\textsubscript{6}): 8.62\delta (s-1H); 8.22\delta (s-1H); 2.75 (s-3H); 2.72 (s-3H). On exposure to moisture, this material begins to decompose and a strong odor of acetic acid is noticeable after a few days.

4-Amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47). 2-Methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (4£), a mixture of 330 mg (1.15 mmol) and 1.0 g of mossy tin, and 15 ml of concentrated hydrochloric acid was placed in a 100 ml round-bottomed flask and heated on a steam bath for 1 hr. The cooled mixture was made basic with 40 g of 50% NaOH and then extracted four times with 20 ml portions of CHCl\textsubscript{3}. The combined CHCl\textsubscript{3} layers were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and evaporated leaving behind a white solid. Recrystallization from medium boiling petroleum ether: benzene (3:1), afforded 260 mg (87.5%) of 47 as white needles, mp 170-171°.

Anal. Calcd for C\textsubscript{12}H\textsubscript{14}F\textsubscript{3}N\textsubscript{3}: C, 56.02; H, 5.49; N, 16.33. Found: C, 56.14; H, 5.60; N, 16.08.

4-Amino-1-ethyl-2-methyl-6-trifluoromethylbenzimidazole (48). A mixture of 1.0 g (3.7 mmol) of 1-ethyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (41), 3.0 g of mossy tin, and 20 ml of concentrated hydrochloric acid was placed in a 100 ml round-bottomed flask and heated on a steam bath for 1 hr. The cooled mixture was made basic with 30 g
of 50% NaOH, and, after adding 30 ml of chloroform, was filtered to remove insoluble inorganics. The chloroform was separated from the filtrate and the aqueous phase was extracted twice more with 20 ml portions of chloroform. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving behind a white solid. Recrystallization of the solid from cyclohexane afforded 750 mg (84%) of 48 as a white solid, mp 158-159°.


4-Amino-2,6-dimethyl-1-propylbenzimidazole (51). A mixture of 1.00 g (4.30 mmol) of 2,6-dimethyl-4-nitro-1-propylbenzimidazole (44), 3.0 g of mossy tin, and 20 ml of concentrated hydrochloric acid was placed in a 100 ml round-bottomed flask and heated on a steam bath for 1.5 hr. The cooled mixture was made basic with 30 g of 50% NaOH, and then extracted four times with 25 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered and evaporated leaving an oil, which solidified when triturated with pentane. Recrystallization of the solid from hexane afforded 0.66 g (75.9%) of 44 as white needles, mp 94-95°.

Anal. Calcd for C₁₂H₁₇N₃: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.79; H, 8.58; N, 20.52.

4-Amino-6-chloro-2-methyl-1-propylbenzimidazole (52). A mixture of 507 mg (2.00 mmol) of 6-chloro-2-methyl-4-nitro-1-propylbenzimidazole (45), 1.5 g of mossy tin, and 20 ml of concentrated hydrochloric acid was placed in a 100 ml round-
bottomed flask and heated on a steam bath for 1 hr. The cooled mixture was made basic with 35 g of 50% NaOH, and, after adding 30 ml of chloroform, was filtered to remove insoluble inorganics. The chloroform was separated from the filtrate and the aqueous phase was extracted twice more with 15 ml portions of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving a white solid. Recrystallization from cyclohexane afforded 387 mg (87%) of 52 as needles, mp 122-123°.

**Anal.** Calcd for C₁₁H₁₄ClN₃: C, 59.06; H, 6.31; N, 18.79. Found: C, 58.88; H, 6.17; N, 18.53.

3,4,5-Triaminobenzotrifluoride (57). A mixture of 10.0 g (40.0 mmol) of 4-amino-3,5-dinitrobenzotrifluoride (21a), 20.0 g of mossy tin, and 150 ml of concentrated hydrochloric acid was placed in a three-necked 500 ml round-bottomed flask, fitted with a condenser and overhead stirrer and was heated on a steam bath for 1.5 hr. The cooled mixture was made basic with 180 g of 50% NaOH and then extracted eight times with 40 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered, and evaporated leaving a white solid residue. Recrystallization of the solid from CCl₄ afforded 5.9 g (82%) of 57 as needles, mp 91.5-92°.

**Anal.** Calcd for C₇H₈F₃N₃·1/2H₂O: C, 42.00; H, 4.53; N, 20.99; F, 28.48; O, 4.00. Found: C, 42.44; H, 4.36; N, 20.65.
3,4,5-Triaminotoluene (60). A mixture of 3.9 g (0.020 m) of 4-amino-3,5-dinitrotoluene (22a), 9.0 g of mossy tin, and 60 ml of concentrated hydrochloric acid was placed in a three-necked 500 ml round-bottomed flask, fitted with a condenser and overhead stirrer, and heated on a steam bath for 1 hr. The cooled mixture was made basic with 80 g of 50% NaOH, and then was extracted four times with 50 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered, and evaporated leaving a white solid residue. Recrystallization of the solid from benzene afforded 1.7 g (63%) of 60 as white needles, mp 100-102.5° (lit. 105°).

7-Amino-2-methyl-5-trifluoromethylbenzimidazole (58). A mixture of 3.16 g (16.5 mmol) of 3,4,5-triaminobenzotri fluoride (57), and 50 ml of benzene was heated under reflux in a 250 ml three-necked round-bottomed flask fitted with a condenser and addition funnel. A solution of 2.70 g (16.7 mmol) of triethylorthoacetate in 30 ml of benzene was added dropwise over a 10 min period. After the addition was complete the mixture was heated under reflux for 12 hr. Evaporation of the solvent afforded a white solid, which was recrystallized from benzene to yield 2.4 g (78.8%) of 58 as white fluffy needles, mp 192-193°.


9-Amino-2,5-dimethylbenzimidazole Monohydrate (61). A mixture of 3.7 g (0.027 mol) of 3,4,5-triaminotoluene (60), and 25 ml of acetic anhydride was heated in a 250 ml round-
bottomed flask on a steam bath for 15 min. After cooling the mixture, 50 ml of 3N hydrochloric acid was added, and the reaction was heated under reflux for 2 hr. The mixture was cooled, made basic with concentrated NH₄OH, and extracted four times with 40 ml portions of CHCl₃. Evaporation of the combined CHCl₃ layers yielded an oily residue, which was treated with 60 ml of 6N hydrochloric acid and heated under reflux for 3 hr. The cooled mixture was made basic with concentrated NH₄OH, and allowed to sit in the refrigerator for 3 hr, resulting in the formation of 3.0 g (62.5%) of 61 as long light-gold needles, mp 97-98.5° (lit.34 100°). This solid was used without further purification.

2-Methyl-7-propionamido-5-trifluoromethylbenzimidazole (59). A mixture of 2.4 g (11 mmol) of 7-amino-2-methyl-5-trifluoromethylbenzimidazole (58) and 50 ml of propionic acid was heated under reflux for 8 hr. After cooling, the mixture was poured into 100 ml of cold 15% NH₄OH solution. The precipitate was collected and allowed to dry. Recrystallization of the solid from benzene (~200 ml) afforded 2.5 g (83.3%) of 59 as a white crystalline solid, mp 167-168°.

Anal. Calcd for C₁₂H₁₂N₃OF₃: C, 53.14; H, 4.46; N, 15.49. Found: C, 52.80; H, 4.84; N, 15.18.

2,5-Dimethyl-7-propionamidobenzimidazole (62). A mixture of 3.0 g (0.017 m) of 7-amino-2,5-dimethylbenzimidazole (61) and 50 ml propionic acid was heated under reflux for 6 hr. The mixture was poured into 100 ml of ice water
and made basic with concentrated NH$_4$OH. The resulting pre-
cipitate was removed by filtration and washed liberally with
water. After drying the solid it was recrystallized from
tetrahydrofuran to yield 2.7 g (75.7%) of 15 as a white
crystalline solid, mp 139° (dec.).

Anal. Calcd for C$_{12}$H$_{15}$N$_3$O: C, 66.34; H, 6.96;
N, 19.34. Found: C, 65.98; H, 6.98; N, 19.27.

2-Methyl-7-N-n-propylamino-5-trifluoromethylbenzimidazole (56). A three-necked 100 ml round-bottomed flask,
fitting with a condenser, addition funnel, and septum was
charged with 12.5 ml (12.5 mmol) of a 1M borane/THF solution.
A solution of 1.355 g (5.00 mmol) of 2-methyl-7-propionamido-
5-trifluoromethylbenzimidazole (59) in 30 ml of dry THF was
added to the mixture over a 10 min period. After the addition
was complete, the mixture was heated under reflux for 3.5 hr.
To the cooled mixture was slowly added 25 ml of 6N hydrochloric
acid. The THF was removed by distillation at atmospheric
pressure. Sodium hydroxide pellets were added to saturate the
aqueous phase and the latter was extracted three times with a
total of 75 ml of ether. The ether layers were evaporated
leaving behind an oil. This oil was redissolved in 20 ml of
6N hydrochloric acid and heated under reflux for 1.5 hr. The
cooled mixture was made basic with concentrated NH$_4$OH, and ex-
tracted three times with 60 ml of ether. The combined ether
layers were dried over Na$_2$SO$_4$, filtered, and evaporated
leaving 805 mg (63%) of a white solid as residue. Recryst-
tallization of the solid from 40% EtOH-H$_2$O afforded 56 as
an amorphous solid, mp 89-90°.
2,5-Dimethyl-7-N-propylaminobenzimidazole (63). A three-necked 250 ml round-bottomed flask, fitted with a condenser, addition funnel, and septum, was charged with 20.5 ml (20.5 mmol) of a 1M borane/THF solution. A solution of 1.77 g (8.20 mmol) of 2,5-dimethyl-7-propionamidobenzimidazole (62) in 80 ml of hot dry THF was added to the mixture over a 10 min period and the reaction was heated under reflux for 3.5 hr. To the cooled mixture was added 60 ml of 6N hydrochloric acid. The THF was removed by distillation at atmospheric pressure. Sodium hydroxide pellets were added to saturate the aqueous phase, and the latter was extracted three times with a total of 60 ml of ether. The ether was evaporated leaving behind an oil which was treated with 60 ml of 6N hydrochloric acid and heated under reflux for 2 hr. After cooling, sodium hydroxide pellets were added until the mixture was basic and the latter was extracted a total of three times with 60 ml of ether. After drying with Na₂SO₄, the ether was evaporated leaving a solid residue. Recrystallization from 40% EtOH-H₂O afforded 1.0 g (60.2%) of 63 as a white amorphous solid, mp 87-88°.

7-Amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53). A mixture of 1.45 g (5.0 mmol) of 2-methyl-7-nitro-1-propyl-6-trifluoromethylbenzimidazole (5), and 30 ml of acetic acid was hydrogenated over 150 mg of platinum oxide.
at low pressure (3 atm) and ambient temperature for 1 hr. The reaction was stopped and the catalyst removed by filtration through a Celite pad. The filtrate was made basic with concentrated \( \text{NH}_4\text{OH} \), and the resulting precipitate was collected on a suction filter. The product was washed copiously with water and allowed to dry. Recrystallization from cyclohexane-benzene (3:1) gave 1.2 g (92%) of 53 as a crystalline solid, mp 142.5-143°.

**Anal.** Calcd for \( \text{C}_{12}\text{H}_{14}\text{N}_3\text{F}_3 \): C, 56.02; H, 5.49; N, 16.33. Found: C, 56.32; H, 5.50; N, 16.42.

7-Amino-1-ethyl-2-methyl-5-trifluoromethylbenzimidazole (55). A mixture of 546 mg (2.00 mmol) of 1-ethyl-2-methyl-7-nitro-5-trifluoromethylbenzimidazole (38) and 20 ml of acetic acid was hydrogenated over 70 mg of platinum oxide at low pressure (3 atm) and ambient temperature for 1 hr. The reaction was stopped and the catalyst was removed by filtration. The filtrate was made basic with concentrated \( \text{NH}_4\text{OH} \), and the resulting precipitate was collected on a suction filter, washed copiously with water, and allowed to dry. Recrystallization from cyclohexane-benzene (3:1) afforded 378 mg (78%) as white needles, mp 143-144°.

**Anal.** Calcd for \( \text{C}_{11}\text{H}_{12}\text{F}_3\text{N}_3 \): C, 54.32; H, 4.97; N, 17.28. Found: C, 54.65; H, 4.79; N, 17.13.

Reduction of 2-Methyl-7-nitro-1-propyl-5-trifluoromethylbenzimidazole (5) Using Tin and Concentrated Hydrochloric Acid. A mixture of 1.4 g (5.0 mmol) of 5, 3.0 g of mossy tin, and 20 ml of concentrated hydrochloric acid was
placed in a 100 ml round-bottomed flask and heated on a steam bath for 1 hr. The cooled mixture was made basic with 30 g of 50% NaOH, and extracted three times with a total of 75 ml of chloroform. The combined chloroform layers were dried (Na$_2$SO$_4$), filtered, and evaporated leaving 1.2 g (92%) of a white solid. Recrystallization of this material from benzene afforded a material which possessed a very broad melting point range (150-190°). The nmr spectrum indicated that this was a mixture of the expected 7-amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53) and an unknown component (54). The unknown 54 was not any of the other possible isomers of 53 (such as 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole, 47, or 2-methyl-7-$n$-propylamino-5-trifluoromethylbenzimidazole, 56), nor was it the result of cleavage (such as 7-amino-2-methyl-5-trifluoromethylbenzimidazole, 58) as shown by tlc and nmr.
SECTION C. REDUCTION OF 2,6-DINITROANILINES

3-sec-Butylamino-4,5-diaminobenzotrifluoride (65e). A mixture of 3.1 g (10 mmol) of 4-sec-butylamino-3,5-dinitrobenzotrifluoride (21e), 10.0 g of mossy tin, and 100 ml of concentrated hydrochloric acid was placed in a 250 ml three-necked round-bottom flask, fitted with an overhead stirrer and condenser, and heated on a steam bath for 1 hr. The cooled mixture was made basic by addition of 120 g of 50% NaOH, and, after 60 ml of chloroform was added, the mixture was filtered to remove insoluble inorganics. The chloroform was separated from the filtrate, and the aqueous solution was extracted twice more with 30 ml portions of chloroform. The combined chloroform layers were dried (MgSO₄), filtered, and evaporated. The residue product was dried under reduced pressure to afford 2.4 g (100%) of 65e as an analytically pure dark oil.


The reduction of (+)-4-sec-butylamino-3,5-dinitrobenzotrifluoride (21i) [α]D²⁰ = +22.0° was accomplished using these same conditions, including the same amounts. Again, 2.4 g of product was isolated. This material was identical in all respects to 65e. The product showed no rotation in methanol solution.
4-Amino-1-sec-butyl-2-methyl-6-trifluoromethylbenzimidazole (50). A mixture of 2.0 g (8.0 mmol) of 3-sec-butylamino-4,5-diaminobenzotrifluoride (65a) and 15 ml of acetic anhydride was stirred briefly in a 250 ml round-bottom flask until the mixture formed a solid mass. The mixture was treated with 40 ml of 3N hydrochloric acid and the mixture was heated under reflux for 2 hr. The cooled mixture was made basic with concentrated NH₄OH, and then extracted three times with a total of 75 ml of chloroform. The chloroform was evaporated and the residue was treated with 30 ml of 6N hydrochloric acid. After heating this solution under reflux for 2 hr, the mixture was cooled with an ice bath and made basic with concentrated NH₄OH. The mixture was extracted three times with a total of 60 ml of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving a white solid. Recrystallization of the residue from hexane afforded 1.7 g (80%) of 50 as a white crystalline solid, mp 115-116°.

Anal. Calcd for C₁₃H₁₆N₃F₃: C, 57.55; H, 5.94; N, 15.49. Found: C, 57.75; H, 6.03; N, 15.65.

Reduction of 4-n-Butylamino-3,5-dinitrobenzotri fluoride (21d) with Mossy Tin and Hydrochloric Acid. A mixture of 10.0 g of mossy tin and 100 ml of concentrated hydrochloric acid was stirred for 10 min in a 250 ml round-bottom flask fitted with a condenser and overhead stirrer. To this mixture was added, all at once, 3.1 g (10 mmol) of 21d. The mixture was heated on a steam bath with vigorous
stirring for 1 hr. After cooling, the mixture was made basic with 130 g of 50% NaOH, and, after adding 50 ml of CHCl₃, was filtered to remove insoluble inorganics. The CHCl₃ was separated from the filtrate and the aqueous phase extracted twice more with 20 ml portions of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving 2.4 g (100%) of a dark oil. The nmr spectrum of this material showed it to contain approximately 95% of 3-n-butylamino-4,5-dinitrobenzotrifluoride (65d) and 5% of 4-n-butylamino-3,5-dinitrobenzotrifluoride (66d). The oil was analytically pure after drying under reduced pressure for 12 hr.

**Anal. Calcd for C₁₁H₁₆F₃N₃: C, 53.43; H, 6.52; N, 16.99. Found: C, 53.25; H, 6.44; N, 16.98.**

Reduction of 4-n-Propylamino-3,5-dinitrobenzotrifluoride (2lc) Using Mossy Tin and Hydrochloric Acid. A mixture of 5.86 g (20.0 mmol) of 2lc, 12.0 g of mossy tin, and 80 ml of concentrated hydrochloric acid was placed in a three-necked 500 ml round-bottom flask, fitted with a condenser and overhead stirrer, and heated on a steam bath for 1 hr. The cooled mixture was made basic with 90 g of 50% NaOH, and, after addition of 50 ml of CHCl₃, was filtered to remove insoluble inorganics. The CHCl₃ was separated from the filtrate, and the aqueous solution was extracted twice more with 25 ml portions of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving 4.2 g (92%) of a dark oil. The nmr spectrum of this material showed it to be a mixture of two isomers, 4-n-propylamino-
3,5-diaminobenzotrifluoride (66c) and 3-n-propylamino-4,5-diaminobenzotrifluoride (65c) in a 2:1 ratio. Trituration of the oil with pentane resulted in the formation of a solid which proved to be 66c, mp 65-66.5°. The pentane mother liquor contained a mixture of both isomers as shown by nmr analysis.

4-(N-Propylamino-3,5-diaminobenzotrifluoride (66c). A mixture of 40 ml of concentrated HCl 6.0 g of mossy tin was heated on a steam bath for 15 min. While the mixture was heating, 2.93 g (10.0 mmol) of 4-(N-propylamino)-3,5-dinitrobenzotrifluoride (21c) was slowly added to the mixture in small amounts. After the addition was completed, about 0.75 hr, the mixture was heated for 0.5 hr and then cooled with an ice bath to 5°. To the mixture was added 75 ml of CHCl₃ and 60 g of 50% NaOH, and the mixture was filtered to remove the insoluble inorganics. The CHCl₃ layer was separated from the filtrate and the aqueous layer was extracted three more times with 25 ml portions of CHCl₃. The combined CHCl₃ layers were washed with 50 ml H₂O, dried over Na₂SO₄, filtered, and evaporated leaving a brown solid residue. This product was only one isomer as indicated by nmr and TLC. Recrystallization from medium boiling petroleum ether and decolorization with Norit gave 1.5 g (65%) of 66c as white needles, mp 69.5-70°. nmr (CDCl₃; in ppm): 6.36 (s-2H); 3.24 (s-5H); 2.98 (t-2H); 1.65 (h-2H); 1.00 (5-3H).

Anal. Calcd for C₁₀H₁₄F₃N₃: C, 51.49; H, 6.05; N, 18.02. Found: C, 51.77; H, 6.06; N, 17.88.
Reduction of 4-Ethylamino-3,5-dinitrobenzotrifluoride (21b) With Mossy Tin and Hydrochloric Acid. A mixture of 10.0 g of mossy tin and 100 ml of concentrated hydrochloric acid was heated in a three-necked 250 ml round-bottom flask, fitted with a condenser and overhead stirrer, on a steam bath for 10 min. To the mixture was added 2.8 g (10 mmol) of 21b in 100 mg portions over 1 hr. After heating an additional 0.5 hr, the mixture was cooled, made basic with 130 g of 50% NaOH, and, after adding 50 ml of CHCl₃, was filtered to remove any insoluble inorganics. The CHCl₃ was separated from the filtrate, and the aqueous solution was extracted twice more with 20 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered, and evaporated leaving 1.8 g (82%) of an oil which solidified after standing for 1 hr. The nmr spectrum of this solid showed it to be a 50-50 mixture of two isomers, 3,4-diamino-5-ethylaminobenzotrifluoride (65b) and 3,5-diamino-4-ethylaminobenzotrifluoride (77b).

The nmr spectrum of this material appears in the appendix.

Reduction of 4-t-Butylamino-3,5-dinitrobenzotrifluoride (21f) with Mossy Tin and Hydrochloric Acid. A mixture of 3.1 g (10 mmol) of 21f, 10 g of mossy tin, and 100 ml of concentrated hydrochloric acid was placed in a three-necked 250 ml round-bottom flask, fitted with an overhead stirrer and condenser, and was heated on a steam bath.
for 1 hr. The cooled mixture was made basic with 140 g of 50% NaOH, and, after adding 40 ml of chloroform, was filtered to remove insoluble inorganics. The chloroform was separated and the aqueous solution was extracted four more times with a total of 100 ml of chloroform. The combined chloroform layers were dried (Na₂SO₄), filtered, and evaporated leaving a white solid. Recrystallization of the residue from CCl₄ afforded 1.4 g (73%) of a white solid, mp 91-92°, identical in all respects to 3,4,5-triaminobenzotrifluoride (57).

Reduction of (+)-4-(α-Methylbenzylamino)-3,5-dinitrobenzotrifluoride (21h) with Mossy Tin and Hydrochloric Acid. A mixture of 1.87 g of 21h, 4.0 g of mossy tin, and 30 ml of concentrated hydrochloric acid was placed in a 100 ml round-bottom flask which was fitted with a condenser, and the flask was heated on a steam bath for 2 hr. The mixture was cooled, then washed with ether to remove the oil droplets which had formed. The aqueous solution was made basic with 40 g of 50% NaOH, and, after addition of 30 ml of CHCl₃, was filtered to remove insoluble inorganics. The CHCl₃ was separated from the filtrate and the aqueous phase was extracted three more times with a total of 90 ml of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving a white solid. Recrystallization from CCl₄ afforded 730 mg (73%) of a white solid, mp 91-92°, which was identical to 3,4,5-triaminobenzotrifluoride (57).
Distillation of the initial ether extract afforded a liquid which appeared to be ethylbenzene by the odor and spectral properties. However, this material had a boiling point range of 96-110°, which is lower than that of ethylbenzene (lit.\(^{35}\) 135°).

4-Anilino-3,5-diaminobenzotri fluoride (66g). A mixture of 3.3 g (10 mmol) of 4-anilino-3,5-dinitrobenzotri fluoride (21g), 10 g of mossy tin, and 100 ml of concentrated hydrochloric acid was placed in a 250 ml round-bottom flask, fitted with a condenser and overhead stirrer, and was heated on a steam bath for 1 hr. The cooled mixture was made basic with 120 g of 50% NaOH, and 50 ml of CHCl\(_3\) was added. After filtering to remove insoluble inorganics, the mixture was extracted three more times with a total of 60 ml of CHCl\(_3\). The combined CHCl\(_3\) layers were dried (MgSO\(_4\)), filtered, and evaporated leaving a white solid. Recrystallization of the residue from cyclohexane afforded 1.9 g (71%) of 66g as white platlets, mp 130-130.5°.


4-n-Propylamino-3,5-diaminotoluene (66k). A three-necked 500 ml round-bottom flask, fitted with a condenser and overhead stirrer, was charged with 120 ml of concentrated hydrochloric acid. Mossy tin (18.0 g) was carefully added, followed by 7.2 g (0.030 m) of 4-n-propylamino-3,5-dinitrotoluene (22b) and the mixture was heated for 1 hr. After cooling to 5° with an ice bath, 75 ml of CHCl\(_3\) was added.
The mixture was made basic with 140 g of 50% NaOH, then filtered to remove the insoluble inorganics. The CHCl₃ layer was separated from the filtrate and the aqueous layer was extracted four more times with 25 ml portions of CHCl₃. The combined CHCl₃ layers were washed with 50 ml H₂O, dried over Na₂SO₄, filtered, and evaporated to give 4.0 g (74.1%) of 66k as a light red oil. This material was used without further purification. nmr (CDCl₃; in ppm): 6.03 (s-2H); 3.44 (broad-5H); 2.84 (t-2H); 2.14 (s-3H); 1.58 (h-2H); 0.96 (t-3H).

Reduction of 4-n-Propylamino-3,5-dinitrochlorobenzene (23b) with Mossy Tin and Hydrochloric Acid. A mixture of 18.0 g of mossy tin and 120 ml of concentrated hydrochloric acid was placed in a 500 ml round-bottom flask, fitted with an overhead stirrer and condenser, and the mixture was heated on a steam bath for 15 min. To the hot mixture was added 7.80 g (30.0 mmol) of 4-n-propylamino-3,5-dinitrochlorobenzene (23b) in portions over a 45 min period. After addition was complete, the mixture was heated for another 0.5 hr, then cooled. The mixture was made basic with 170 g of 50% NaOH, and, after adding 50 ml of CHCl₃, was filtered to remove insoluble inorganics. The CHCl₃ was separated from the filtrate and the aqueous solution was extracted twice more with 30 ml portions of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving behind 4.6 g (81%) of a dark oil. The nmr spectrum of this material showed that it was a 50-50 mixture of two isomers, 3,4-
diamino-5-n-propylaminochlorobenzene (65j) and 3,5-diamino-4-n-propylaminochlorobenzene (66j). An attempt was made to separate these materials by column chromatography. The oil was placed on a column of basic alumina (42x2.5 cm), and eluted with a (1:10) CHCl₃/hexane mixture. After 19 hr, 1.8 g of a homogeneous material had been obtained. The nmr spectrum showed that this was 66j as evidenced by the two proton singlets at 6.22 ppm for the aromatic protons. After this material had eluted, 0.5 g of material was collected which was a mixture of two isomers. Further elution, however, did not yield any more material, despite the fact that the polarity of the eluent was increased to 100% chloroform. Apparently, 65j remained bound to the column. Thus, chromatography did allow for the isolation of pure 66j, but 65j could not be recovered using this technique.

Catalytic Reduction of (+)-4-sec-Butylamino-3,5-dinitrobenzotrifluoride (21i). A mixture of 4.8 g (15 mmol) of 21i and 100 ml of 95% ethanol was hydrogenated over 400 mg of platinum oxide at low pressure (3 atm) and ambient temperature for 2 hr. The reaction was stopped and the catalyst was removed by filtration. The filtrate was evaporated leaving behind an oil whose nmr spectrum indicated that it contained approximately 85% of 4-sec-butylamino-3,5-diaminobenzotrifluoride (66i) and 15% of 3-sec-butylamino-4,5-diaminobenzotrifluoride (65e). The oil crystallized on standing. Recrystallization of the solid from hexane afforded 2.7 g (73%) of pure 66i, mp 62-63°. This material was optically active; [α]D¹⁷ = -25.3°.
Anal. Calcd for C\textsubscript{11}H\textsubscript{16}N\textsubscript{3}F\textsubscript{3}: C, 53.43; H, 6.52; N, 17.00. Found: C, 53.59; H, 6.50; N, 16.93.

In the same manner, racemic 4-sec-butylamino-3,5-dinitrobenzotrifluoride was reduced to a 85:15 mixture of racemic 4-sec-butylamino-3,5-diaminobenzotrifluoride (66e) and 65e. The yield of 66e as well as physical properties (with the exception of optical activity) were the same as for 66i.

Catalytic Reduction of 4-Ethylamino-3,5-dinitrobenzotrifluoride (21b). A mixture of 3.2 g (11 mmol) of 21b and 100 ml of 95% ethanol was hydrogenated over 200 mg of platinum oxide at low pressure (3 atm) and ambient temperature for 2 hr. The reaction was stopped and the catalyst was removed by filtration. Evaporation of the filtrate left an oil which contained three components, 4-ethylamino-3,5-diaminobenzotrifluoride (66b), 3-ethylamino-4,5-diaminobenzotrifluoride (65b), and 7-amino-2-methyl-5-trifluoromethylbenzimidazole (58), based on the nmr spectrum. The amount of oil recovered was 1.7 g (71%). To confirm the presence of 65b, 66b, and 58, this mixture was converted to a mixture of benzimidazoles, authentic samples of which were already available.

Thus, 1.7 g of the oil was treated with 10 ml of acetic anhydride and heated briefly. The cooled mixture was added to 40 ml of 3N hydrochloric acid and the mixture heated under reflux for 2 hr. The cooled mixture was made basic with con-
centrated NH$_4$OH, and extracted three times with a total of 60 ml of CHCl$_3$. The combined CHCl$_3$ layers were evaporated and the residue dissolved in 40 ml of 6N hydrochloric acid. The solution was heated under reflux for 2 hr, then cooled, made basic with concentrated NH$_4$OH, and extracted three times with a total of 60 ml of CHCl$_3$. The combined CHCl$_3$ layers were dried (Na$_2$SO$_4$), filtered, and evaporated leaving 1.6 g of solid. The nmr spectrum of this material showed the presence of 58, as well as 4-amino-1-ethyl-2-methyl-6-trifluoromethylbenzimidazole (48) and 7-amino-1-ethyl-2-methyl-5-trifluoromethylbenzimidazole (55). Both 48 and 55 were obviously derived from the corresponding o-phenylenediamines formed in the reduction. The presence of 58, 48, and 55 was further confirmed by tlc.

**Catalytic Reduction of 4-n-Propylamino-3,5-dinitrobenzotrifluoride (21c) in the Presence of Acid.** A mixture of 3.80 g (13.0 mmol) of 21c, 50 ml of 95% ethanol, and 3 ml of concentrated hydrochloric acid was hydrogenated over 300 mg of platinum oxide at low pressure (3 atm) and ambient temperature for 2 hr. The reaction was stopped and the catalyst was removed by filtration. Evaporation of the filtrate left an oil which was treated with a dilute NH$_4$OH solution. This mixture was extracted three times with a total of 60 ml of CHCl$_3$. The combined CHCl$_3$ layers were dried (Na$_2$SO$_4$), filtered, and evaporated leaving a dark oil. The nmr spectrum showed that this oil contained a mixture of 3,4-diamino-5-n-propylaminobenzotrifluoride (65c), 3,5-diamino-4-n-propylaminobenzotrifluoride (66c), and unidentifiable components.
SECTION D. SYNTHESIS AND REACTIONS OF AMINOBENZIMIDAZOLES

4-Amino-1-butyl-2-methyl-6-trifluoromethylbenzimidazole (49). A solution of 2.0 g (8.1 mmol) of 3-(n-butylamino)-4,5-diaminobenzotrifluoride (65d) in 16 ml of acetic anhydride was stirred until the mixture solidified (5 min); 40 ml of 3N HCl was added, and the mixture was heated under reflux for 3 hr. The mixture was cooled, made basic with concentrated NH₄OH, and extracted three times with 25 ml portions of ether. The combined ether extracts were evaporated leaving a brown oil, whose ir spectrum indicated the presence of a secondary amide. The oil was, therefore, heated under reflux for 2 hr in 6N HCl. After cooling, the mixture was made basic with concentrated NH₄OH and extracted three times with 25 ml portions of ether. The combined ether extracts were dried over Na₂SO₄, filtered, and evaporated leaving an oil which crystallized after 5-10 min. Recrystallization of the solid from medium boiling petroleum ether afforded 1.8 g (81.8%) of 49 as white needles, mp 129-129.5°.


7-Amino-1-sec-butyl-2-methyl-5-trifluoromethylbenzimidazole (67). A mixture of 1.2 g (5.0 mmol) of 4-sec-butylamino-3,5-diaminobenzotrifluoride (66e) and acetic anhydride (10 ml) was stirred briefly. To this mixture was added 40 ml of 3N hydrochloric acid, and the solution was heated under reflux for 2 hr. The cooled mixture was made
basic with concentrated NH$_4$OH, and then extracted three times with a total of 60 ml of CHCl$_3$. The combined CHCl$_3$ layers were evaporated, and the residue was dissolved in 30 ml of 6N hydrochloric acid. After heating under reflux for 2 hr, the mixture was cooled, made basic with concentrated NH$_4$OH, and extracted three times with a total of 60 ml of CHCl$_3$. The combined CHCl$_3$ layers were dried (MgSO$_4$), filtered, and evaporated leaving an oil which solidified after triturating with pentane. Recrystallization of the solid from cyclohexane afforded 1.1 g (85%) of a white solid, mp 99-100°.

Anal. Calcd for C$_{13}$H$_{16}$F$_3$N$_3$: C, 57.55; H, 5.94; N, 15.49. Found: C, 57.64; H, 6.03; N, 15.31.

The use of (-)-sec-butylamino-3,5-diaminobenzotri-fluoride (66i) in this reaction with the conditions and amounts specified above afforded (-)-7-amino-1-sec-butyl-2-methyl-5-trifluoromethylbenzimidazole (67a) also in 85% yield. This compound, mp 94-96°, was optically active, $[\alpha]_{D}^{17} = -4.7°$.

7-Amino-2-methyl-1-phenyl-5-trifluoromethylbenzimidazole (68). A mixture of 1.5 g (6.0 mmol) of 4-anilino-3,5-diaminobenzotri fluoride (66g) and 12 ml of acetic anhydride was placed in a 100 ml round-bottom flask and heated on a steam bath for 10 min. The cooled mixture was treated with 40 ml of 3N hydrochloric acid and heated under reflux for 2.5 hr. After cooling, the mixture was made basic with concentrated NH$_4$OH, and extracted four times with a total of 80 ml
of CHCl₃. The combined CHCl₃ layers were evaporated and the residue was dissolved in 30 ml of 6N hydrochloric acid and heated under reflux for 2.5 hr. The cooled mixture was made basic with concentrated NH₄OH and extracted three times with a total of 45 ml of CHCl₃. The combined CHCl₃ layers were dried (Na₂SO₄), filtered, and evaporated leaving a white solid. Recrystallization of the residual solid from cyclohexane afforded 1.4 g (82%) of 68 as needles, mp 153-154°.


4-Amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47). A solution of 4.1 g (17 mmol) of 4-(n-propylamino)-3,5-diaminobenzotrifluoride (66c) in 35 ml of acetic anhydride was stirred until it solidified (5 min), 80 ml of 3N HCl was added, and the reaction was heated under reflux for 3 hr. The mixture was cooled, made basic with concentrated NH₄OH, and extracted three times with 30 ml portions of CHCl₃. The combined CHCl₃ layers were evaporated leaving an off-white solid as residue which was added to 60 ml of 6N HCl and heated under reflux for 2 hr. The mixture was made basic with concentrated NH₄OH and extracted three times with 30 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered and evaporated leaving a solid residue. Recrystallization of the solid from medium-boiling petroleum ether-benzene (3:1 ratio) gave 3.5 g (80.1%) of 47 as white fluffy needles, mp 170-171°. This material was identical to that 47 made previously.
7-Amino-2,5-dimethyl-1-propylbenzimidazole (64). A mixture of 4.0 g (22 mmol) of 4-n-propylamino-3,5-diamino-toluene (66k) and 20 ml of acetic anhydride was placed in a 250 ml round-bottom flask and heated on a steam bath for 15 min. After cooling, the mixture was treated with 60 ml of 3N hydrochloric acid and then heated under reflux for 2.5 hr. The mixture was cooled, made basic with concentrated NH₄OH, and extracted four times with 25 ml portions of CHCl₃. The combined CHCl₃ layers were evaporated, and the residue was added to 40 ml of 6N HCl and heated under reflux for 2.5 hr. The mixture was made basic with concentrated NH₄OH and extracted three times with 30 ml portions of CHCl₃. The combined CHCl₃ layers were dried over Na₂SO₄, filtered, and evaporated leaving behind a crude solid. Recrystallization of the solid from 25% aqueous ethanol afforded 2.3 g (51.1%) of 1 as light brown needles, mp 185-186°.

Anal. Calcd for C₁₂H₁₇N₃: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.87; H, 8.54; N, 20.73.

7-Amino-5-chloro-2-methyl-1-propylbenzimidazole (69). A mixture of 0.70 g (3.7 mmol) of 4-n-propylamino-3,5-diaminochlorobenzene (66j) and 40 ml of acetic anhydride was placed in a 50 ml round-bottom flask and heated on a steam bath for 10 min. After cooling, the mixture was treated with 12 ml of 3N hydrochloric acid and the mixture was heated under reflux for 2.5 hr. The mixture was cooled, made basic with concentrated NH₄OH, and extracted three times with a total of 45 ml of CHCl₃. The combined CHCl₃ layers were evaporated and the residue was dissolved in 25 ml of 6N hydrochloric acid
and heated under reflux for 2.5 hr. The cooled mixture was made basic with concentrated \( \text{NH}_4\text{OH} \) and extracted three times with a total of 30 ml of CHCl\(_3\). The combined CHCl\(_3\) layers were dried (\( \text{Na}_2\text{SO}_4 \)), filtered, and evaporated leaving a brown solid. Recrystallization from 40% aqueous ethanol and decolorization afforded 0.55 g (64%) of 69 as a crystalline solid, mp 157-158°.

**Anal.** Calcd for C\(_{11}\)H\(_{14}\)ClN\(_3\): C, 59.06; H, 6.31; N, 18.79. Found: C, 58.79; H, 6.67; N, 18.73.

**Reaction of 4-n-Propylamino-3,5-diaminobenzotri-fluoride (66c) with Triethylorthoacetate.** A solution of 450 mg (19.3 mmol) of 66c in 25 ml of benzene was added to a three-necked 100 ml round-bottom flask, fitted with an addition funnel and condenser, and heated under reflux. A solution of 324 mg (20.0 mmol) of triethylorthoacetate was added over a 20 min period. After the addition was complete the mixture was heated under reflux for 12 hr. The mixture was cooled and the benzene was evaporated leaving a viscous oil. The oil was dissolved in a minimal amount of ether, and then a large amount of pentane was added causing the precipitation of 126 mg (25%) of 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47). After removing 47 by filtration, the filtrate was evaporated to afford 250 mg of an oil. The nmr spectrum of this material indicated that the oil contained 2-methyl-7-n-propylamino-5-trifluoromethyl-benzimidazole (56) and 47 in a 3:1 ratio.
l-n-Butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (42). A solution of 1.0 g (14 mmol) of sodium nitrite in 5 ml of concentrated H$_2$SO$_4$ in a 150 ml beaker was cooled in an ice bath and a cooled solution of 1.44 g (5.3 mmol) of 4-amino-1-butyl-2-methyl-6-trifluoromethylbenzimidazole (49) in 10 ml of glacial acetic acid was dropped slowly into the cold solution of nitrosylsulfuric acid with vigorous stirring. Throughout the addition and for 30 min afterward the temperature was kept below 20°. Dry ether (100 ml) was added slowly with stirring, and the temperature of the mixture was kept at 0° for 1 hr while the stirring was continued. After 0.5 hr a solid formed and at the end of 1 hr the white precipitate was removed by filtration and washed vigorously with ether and then with a 3:1 mixture of ether-ethanol. The solid was then dissolved in 10 ml of ice water.

A saturated aqueous solution containing 5.0 g of copper sulfate was treated with a similar solution of 5.0 g of sodium sulfite. The greenish-brown precipitate was collected, washed with water, and then stirred into a solution containing 10.0 g (0.145 m) of sodium nitrite in 40 ml of H$_2$O contained in a 400 ml beaker.

The cold aqueous solution of the diazonium salt was added slowly to the copper solution. A few milliliters of ether was added to break the foam which formed. The mixture was stirred for 1 hr, and then 100 ml of CHCl$_3$ was added. The mixture was filtered to remove any insoluble matter, and the CHCl$_3$ layer was separated. The aqueous phase was ex-
tracted three additional times with 25 ml portions of CHCl₃, and the combined CHCl₃ layers were washed twice with 100 ml of water and then twice with 5% sodium bicarbonate solution. The CHCl₃ solution was dried over K₂CO₃, filtered, and evaporated leaving a tan solid residue. Recrystallization of the solid from 40% aqueous ethanol with decolorization with Norit gave 0.40 g (25%) of compound 42 as white needles, mp 102-102.5°, identical in all respects (ir, nmr, and mixed mp) to that made previously by the butylation of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4).

2-Methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40). A solution of 1.0 g (14 mmol) of sodium nitrite in 5 ml of concentrated sulfuric acid in a 150 ml beaker was cooled in an ice bath and a chilled solution of 1.40 g (5.4 mmol) of 4-amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47) in 10 ml of glacial acetic acid was dropped slowly into the cold solution of nitrosylsulfuric acid with vigorous stirring. Throughout the addition and for 0.5 hr afterward the temperature was kept below 20°. Dry ether (100 ml) was added slowly with stirring, and the temperature of the mixture was kept at 0° for 1 hr while stirring was continued. After 0.5 hr a solid formed and at the end of 1 hr, the white precipitate was removed by filtration and washed vigorously with ether and a 3:1 mixture of ether-ethanol. The solid was then dissolved in 10 ml of ice water.

A saturated aqueous solution containing 5.0 g of copper sulfate was treated with a similar solution of 5.0 g of sodium sulfite. The greenish-brown precipitate was
collected, washed with water, and then stirred into a solution containing 10.0 g (0.145 m) of sodium nitrite in 40 ml of H₂O contained in a 400 ml beaker.

The cold aqueous solution of the diazonium salt was added slowly to the copper solution. A few milliliters of ether was added to break the foam which formed. The mixture was stirred for 1 hr, and then 100 ml of CHCl₃ was added. The mixture was filtered to remove any insoluble matter, and the CHCl₃ layer was separated. The aqueous phase was extracted three additional times with a total of 75 ml of CHCl₃ and the combined CHCl₃ layers were washed twice with 50 ml of water. The chloroform solution was dried (K₂CO₃), filtered, and evaporated leaving a solid. Recrystallization of this material from 40% aqueous ethanol with decolorization with Norit afforded 0.65 g (43%) of 40 as white needles, mp 131.5-132°. This material was identical in all respects (ir, nmr, mixed mp) to 40 prepared by alkylation of 2-methyl-4-nitro-6-trifluoromethylbenzimidazole (4).

1-sec-Butyl-2-methyl-4-nitro-6-trifluoromethylbenzimidazole (43). A solution of 1.0 g (14 mmol) of sodium nitrite in 5 ml of concentrated sulfuric acid in a 150 ml beaker was cooled in an ice bath and a chilled solution of 1.44 g (5.30 mmol) of 4-amino-1-sec-butyl-2-methyl-6-trifluoromethylbenzimidazole (50) in 10 ml of glacial acetic acid was dropped slowly into the cold solution of nitrosyl-sulfuric acid with vigorous stirring. Throughout the addition and for 0.5 hr afterward, the temperature was kept
below 20°. Dry ether (100 ml) was added slowly with stirring, and the temperature of the mixture was kept at 0° for 1 hr while stirring was continued. After 1 hr, the oil which precipitated still had not crystallized, despite vigorous scratching. The ether was decanted and the oil was dissolved in 20 ml of cold water.

A saturated aqueous solution containing 5.0 g of copper sulfate was treated with a similar solution of 5.0 g of sodium sulfite. The greenish-brown precipitate was collected, washed with water, and then stirred into a solution containing 10.0 g (0.145 m) of sodium nitrite in 40 ml of water contained in a 400 ml beaker.

The cold aqueous solution of the diazonium salt was added slowly to the copper solution. A few milliliters of ether was added to break the foam which formed. The mixture was stirred for 1 hr, and then 100 ml of CHCl₃ was added. The CHCl₃ was separated and the aqueous phase was extracted three more times with a total of 60 ml of CHCl₃. The combined CHCl₃ layers were evaporated and the residue was dissolved in 50 ml of 6N hydrochloric acid. The aqueous solution was washed twice with CHCl₃, then made basic with concentrated NH₄OH. The aqueous solution was extracted four times with a total of 60 ml of CHCl₃. The combined CHCl₃ layers were dried (K₂CO₃), filtered, and evaporated leaving behind an oil. The oil was boiled in 100 ml of hexane and the hexane was decanted. Evaporation of the hexane afforded a tan solid. Recrystallization of the solid from hexane gave 507 mg (32%) of 43 as tan needles, mp 121-121.5°. This
material gave spectra which were identical to those of synthesized by alkylation of 4.

**Anal.** Calcd for C_{13}H_{14}F_{3}N_{3}O_{2}:  C, 51.83; H, 4.68; N, 13.95.  Found:  C, 52.06; H, 4.87; N, 13.70.

4-(a,a'-Dichloroacetimidino)-3-nitrobenzotrifluoride (73). A mixture of 3.0 g (14 mmol) of 4-amino-3-nitrobenzo- trifluoride (71) and 20 ml of α-chloroacetyl chloride was heated under reflux for 8 hr. The cooled mixture was poured into 200 ml of ice water and stirred for 15 min. A white precipitate formed and this was removed by filtration and allowed to dry. Recrystallization of the solid from CCl_{4} afforded 3.3 g (66%) of 73 as white platlets, mp 144.5-145.5°.

**Anal.** Calcd for C_{11}H_{7}Cl_{2}F_{3}N_{2}O_{4}:  C, 36.79; H, 1.96; N, 7.80.  Found:  C, 36.96; H, 2.50; N, 7.69.

4-(α-Chloroacetamido)-3-nitrobenzotrifluoride (70). A mixture of 4.12 g (20.0 mmol) of 4-amino-3-nitrobenzotri- fluoride (71) in 100 ml of toluene was briefly stirred and to this was added 2.37 g (21.0 mmol) of α-chloroacetyl chloride. The mixture was heated under reflux for 17 hr. The solvent was then evaporated leaving a white solid. Recrystallization of the solid from hexane afforded 5.0 g (88%) of 70 as white fluffy needles, mp 98-98.5°.

**Anal.** Calcd for C_{9}H_{6}ClF_{3}N_{2}O_{3}:  C, 38.25; H, 2.14; N, 9.91.  Found:  C, 38.39; H, 2.07; N, 9.71.
SUMMARY

The syntheses of 2,6-dinitroanilines were accomplished by the nucleophilic substitution of the halide of the corresponding 2,6-dinitrochlorobenzenes by amines. The mono-reduction of the 2,6-dinitroanilines resulted in the formation of 3-nitro-o-phenylenediamines. Monoreduction could be effected using a sodium sulfide-sodium bicarbonate solution although this method frequently gave low yields. Catalytic hydrogenation was also used and higher yields were realized. This method, however, was not of synthetic value for those 2,6-dinitroanilines having a halogen on the ring or an alkyl group on the amino function for undesirable side reactions occur. The 3-nitro-o-phenylenediamines were converted to 7-nitrobenzimidazoles in good to excellent yields using standard procedures. This overall reaction sequence proved easily adaptable to large scale preparations of these benzimidazoles.

Alkylation and acylation of 7-nitrobenzimidazoles was found to occur exclusively on that heterocyclic nitrogen away from the nitro group thereby leading to 1-substituted-4-nitrobenzimidazoles. The nitro group in these benzimidazoles, as well as those in non-alkylated benzimidazoles, was found to be reduced in high yield using tin and hydrochloric acid. The 1-alkyl-7-nitrobenzimidazoles, however, were best reduced by catalytic hydrogenation with acetic acid as
solvent. It was evident from the spectral data for the compounds that within a series of substituted benzimidazoles the location of a substituent could be determined by nmr spectroscopy.

The complete reduction of 2,6-dinitroanilines to the triaminobenzenes was done with tin and hydrochloric acid. Although reduction of both nitro groups readily occurred, a concomitant migration of the alkyl group from the central nitrogen to a peripheral nitrogen also took place. The amount of migration depended on the nature of the substituent. Those 2,6-dinitroanilines containing N-alkyl groups which can easily be eliminated afforded the unsubstituted triaminobenzenes. The phenyl group did not rearrange. Experimental evidence indicated that this unsymmetrical nitrogen hop (UNH rearrangement) occurred by a free-radical mechanism.

The total reduction of 2,6-dinitroanilines using catalytic hydrogenation was less straightforward, for the products were the rearranged triaminobenzene, the unrearranged triaminobenzene, unidentifiable side products, and, in one case, a benzimidazole. The products from the reductions were highly dependent on the solvent system employed.

The substituted triaminobenzenes were converted to the corresponding amino-benzimidazoles in good yield. These reactions afforded the expected benzimidazoles with one exception. When 4-\textit{n}-propylamino-3,5-diaminobenzotrifluoride was the substrate, the benzimidazole that was formed was the result of a rearrangement, during the cyclization process,
of the propyl group to a peripheral nitrogen. This rearrangement distinctly differed from the UNH rearrangement and represents a second type of N to N' alkyl shift.

The conversion of 1-alkyl-4-aminobenzimidazoles to 1-alkyl-4-nitrobenzimidazoles was accomplished in moderate yields by a Sandmeyer reaction. The 1-alkyl-7-aminobenzimidazoles, however, could not be converted to the corresponding nitro benzimidazoles either by the Sandmeyer reaction or by oxidation with peracids. In general, the synthesis of N-alkyl-nitrobenzimidazoles was best achieved by either cyclization of the nitro-o-phenylenediamine or by alkylation of the N-unsubstituted benzimidazoles.

The discovery of these novel rearrangements is of importance since a number of 2,6-dinitroanilines are used commercially as herbicides. The fact that these compounds are chemically converted to products of structural rearrangement suggest that similar conversions may occur in the bacterial metabolism or weathering of the herbicides. These potential metabolites have not been detected previously and their physiological properties have not been studied.
REFERENCES


PART I

APPENDIX
A-1. 2-Methyl-7-nitro-5-trifluoromethylbenzimidazole (4).
A-2. 2-Methyl-7-nitro-1-propyl-5-trifluoromethylbenzimidazole (5).
A-3. 2-Methyl-4-nitro-1-propyl-6-trifluoromethylbenzimidazole (40).
A-4. 4-Amino-2-methyl-1-propyl-6-trifluoromethylbenzimidazole (47).
A-5. 7-Amino-2-methyl-1-propyl-5-trifluoromethylbenzimidazole (53).
A-6. 2-Methyl-7-n-propylamino-5-trifluoromethylbenzimidazole (56).
A-7. 4-Amino-2,6-dimethyl-1-propylbenzimidazole (51).
A-8. 7-Amino-2,5-dimethyl-1-propylbenzimidazole (64).
A-9. 2,5-Dimethyl-7-n-propylamino-benzimidazole (63).
A-10. 7-Amino-2-methyl-5-trifluoromethylbenzimidazole (58).
A-11. 7-Amino-2,5-dimethylbenzimidazole (61).
Product mixture from Cyclization of 4-n-Propylamino-3,5-diaminobenzotrifluoride (66c) with Triethylorthoacetate.
A-14. 3-sec-Butylamino-4,5-diaminobenzotrifluoride (65e).
A-15. 4-sec-Butylamino-3,5-diaminobenzotrifluoride (66e).
A-16. Mixture of Triamines from Tin/HCl Reduction of 4-\(\text{u}\)-Propylamino-3,5-dinitrobenzotrifluoride (21c).
A-17. 4-n-Propylamino-3,5-diaminobenzotrifluoride (66c).
A-18. Product Mixture from Tin/HCl Reduction of 4-n-Propylamino-3,5-dinitrochlorobenzene (23b).
A-19. 4-n-Propylamino-3,5-diaminochlorobenzene (66j).
A-20. Product mixture from Tin/HCl reduction of 4-Ethylamino-3,5-dinitrobenzotrifluoride (21b).
PART II
THE THREE-AXIAL ALKYL EFFECT
INTRODUCTION

Benzylic methylene hydrogens which are not interchanged by reflection through a mirror plane are diastereotropic. So defined these hydrogens must be nonequivalent in the nuclear magnetic resonance (nmr) spectrum. However, although hydrogen atoms of a particular methylene group can be diastereotopic, this factor alone may not be sufficient for them to appear as nonequivalent. If the magnetic environments of two hydrogens are not particularly different, for example, when the chirality is far removed from the hydrogens in question, the diastereotopic hydrogens will appear as a singlet. In such a case, these hydrogens are considered to exhibit accidental equivalence.

The use of magnetic nonequivalence of diastereotopic hydrogens has proved useful for studies on the stereochemistry of cyclic amines. Lyle and coworkers, in a study of a series of N-benzylpiperazine derivatives, formulated a conformational relationship with observable nonequivalence of the methylene protons of a benzyl substituent. They found that an N-benzyl group attached to a six-membered ring adjacent to a chiral center will exhibit an AB quartet for the methylene protons in the nmr spectrum if the substituent was equatorial. If, however, the substituent was axial, the magnetic nonequivalence of the methylene protons was not observable, and these protons appeared in the nmr as a singlet.
This work was extended by Lyle and Pridgen\textsuperscript{3} to include N-benzylpiperidines with a 3-substituent. A series of cis-1-benzyl-3,4-disubstituted piperidines (1) were prepared by the hydrogenation of the corresponding pyridines. Although it was initially believed that the chirality at the three position was too far from the methylene protons of the N-benzyl group to affect the magnetic environment of these diastereotropic protons, the signals for the methylene protons in the cis isomers (1a-c) all appeared as AB quartets of 10-12 Hz difference in chemical shifts. However, in the trans-isomer 2, the effect of the 3-substituent on the methylene protons was undetectable and the diastereotopic protons appeared as a singlet.

The explanation for the difference between the cis and trans isomers stemmed from a consideration of the chair conformations of each (Scheme 1). Calculations showed that for the cis-isomer, the chair conformer in which the 3-substituent is axial should be present in excess to the extent of 70\% in the conformational equilibrium. Since the 4-substituent in any conformation is symmetrically disposed toward the N-benzyl group, it was apparent that it was the 3-axial substituent that was causing the observed nonequivalence of the diastereotropic protons. On the other hand, the stable chair conformer for the trans-isomer is that in which both the 3- and 4-substituents are equatorial. Thus, the equatorial alkyl group in the three position did not produce an observable, magnetic, anisotropic effect on the diastereotropic protons.
**Scheme 1**

1. $R = \text{CH}_3$, $R' = \text{C}_2\text{H}_5$  \( \Delta \nu = 12.2 \)
2. $R = \text{C}_2\text{H}_5$, $R' = \text{CH}_3$  \( \Delta \nu = 10.4 \)
3. $R = \text{CH}_3$, $R' = \text{CH}_3$  \( \Delta \nu = 10.0 \)
4. $R = \text{CH}_3$, $R' = \text{C}_2\text{H}_5$
Further information was obtained when 3-alkyl-1-benzylpiperidines were studied. The N-methylene protons of 1-benzyl-3-methylpiperidine (3a) and 1-benzyl-3-ethylpiperidine (3b) exhibited accidental equivalence and appeared as a singlet in the nmr spectrum. This was as predicted since the alkyl group in these piperidines should be equatorial. However, the N-methylene protons of 1-benzyl-3-isopropylpiperidine (3c) and 1-benzyl-3-t-butylpiperidine (3d) appeared as AB quartets with the chemical shift differences (Δν) of 6.7 and 13.0 Hz, respectively, for the diastereotopic hydrogens. The fact that 3c and 3d exhibit an observable, magnetic, anisotropic effect was attributed to the relative stabilities of the rotomers about the bond attaching these groups to the three position; the more stable rotomer (or rotomers) of 3c and 3d have a methyl group in a pseudoaxial arrangement.

\[ \text{PhCH}_2\text{N} \quad \text{H} \]

\[ \text{CH}_3 \quad \text{R} \]

\[ \text{CH}_3 \]

3c \hspace{1cm} R=H
3d \hspace{1cm} R=CH₃
It therefore seemed clear that the diastereotopic, benzylic protons of a substituted 1-benzylpiperidine appear as an AB quartet in the nmr spectrum if a 3-alkyl substituent is either axially oriented or is a branched chain and equatorial. This phenomenon has been christened the "Three-Axial Alkyl Effect", and it has been used as a stereochemical probe for benzhydroquinolines\textsuperscript{4}, as well as other piperidines.\textsuperscript{5}

To understand fully the effects governing the "Three-Axial Alkyl Effect", a more systematic study of 1-benzyl-3,4-disubstituted piperidines was in order. It was hoped that such a study would further elucidate the parameters required for nonequivalence thereby leading to a fuller comprehension of this effect. The piperidines that were selected for this study were \textit{cis-}4-amino-1-benzyl-3-methylpiperidine (4), \textit{cis-}4-n-amylamino-1-benzyl-3-methylpiperidine (5), \textit{cis-}1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6), \textit{cis-}4-n-amylamino-1-benzyl-3-ethylpiperidine (7), and \textit{cis-}1-benzyl-3-ethyl-4-(N-pyrrolidino)-piperidine (8). The corresponding \textit{trans-}isomers (4a, 5a, 6a, 7a, and 8a) were also of interest for this study.
The choice of the substituent at the four position was based on the relative sizes of primary, secondary, and tertiary amino functions. It was indicated previously that the cis-isomer of a compound such as 4 should exist as an equilibrium of both chair conformations. As the size of the 4-substituent increases, the equilibrium is shifted toward that conformer with the 3-axial-4-equatorial substituents. According to the "Three-Axial Alkyl Effect", enrichment of the 3-axial conformer should also result in the N-methylene protons feeling a greater magnetic anisotropic effect. Thus, if the hypothesis is valid, the N-methylene protons of 4 should exhibit a smaller difference in the chemical shifts of the diastereotopic hydrogens than that for 6. Also, the chemical shift difference for 8 (3-ethyl substituent) should be larger than that for 6 (3-methyl substituent) due to the difference in the size of the group at the 3-position. In all cases it was expected that the trans-isomers (4a-8a) would exhibit a singlet for the N-methylene protons.
RESULTS AND DISCUSSION

A. Syntheses of the cis-4-Alkylamino-3-alkyl-1-benzylpiperidines

The piperidines selected for this study were novel compounds; however, it was envisioned that they might all be prepared from a common intermediate. The versatility of such an intermediate was critical in that it must be capable of undergoing a variety of transformations at the 3- and 4- positions, as well as have a potential N-benzyl function. Furthermore, it was necessary that this material be readily available in large quantities.

A compound which met these requirements was ethyl N-benzoyl-4-piperidone-3-carboxylate (9), which had been prepared previously by Baty and coworkers. The fact that 9 is a β-keto ester is advantageous in that alkyl groups can be introduced easily at the 3-position by first treatment with a strong base, followed by reaction with the appropriate alkyl halide. Once alkylated, the ester function can be removed by hydrolysis and decarboxylation to afford the 3-alkyl-1-benzoyl-4-piperidone. Thus, 9 can lead to both the methyl and ethyl series of piperidines.
The conversion of the 4-keto moiety into an amino function can be accomplished by one of the many types of reductive amination procedures currently available. Thus, the formation of a derivative such as an oxime, enamine, or imine, followed by reduction would give the appropriate 4-amino function. It was anticipated that reduction by catalytic hydrogenation would give the cis-isomer, and that reduction by other methods such as formic acid would give the more thermodynamically-stable, trans-isomer.
Treatment of benzamide with sodium hydride followed by addition of two equivalents of ethyl acrylate gave a 60% yield of 9. This material was alkylated easily using sodium hydride as the base, 1,2-dimethoxyethane as solvent, and an appropriate alkyl halide. Thus, ethyl N-benzoyl-3-methyl-4-piperidone-3-carboxylate (10), and ethyl N-benzoyl-3-ethyl-4-piperidone-3-carboxylate (11) were prepared in 85% and 67% yields, respectively. Baty and coworkers reported that these β-keto esters could be decarboethoxylated by heating under reflux in glacial acetic acid. However, this method was unsuccessful for the preparation of N-benzoyl-3-methyl-4-piperidone (12) and only unreacted 10 was recovered. Decarboethoxylation could be effected quite rapidly by heating a solution of 10 and 6N hydrochloric acid under reflux. Since hydrolysis of the N-benzoyl group occurred simultaneously, the product had to be treated with benzoyl chloride to reintroduce the benzoyl group thereby affording 12 in 45% overall yield. N-Benzoyl-3-ethyl-4-piperidone (13) was prepared in the same fashion in lower yield (35%).
The next step in the synthetic scheme called for the conversion of the 4-keto moiety into the appropriate amino function. When treated with pyrrolidine\textsuperscript{10} both 12 and 13 afforded the corresponding enamines in quantitative yield. These enamines were immediately reduced to only one isomer using catalytic hydrogenation, presumably the \textit{cis}-3-alkyl-1-benzoyl-4-\textit{(N-pyrrolidino)}-piperidines. These compounds were not characterized, but were immediately reduced with lithium aluminum hydride to afford \textit{cis}-1-benzyl-3-methyl-4-\textit{(N-pyrrolidino)}-piperidine (6), and \textit{cis}-1-benzyl-3-ethyl-4-\textit{(N-pyrrolidino)}-piperidine (8) in good yields. The structures of both 6 and 8 were confirmed by spectral data as well as combustion analyses.

\[
\begin{align*}
12, 13 & \quad \rightarrow \quad \begin{align*}
\text{R} & \quad \rightarrow \quad \begin{align*}
\text{C}_6\text{H}_5\text{C}=\text{O} & \quad \rightarrow \quad \text{C}_6\text{H}_5\text{C}=\text{O} \\
\text{R} & \quad \rightarrow \quad \begin{align*}
\text{C}_6\text{H}_5\text{CH}_2 & \\
6 & \quad \text{R}=\text{CH}_3 \\
8 & \quad \text{R}=\text{C}_2\text{H}_5
\end{align*}
\end{align*}
\end{align*}
\end{align*}
\]
This same general procedure was also successful for the synthesis of cis-4-n-amylamino-l-benzyl-3-ethylpiperidine (7), and cis-4-n-amylamino-l-benzyl-3-methylpiperidine (5). Thus, the 3-alkyl-N-benzoyl-4-piperidones 12 and 13 were treated with n-amylamine to afford their respective imines which were reduced under catalytic hydrogenation to the corresponding 3-alkyl-4-n-amylamino-l-benzoylpiperidines. Reduction of these amides with lithium aluminum hydride gave 5 and 7, respectively. The nmr spectra of 5, 6, 7, and 8 will be discussed in section D.
B. Syntheses of cis- and trans-4-Amino-1-benzyl-3-methyl-piperidine (4 + 4a).

There are numerous procedures for the conversion of a ketone to a primary amine function. The method which seemed most direct was the formation of the oxime of N-benzoyl-3-methyl-4-piperidone (12) and treatment of this compound with lithium aluminum hydride (LAH) to reduce both the oximino and tertiary amide functions.

![Chemical Structures]

Reaction of 12 with hydroxylamine in 10% sodium hydroxide gave the oxime, 14, in moderate yield. Reduction of this material with LAH afforded a colorless liquid whose nmr spectrum contained two overlapping doublets for the methyl group at approximately 1.0 ppm. That more than one doublet was present seemed to indicate that the product was a mixture, probably of two isomers, and this was confirmed by tlc which showed the presence of two components. Spectral data and elemental analysis confirmed that the product was a 50-50 mixture of cis- and trans-4-amino-1-benzyl-3-methyl-
piperidine (4 + 4a). This was also substantiated by further reactions of this material. Thus, this mixture of 4 and 4a was converted to a mixture of the corresponding succinimides by reaction with succinic anhydride\textsuperscript{12}, and this mixture, in turn, was reduced with LAH to give a product which was a 50-50 mixture of cis- and trans-1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6 and 6a). The presence of the cis isomer (6) was established by the nmr spectrum which contained a doublet for the methyl group at 1.12 ppm and an AB quartet for the N-benzyl methylene protons; these signals are identical to 6 which had been prepared by another method. The presence of the trans-isomer (6a) was indicated by a doublet for the methyl group at 0.94 ppm and a singlet for the N-benzyl methylene protons at 3.46 ppm. (The nmr spectra of these compounds are discussed in section D).

Since reduction of the oxime with LAH afforded a mixture of cis and trans-isomers, reduction by catalytic hydrogenation was explored as a means of preparing exclusively the cis isomer. Since oximes are reported to afford predominantly the cis-isomer when hydrogenated in acidic medium, this study seemed worthwhile.\textsuperscript{8} The catalytic hydrogenation of 14 was accomplished by two methods: (1) using 5% palladium on charcoal as the catalyst in ethanol with 2 ml of concentrated hydrochloric acid added and (2) using platinum oxide as catalyst with absolute ethanol with 1 ml of chloroform as solvent.\textsuperscript{13} The product was then reduced with LAH
to afford the 4-amino-1-benzyl-3-methylpiperidine. Surprisingly, both types of catalytic reductions resulted in the formation of a 50-50 mixture of 4 and 4a, the same mixture formed by the LAH reduction of the oxime. Obviously, the 3-methyl substituent does not exert a bias to give exclusively the cis isomer. Either reduction from either side of the ring is occurring, or else equilibration is taking place.

The final procedure that was attempted for the reductive amination of piperidone 12 was that of Borch which entails the reaction of a carbonyl compound with ammonium acetate in the presence of sodium cyanoborohydride.14 The initial step in this reaction probably is the formation of an imine which is reduced in situ to the amine. Reaction of 12 under these conditions afforded a product, the ir spectrum of which showed no trace of the keto function but had a broad NH2 absorption at 3350 cm⁻¹. Treatment of this material with LAH again afforded a 50-50 mixture of 4 + 4a. The Borch procedure for reductive amination, therefore, does not specifically afford one isomer.
Attempts were made to separate this mixture by column chromatography. However, despite using basic alumina with a variety of eluents, separation could not be realized. Distillation was also tried but these isomers had boiling points too nearly the same, and so this procedure was unsuccessful. No further attempts were made for the specific preparation of 4.

C. Attempted Syntheses of the trans-4-Alkylamino-3-alkyl-1-benzylpiperidines

At the outset of this project it was assumed that catalytic hydrogenation of the enamine(s) (as well as the imines) of the 3-alkyl-1-benzoyl-4-piperidones would lead to the corresponding cis isomers, and that reduction by chemical methods would afford predominantly the trans isomers. Since the synthesis of the cis isomers had been realized, attention was turned to other methods of reducing enamine(s).
A relatively simple and high yield reduction of enamines involves treatment of this substrate with formic acid. Presumably the enamine is protonated by the acid, and the formate anion acts as a source of hydride to give the reduced species along with the evolution of carbon dioxide.

\[
R_1R_2C=CHNR_1R_2 + HCO_2H \rightarrow R_1R_2CHCH=NR_1R_2 + HCO_2^-
\]

\[
\rightarrow R_1R_2CHCHNR_1R_2 + CO_2
\]

Conversion of N-benzoyl-3-methyl-4-piperidone (12) to the enamine, followed by reaction with formic acid afforded an oil, the ir spectrum of which showed no trace of the keto-function. Reduction of this material with LAH afforded a product which consisted of approximately 95% cis and 5% trans 1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6 and 6a) as estimated from the nmr spectrum.
When the same reactions were carried out on N-benzoyl-3-ethyl-4-piperidone (13), the product that was isolated contained a more significant quantity of the trans isomer although the cis isomer was still the major component. Apparently, the formate anion approaches the immonium function from the side opposite to the alkyl group thereby generating the cis isomer.

That the less stable isomer is formed in the reduction of enamines is not unusual. A study of the steric course of LAH reductions of the immonium salt of 4-t-butyl-cyclohexanone showed that equal amounts of the cis and trans isomers are formed.\(^{15}\)
Since chemical reduction methods did not produce the trans isomers, another approach was investigated. Richer and Perleman\textsuperscript{16} have reported that the benzylimine of 4-t-butylcyclohexanone can be equilibrated with base to give a 9:1 trans-cis mixture of the corresponding benzaldimines. This same procedure was considered as a method to obtain similar mixtures which on hydrolysis would give an excess of trans-4-amino-1-benzoyl-3-methylpiperidine.
Thus, 12 was treated with benzylamine and the imine was treated with sodium hydride, followed by acidic hydrolysis. The product was isolated and reduced with LAH. Unfortunately, this material was shown to be a complex mixture by tlc and nmr, and 4a could not be isolated. No further attempt was made to prepare the trans isomers using this method.

D. Discussion of the NMR Spectra of the N-Benzyl-3,4-disubstituted Piperidines

The purpose of preparing the various N-benzyl-3,4-disubstituted piperidines, outlined in sections A, B, and C, was to obtain data concerning the parameters governing the "Three-Axial Alkyl Effect". In particular, it was anticipated that the N-benzyl methylene protons would appear magnetically non-equivalent in the cis isomers, and accidentally equivalent in the trans isomers. In considering those compounds in which the N-benzyl methylene protons were non-equivalent, it was also important to determine the degree of the magnetic anisotropic effect. The difference in chemical shift on the frequency separation ($\Delta \nu$) of the positions of absorption of the interacting nuclei were determined.$^{17}$ Mathematically, $\Delta \nu$ can be expressed by

$$\Delta \nu = \sqrt{|1-3|^2 - J_{AB}^2}$$
where \( J_{AB} \) is the coupling constant and \(|1-3|\) is the separation in Hz between the first and third peaks of the quartet.

The nmr data that were obtained for these compounds are listed in Table 1. As was expected, cis-4-n-amylamino-l-benzyl-3-methypiperidine (5), cis-4-n-amylamino-1-benzyl-3-ethylpiperidine (7), cis-1-benzyl-3-methyl-4-(N-pyrrolidino)piperidine (6), and cis-1-benzyl-3-ethyl-4-(N-pyrrolidino)piperidine (8), all showed AB quartets for their respective N-methylene protons. The relative \( \Delta \nu \) values for 5, 6, 7, and 8 also proved to be consistent with the "Three-Axial Alkyl Effect". The 4-pyrrolidino substituent in 6 and 8 has a strong influence on the conformational equilibrium of each compound, since this moiety tends to be equatorial. Thus, the 4-equatorial-3-axial conformer should be in excess in the equilibrium mixture of these piperidines. The \( \Delta \nu \) for these compounds is, in fact, quite large (16.1 and 21.0 Hz, respectively). On the other hand, 5 and 7 have a secondary amino function (n-amylamine) at the 4-position and, although this too would be expected to exert a bias toward the 4-equatorial-3-axial conformer, the free energy differences between conformers is not as great. The \( \Delta \nu \) values for 5 and 7, therefore, are smaller at 10.3 and 13.4 Hz, respectively. These results also indicate that as the size of the 3-substituent increases, the chemical shift difference of the N-methylene protons increases also.
Table 1. NMR Data for the 3-Alkyl-4-amino-1-benzylpiperidines

![Chemical Structure](image)

| Compound | R'   | R_1 | R_2   | Multiplicity | J_{AB} (Hz) | |1-3| (Hz) | Chemical Shifts (ppm) | \(\Delta\nu\) |
|----------|-----|-----|-------|--------------|-------------|---------|----------------------|-----------|
| 4 (cis)  | CH₃ | H   | H     | singlet      | ----        | --      | 3.41                 | ----      |
| 4a (trans) | CH₃ | H   | H    | singlet      | ----        | --      | 3.41                 | ----      |
| 5 (cis)  | CH₃ | H   | C₅H₁₁ | quartet     | 13.5        | 17      | 3.47; 3.37           | 10.3      |
| 6 (cis)  | CH₃ | - (CH₂)₄- | H     | quartet     | 13.5        | 21      | 3.48; 3.32           | 16.1      |
| 6a (trans) | CH₃ | - (CH₂)₄- | H    | singlet      | ----        | --      | 3.46                 | ----      |
| 7 (cis)  | C₂H₅ | H   | C₅H₁₁ | quartet     | 13.5        | 19      | 3.43; 3.30           | 13.4      |
| 8 (cis)  | C₂H₅ | - (CH₂)₄- | H     | quartet     | 13.5        | 25      | 3.52; 3.31           | 21.0      |
| 8a (trans) | C₂H₅ | - (CH₂)₄- | H    | quartet      | 13.5        | 18_²  | 3.46; 3.34           | 11.9_²    |

*aAll spectra were run in CDCl₃. J_{AB} and |1-3| were measured at sweep width 270.

_²This represents an estimated value obtained from a mixture of 8 + 8a.
The fact that the N-methylene protons of trans-1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6a) exhibit accidental equivalence is consistent with the "Three-Axial Alkyl Effect", since the three and four substituents are equatorial in this case. However, the magnetic non-equivalence for these protons (Δν = 11.9 Hz) in trans-1-benzyl-3-ethyl-4-(N-pyrrolidino)-piperidine (8a) was unexpected. Lyle and Pridgen\(^3\) did observe magnetic non-equivalence for 3-equatorial substituents capable of existing as pseudoaxial rotamers. This had not been observed for 3-ethyl substituents, however. It seems likely, therefore, that the 4-pyrrolidino group is affecting the relative population of rotamers about the ethyl-ring bond of 8.
A consideration of the three major rotomers (A, B, and C) reveals that the most stable rotomer would be expected to be B. In B the methyl group is directed away from the pyrrolidine ring, as opposed to C where this interaction is unfavorable. Furthermore, there is only one alkyl-methyl gauche interaction in B, whereas A has two such interactions. Thus, it seems that the pyrrolidine ring is causing an increase in the relative population of B at the expense of C. That rotomer B exerts a magnetic anisotropic effect is not surprising, since the methyl group is directed toward the benzylic protons.

It should be stressed, however, that the "Three-Axial Alkyl Effect" is valid for stereochemical determinations because the cis isomer, B, has a much larger $\Delta\nu$ (21.0 Hz) than the trans isomer, 8a, (11.9 Hz). Thus, this technique is
still quite effective as a stereochemical probe.

The N-benzyl methylene protons of both the **cis** and **trans** isomers of 4-amino-1-benzyl-3-methylpiperidine (4 and 4a) are accidentally equivalent. Although this would be predicted for 4a, the singlet for 4 was unexpected. A consideration of the relative stability of the two chair conformers of 4 (4 ax and 4 eq) is necessary to explain these results.

![Image of molecular structures](image)

The 4-axial amino group in 4 eq should introduce an unfavorable steric strain described\(^{19}\) in terms of \(-\Delta G_{\text{NH}_2}^\circ\) of \(\sim 1.1\) kcal/mol. The 3-axial methyl group in 4 ax should also introduce a strain, but although \(-\Delta G_{\text{CH}_3}^\circ\) is given as 1.7 kcal/mol in cyclohexane\(^{19}\), this value should be smaller in this piperidine since one syn axial hydrogen has been replaced by the nitrogen free pair. A specific example of this was shown by Katritsky\(^{20}\), who found that \(-\Delta G_{\text{CH}_3}^\circ\) for a 3-methyl substituent in N-t-butyl-3-methyl-4-piperidone was 0.3 kcal/mol lower than the \(-\Delta G_{\text{CH}_3}^\circ\) for the methyl group in 4-t-butyl-2-methyl cyclohexanone. Using such an approx-
imation in this case, we can estimate that $-\Delta G^\circ$ for $ax$ should be 1.4 kcal/mol. Thus, in the $eq - ax$ equilibrium, $eq$ is favored by 0.3 kcal/mol and should therefore be present in excess to the extent of $\approx62\%$. Obviously, the amount of $ax$ present in the equilibrium is insufficient to cause a measurable magnetic anisotropic effect on the N-benzyl methylene protons.

It is of interest to apply the same analysis for the 4-pyrrolidino derivative, 6. Although the $-\Delta G^\circ$ for a pyrrolidine group is not available, that for a dimethylamino group ($-\Delta G^\circ_{N(CH_3)_2} = 2.1$ kcal/mol) can be used despite the fact that this represents a minimum value.

$$\text{C}_6\text{H}_5\text{CH}_2\text{N}$$

Again assuming that the 3-axial methyl group has a $-\Delta G^\circ_{CH_3} = 1.4$ kcal/mol, the 6 ax isomer is favored at the very least by 0.7 kcal/mol and therefore is present in excess to the extent of $\approx76\%$. Thus, the "Three-Axial Alkyl Effect" would be expected to be, and indeed is, quite large.
EXPERIMENTAL

General

Melting Points. Melting points were determined with a Thomas Hoover Capillary Melting Point Apparatus and were not corrected.

Boiling Points. Boiling points were measured at the pressure indicated in parentheses and are uncorrected.

Elemental Analyses. Elemental analyses were determined at the University of New Hampshire with an F and M Model 185 carbon, hydrogen, and nitrogen analyzer. Ms. Deanna Cardin performed the analyses for which the author expresses appreciation.

Infrared Spectra. Infrared spectra were recorded on a Perkin-Elmer Infracord Spectrophotometer and were calibrated with polystyrene at 1601.4 cm$^{-1}$. Samples were recorded as neat films between sodium chloride plates.

Nuclear Magnetic Resonance Spectra. All nuclear magnetic resonance spectra were recorded on a JEOL Model MH-100 spectrometer and chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (TMS) as an internal standard.
**Ethyl N-Benzoyl-4-piperidone-3-carboxylate (9).** A mixture of 60.5 g (0.50 m) of benzamide and 1.0 L of dry toluene was stirred in a three necked 2 L round-bottom flask fitted with a condenser and overhead stirrer. To this was added the sodium hydride remaining after washing 21.0 g (0.50 m) of a 57% sodium hydride-paraffin oil dispersion with pentane. The mixture was heated under nitrogen at reflux for 1 hr. The mixture was cooled, and ethyl acrylate (150 g, 1.5 m) was added all at once. The flask was fitted with a 20 cm Vigereux column and distillation head. The mixture was slowly heated until ethanol distilled out (2-3 hr). After all the ethanol had been removed and the temperature had risen to 95°, heating was halted and the mixture was allowed to cool to room temperature. The mixture was treated with 750 ml of water, enough to dissolve the solid which had precipitated. The aqueous layer was separated and the organic phase was washed with 100 ml of water. The combined aqueous layers were acidified to pH 3 with 6N hydrochloric acid. The acidified mixture was extracted with chloroform (3 x 100 ml) and the combined chloroform extracts were washed with salt water, dried (Na$_2$SO$_4$), filtered, and evaporated to give 83.0 g (60.4%) of substantially pure 9 as the reported red syrup. After drying under reduced pressure, this material was sufficiently pure for use in subsequent reactions.
Ethyl N-Benzoyl-3-methyl-4-piperidone-3-carboxylate (10). A mixture of 87.5 g (0.32 m) of ethyl N-benzoyl-4-piperidone-3-carboxylate (9) 13.3 g (0.32 m) of a 57% sodium hydride-paraffin oil dispersion, and 400 ml of dry 1,2-dimethoxyethane was placed in a three necked 1 liter round-bottom flask fitted with a condenser and overhead stirred. The mixture was heated under reflux for 2 hr under nitrogen. The mixture was cooled to 5° and to it was added 113.4 g (0.80 m) of methyl iodide. The mixture was again heated under reflux for 40 hr. The cooled mixture was treated with 300 ml of water and was extracted three times with a total of 300 ml of chloroform. The combined chloroform extracts were washed successively with 100 ml portions of 5% NaOH, 5% HCl, and saturated salt solution and then were dried (Na₂SO₄) filtered, and evaporated leaving 78.5 g (85%) of 10 as the reported dark yellow oil. This material was used without further purification.

N-Benzoyl-3-methyl-4-piperidone (12). A mixture of 60.0 g (0.21 m) of ethyl N-benzoyl-3-methyl-4-piperidone-3-carboxylate (10), and 350 ml of 6N hydrochloric acid was heated under reflux in a 1 l round-bottom flask for 2 hr. The mixture was cooled to 5° and then filtered to remove the benzoic acid which precipitated. The filtrate was washed four times with 100 ml portions of ether to remove any additional amounts of benzoic acid. The aqueous phase was evaporated, and the viscous red residue was dissolved in 100 ml of distilled water. The mixture was made basic with
10% NaOH, and 29.5 g (0.21 m) of benzoyl chloride was added slowly maintaining the basic condition. After the addition was completed, the mixture was extracted three times with a total of 300 ml of chloroform. The combined chloroform layers were washed successively with 100 ml portions of 5% NaOH, 5% HCl, and saturated salt solution, and then were dried (Na₂SO₄), filtered, and evaporated leaving a brown oil. This material could be purified by distillation (bp 188°, 1.7 mm of Hg); however, the yields were low due to extensive decomposition. For this reason, column chromatography was the method of choice for purification. The oil was placed on a basic alumina column (25 x 5 cm) and eluted with chloroform. The product eluted rapidly and 20.1 g (44%) of 12 was obtained as a colorless oil.

This material was analyzed as the oxime, mp 154-156°, prepared by the method of Shriner, Fuson, and Curtin.¹⁸ Recrystallized from aqueous ethanol, the oxime had a mp of 154-155°.

**Anal.** Calcd for C₁₃H₁₆N₂O₂: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.19; H, 6.80; N, 11.98

**Ethyl N-Benzoyl-3-ethyl-4-piperidone-3-carboxylate** (11). A mixture of 93.2 g (0.34 m) of ethyl N-benzoyl-4-piperidone-3-carboxylate (9), 14.3 g (0.34 m) of a 57% sodium hydride-paraffin oil dispersion, and 375 ml of dry 1,2-dimethoxyethane was placed in a three necked 1 liter round-bottom flask fitted with an overhead stirrer and a condenser.
The mixture was heated under reflux for 2 hr under nitrogen. The mixture was cooled to 5° and to it was added 156 g (1.0 m) of ethyl iodide. The mixture was again heated under reflux for 40 hr. The cooled mixture was treated with 300 ml of water and was extracted three times with a total of 300 ml of chloroform. The combined chloroform extracts were washed successively with 100 ml portions of 5% NaOH, 5% HCl, and saturated salt solution. The extracts were dried (Na₂SO₄), filtered, and evaporated leaving 68.5 g (67%) of 11 as a light brown oil. This was used without further purification.

N-Benzoyl-3-ethyl-4-piperidone (13). A mixture of 68.5 g (0.226 m) of ethyl N-benzoyl-3-ethyl-4-piperidone-3-carboxylate (11), and 250 ml of 6N hydrochloric acid was heated under reflux in a 1 l round-bottom flask for 2 hr. The mixture was cooled to 5°, then filtered to remove the benzoic acid which precipitated. The filtrate was washed four times with 100 ml portions of ether to remove any additional amounts of benzoic acid. The aqueous phase was evaporated, and the viscous red residue was dissolved in 100 ml of distilled water. The mixture was made basic with 10% NaOH, and 31.8 g (0.226 m) of benzoyl chloride was added slowly while keeping the mixture basic. After the addition was completed, the mixture was stirred vigorously at room temperature for 3 hr. The mixture was extracted three times with a total of 300 ml of chloroform. The combined chloroform layers were washed successively with 100 ml portions of 5% NaOH, 5% HCl, and saturated salt solution. The organic
layer was dried (Na$_2$SO$_4$), filtered, and evaporated leaving a red oil. This material was purified by placing it on a basic alumina column (30 x 5 cm) and using chloroform as eluent. The product was isolated as 18.1 g (35%) of cis as a colorless oil. This material was analyzed as the 2,4-dinitrophenyl-hydrazine derivative (mp 197-198°) which was prepared by the method of Shriner, Fuson, and Curtin.$^{18}$

**Anal.** Calcd for $C_{20}H_{21}N_5O_5$: C, 58.39; H, 5.15; N, 17.02. Found: C, 57.95; H, 5.15; N, 16.89.

**cis-1-Benzyl-3-methyl-4-(N-pyrrolidino)-piperidine** (6). A mixture of 2.17 g (10.0 mmol) of N-benzoyl-3-methyl-4-piperidone (10), 0.1 g of p-toluenesulfonic acid, 2.84 g (40.0 mmol) of pyrrolidine and 40 ml of benzene was placed in a 100 ml round-bottom flask. The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 2.7 g (100%) of a viscous orange oil. This was dissolved in 100 ml of 1,2-dimethoxyethane and to this solution was added 1.9 g (10.0 mmol) of p-toluenesulfonic acid, and 270 mg of platinum oxide. This mixture was hydrogenated at ambient temperature and low pressure (3 atm) for 1 hr. The reaction was stopped and the catalyst was removed by filtration. Evaporation of the filtrate afforded a colorless oil which was dissolved in 50 ml of 10% hydrochloric acid. The acidic solution was washed twice with 25 ml portions of chloroform, and then was made basic with 10% NaOH. The aqueous solution was extracted three times with a total of 45 ml of chloroform. The combined chloroform layers were
dried over K$_2$CO$_3$, filtered, and evaporated leaving 1.35 g (50%) of a foul smelling liquid. The material was dissolved in 40 ml of anhydrous ether and to this was added 275 mg (7.5 mmol) of lithium aluminum hydride. The mixture was heated under reflux for 10 hr. After cooling, 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted, dried over K$_2$CO$_3$, and filtered. Gaseous hydrogen chloride was bubbled into the filtrate. The hydrochloride which precipitated was separated by filtration and dissolved in 50 ml of H$_2$O. The aqueous solution was washed with chloroform then made basic with 10% NaOH and extracted three times with 15 ml portions of chloroform. The combined chloroform extracts were dried (K$_2$CO$_3$), filtered, and evaporated, leaving 0.8 g (62%) of 6 as a colorless liquid. This material was purified by chromatography over a basic alumina column (21 x 1.5 cm) using chloroform as the eluent. The nmr spectrum of this material appears in the appendix.

**Anal. Calcd for C$_{17}$H$_{26}$N$_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 79.25; H, 10.54; N, 10.96.**

**cis-4-α-Amylamino-1-benzyl-3-methylpiperidine (5).**
A mixture of 2.17 g (10.0 mmol) of N-benzoyl-3-methyl-4-piperidone (12), 8.7 g (0.10 m) of n-amyamine, 0.1 g of p-toluenesulfonic acid, and 40 ml of benzene was placed in a 100 ml round-bottom flask. The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 2.9 g (100%) of a viscous oil, which was dissolved in 150 ml
of 1,2-dimethoxyethane. After adding 1.9 g (10.0 mmol) of p-toluenesulfonic acid, the mixture was hydrogenated over 280 mg of platinum oxide at ambient temperature and low pressure (3 atm) for 10 hr. The reaction was stopped and 50 ml of water was added to dissolve the precipitated salt. The mixture was filtered to remove the catalyst, and the filtrate was acidified with 50 ml of 3N hydrochloric acid, then washed with chloroform. The mixture was made basic with 10% NaOH, then extracted three times with a total of 75 ml of chloroform. The combined chloroform extracts were dried (Na₂SO₄), filtered, and evaporated leaving 1.4 g (50%) of a foul smelling oil. This was dissolved in 50 ml of anhydrous ether and 275 mg of lithium aluminum hydride was slowly added. The mixture was heated under reflux for 12 hr. After cooling, 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted, dried (Na₂SO₄), and filtered. Gaseous hydrogen chloride was bubbled into the filtrate, and the resulting precipitate was removed by filtrate, and dissolved in 40 ml of H₂O. This was made basic with 10% NaOH, and extracted three times with a total of 45 ml of chloroform layers were dried (Na₂SO₄), filtered, and evaporated leaving 0.7 g of 5 as a colorless oil. This oil was purified on a basic alumina column (21 x 1.5 cm) with chloroform as eluent. The nmr spectrum of this compound appears in the appendix.
cis-1-Benzyl-3-ethyl-4-(N-pyrrolidino)-piperidine

(8). A mixture of 2.31 g (20.0 mol) of N-benzoyl-3-ethyl-4-piperidone (13), 0.1 g of p-toluenesulfonic acid, 2.84 g (40.0 mmol) of pyrrolidine, and 40 ml of benzene was placed in a 100 ml round-bottom flask. The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 2.9 g (100%) of a yellow oil. This was dissolved in 100 ml of 1,2-dimethoxyethane and to this solution was added 1.9 g (10.0 mmol) of p-toluenesulfonic acid. The mixture was hydrogenated over 280 mg of platinum oxide at ambient temperature and low pressure (3 atm) for 8 hr. The reaction was stopped and the catalyst was removed by filtration. Evaporation of the filtrate afforded an oil which was dissolved in 50 ml of 10% hydrochloric acid. The aqueous solution was washed with chloroform and then made basic with 10% NaOH. The mixture was extracted three times with a total of 45 ml of chloroform. The combined chloroform extracts were dried (Na₂SO₄), filtered, and evaporated leaving 1.4 g (50%) of an oil. This was dissolved in 50 ml of anhydrous ether, and, after 270 mg (7 mmol) of lithium aluminum hydride was added, the mixture was heated under reflux for 10 hr. The mixture was cooled with an ice bath and 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted,
dried \( \text{(Na}_2\text{SO}_4) \) and filtered. Gaseous hydrogen chloride was bubbled into the filtrate. The hydrochloride which precipitated was separated by filtration and dissolved in 50 ml of \( \text{H}_2\text{O} \). The aqueous solution was washed with chloroform, then made basic with 10% NaOH and extracted three times with a total of 45 ml of chloroform. The combined chloroform extracts were dried \( \text{(Na}_2\text{SO}_4) \), filtered, and evaporated, leaving 1.2 g (82%) of \( 8 \) as a colorless oil. The product was purified by chromatography over a basic alumina column (23 x 1.5 cm) using chloroform as the eluent. The nmr spectrum of this material appears in the appendix.

**Anal.** Calcd for \( \text{C}_{18}\text{H}_{28}\text{N}_2 \): C, 79.36; H, 10.36; N, 10.28. Found: C, 79.54; H, 10.33; N, 10.29.

**cis-4-n-Amylamino-1-benzyl-3-ethylpiperidine (7).**

A mixture of 2.31 g (10.0 mmol) of \( \text{N-benzoyl-3-ethyl-4-piperidone (13)} \), 8.7 g (0.10 m) of \( \text{n-amylamine, 0.1 g of p-toluenesulfonic acid, and 40 ml of benzene was placed in a 100 ml round-bottom flask. The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 3.0 g (100%) of a dark yellow oil, which was dissolved in 150 ml of 1,2-dimethoxyethane. After adding 1.9 g (10.0 mmol) of \( \text{p-toluenesulfonic acid, the mixture was hydrogenated over 280 mg of platinum oxide at ambient temperature and low pressure (3 atm) for 10 hr. The reaction was stopped and 75 ml of water was added to dissolve the precipitated salt. The mixture was filtered to remove the catalyst and the**
The filtrate was made basic with solid potassium carbonate. The aqueous solution was extracted three times with a total of 75 ml of chloroform. The combined chloroform layers were extracted three times with 1% aqueous hydrochloric acid (15 ml portions). The combined acid extracts were made basic with 10% NaOH, and extracted three times with a total of 45 ml of chloroform. The combined chloroform extracts were dried (Na$_2$SO$_4$), filtered, and evaporated leaving 1.7 g (57%) of an oil. This was dissolved in 40 ml of anhydrous ether and to this was slowly added 300 mg (7.5 mmol) of lithium aluminum hydride. This mixture was heated under reflux for 10 hr. The mixture was cooled and 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted, dried (Na$_2$SO$_4$), and filtered. Gaseous hydrogen chloride was bubbled into the filtrate; and the resulting precipitate was separated by filtration and dissolved in 40 ml of water. This solution was made basic with 10% NaOH and extracted three times with a total of 45 ml of chloroform. The combined chloroform layers were dried (Na$_2$SO$_4$), filtered, and evaporated leaving 0.7 g of 7 as a colorless oil. This material was purified by conversion to the dihydrochloride and recrystallizing the salt from ethanol-ether. Subsequent conversion of the salt back to the amine afforded analytically pure 7. The nmr spectrum of 7 appears in the appendix.

**Anal.** Calcd for C$_{19}$H$_{32}$N$_2$: C, 79.11; H, 11.18; N, 9.71. Found: C, 78.93; H, 11.05; N, 9.52.
N-Benzoyl-3-methyl-4-piperidone Oxime (14).  Hydroxyamine hydrochloride (10.0 g, 0.14 m) was dissolved in 20 ml of water, and a solution of 6.0 g of sodium hydroxide in 20 ml of water was added. N-Benzoyl-3-methyl-4-piperidone (12; 3.9 g, 0.18 m) was added dropwise to the stopped mixture. A small amount of methanol (8 ml) was added to promote homogeneity. The mixture was allowed to stir for 7 hr. The resulting precipitate was separated by filtration and allowed to dry giving 2.9 g of 14, mp 126-132°. Recrystallization of this compound from 40% ethanol-water afforded 2.1 g (51%) of 14 as a white crystalline solid, mp 149-152° (analytically pure 14 melts at 154-155°). This compound was sufficiently pure for use in subsequent reactions.

Reduction of N-Benzoyl-3-methyl-4-piperidone Oxime (14) with Lithium Aluminum Hydride (LAH).  A mixture of 1.10 g (27 mmol) of LAH and 50 ml of anhydrous ether was placed in a 100 ml round-bottom flask and cooled to 5° with an ice bath. To this was slowly added 2.0 g (8.6 mmol) of N-benzoyl-3-methyl-4-piperidone oxime (14), and after the addition was completed, the mixture was heated under reflux for 8 hr. To the cooled mixture 10% NaOH was added dropwise until all of the LAH had undergone reaction. The ether solution was decanted, dried (Na₂SO₄), filtered, and evaporated leaving 1.4 g (80%) of a colorless liquid, bp 83° at 0.3 mm of Hg. The nmr spectrum of this material indicated that it was a 50-50 mixture of the cis and trans isomers of 4-amino-1-benzyl-3-methyl piperidine (4 and 4a)
as shown by the appearance of two doublets at 0.89 ppm and 0.85 ppm for the methyl protons. The presence of two isomers was confirmed by tlc. The material was converted to dihydrochloride, mp 287-289°, for elemental analysis.

**Anal. Calcd for C_{13}H_{22}Cl_{2}N_{2}:**  C, 56.32; H, 8.00; N, 10.11. **Found:**  C, 56.47; H, 8.02; N, 10.07.

**Catalytic Reduction of N-Benzoyl-3-methyl-4-piperidone (14) Followed by Reduction with LAH.** A mixture of 4.5 g (19 mmol) of 14, 75 ml of absolute ethanol and 3.0 g (25 mmol) of chloroform was hydrogenated over 100 mg of platinum oxide at ambient temperature and low pressure (3 atm) for 18 hr, according to the method of Secrist and Logue. The reaction was stopped and the catalyst was removed by filtration. Evaporation of the filtrate afforded a glass-like solid. This was partitioned between 150 ml of water and 30 ml of ether. The ether layer was separated and the aqueous phase was washed twice more with 30 ml portions of ether. Evaporation of the combined ether layers afforded 1.3 g of unreacted oxime. The aqueous solution was made basic with potassium carbonate, then extracted five times with a total of 100 ml of chloroform. The combined chloroform extracts were dried over Na_{2}SO_{4}, filtered, and evaporated leaving 2.5 g (61% yield, 88% conversion) of a viscous oil. This oil was dissolved in 40 ml of anhydrous ether and 570 mg (15 mmol) of LAH was slowly added. The mixture was heated under reflux for 12 hr. The mixture was
cooled with an ice bath and 10% NaOH was added dropwise until all the LAH had reacted. The ether solution was de­
canted, dried (\(\text{Na}_2\text{SO}_4\)), filtered, and evaporated leaving 1.7 g (77%) of a light yellow liquid. This was purified by chromatography over a basic alumina column (23 x 2.5 cm) using a 10% methanol-chloroform solution as eluent. Unfortu­
nately, only 0.9 g of product could be collected from the column. Apparently, the remainder of the material remained bound to the alumina. The material which was recovered was shown by spectral data to be a mixture of the cis and trans isomers of 4-amino-1-benzyl-3-methylpiperidine (4 and 4a). Furthermore, this material was converted to the dihydro­
chloride which had the same melting point (287-289°) as previous mixtures of 4 and 4a.

Conversion of N-Benzoyl-3-methyl-4-piperidone (12) to 4 + 4a Using Borch's Reagent. A mixture of 2.17 g (10.0 mmol) of (12), 7.7 g (0.10 m) of ammonium acetate, 0.45 g (7.0 mmol) of sodium cyanoborohydride, and dry methanol was placed in a 125 ml Erlenmeyer and allowed to stir at room temperature for 62 hr. The mixture was acidi­
ified with concentrated hydrochloric acid, then concentrated to 10 ml. Distilled water (50 ml) was added and the mixture was washed three times with a total of 60 ml of ether. The aqueous solution was made basic with solid potassium hydroxide, and was extracted three times with a total of 75 ml of chloroform. The combined chloroform extracts were
dried (Na₂SO₄), filtered, and evaporated leaving 1.5 g of a colorless oil. The ir spectrum of this material showed the presence of NH₂ (3350 cm⁻¹) and no keto group. However, nmr and tlc showed the presence of two isomers. An attempt was made to separate the isomers by chromatography. Unfortunately, separation was not achieved and the chromatography resulted in the isolation of 1.0 g (45%) of this mixture. The material was dissolved in 50 ml of anhydrous ether and 190 mg of lithium aluminum hydride was slowly added. The mixture was heated under reflux for 10 hr, and after cooling with an ice bath, 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted, dried (Na₂SO₄), filtered, and evaporated leaving 0.51 g (54%) of a liquid, whose nmr spectrum was identical with those previously obtained for 50-50 mixtures of cis and trans 4-amino-1-benzyl-3-methylpiperidine (4 and 4a).

Conversion of a Mixture of 4 and 4a into a Mixture cis and trans-1-Benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6 and 6a). A solution of 1.0 g (5.0 mmol) of a 50-50 mixture of 4 and 4a (prepared by the reduction of N-benzoyl-3-methyl-4-piperidone oxime with LAH), 0.5 g (5.0 mmol) of succinic anhydride, 5 drops of triethylamine, and 25 ml of toluene was heated under reflux for 3.5 hr. The solution was evaporated and the oil residue was heated at 170° for 1 hr. During this time, bubbling of the oil was noted.
The material was allowed to cool, and after addition of 25 ml of water, the mixture was extracted three times with a total of 45 ml of ether. The combined ether extracts were dried (K₂CO₃), filtered, and evaporated leaving 0.6 g (43%) of a light red oil. The ir spectrum of this material indicated that the product was indeed an imide (1760 and 1700 cm⁻¹). This material was dissolved in 30 ml of anhydrous ether, and after slowly adding 190 mg of lithium aluminum hydride, was heated under reflux for 10 hr. After cooling with an ice bath, 10% NaOH was added dropwise until the excess lithium aluminum hydride had reacted. The ether solution was decanted, dried (Na₂SO₄), filtered, and evaporated leaving 0.5 g (100%) of a colorless liquid. The ir spectrum indicated that all the carbonyl groups had been reduced and tlc showed the presence of two isomers. This was confirmed by the nmr spectrum which showed that the product was a 50-50 mixture of cis-1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6; methyl doublet at 1.12 ppm, AB quartet for the benzyl protons), and trans-1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6a; methyl doublet at 0.94 ppm, a singlet at 3.46 ppm for the benzyl protons).

Reduction of the Enamine of N-Benzoyl-3-methyl-4-piperidone (12) with Formic Acid Followed by Reduction with LAH. A mixture of 2.17 g (10.0 mmol) of 12, 0.1 g of p-toluenesulfonic acid, 2.84 g (40.0 mmol) of pyrrolidine and 40 ml of benzene was placed in a 100 ml round-bottom flask.
The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 2.9 g (100%) of a yellow oil. This oil was treated with 0.60 g (11.0 mmol) of formic acid (88%), and this mixture was heated neat at 60-70° for 2 hr. The mixture was cooled and dissolved in 30 ml of 3N hydrochloric acid. The acid solution was washed with ether, then made basic with 10% NaOH. The aqueous solution was extracted three times with 25 ml portions of ether. The combined ether extracts were dried (K₂CO₃), filtered, and evaporated leaving 2.0 g (74%) of a light red oil. This was dissolved in 50 ml of dry ether and 380 mg (10.0 mmol) of LAH was added. The mixture was heated under reflux for 12 hr. To the cooled mixture was added 10% NaOH dropwise until all the excess LAH had reacted. The ether solution was filtered, then dried over Na₂SO₄, filtered, and evaporated leaving 1.6 g, (84%) of a liquid. The nmr spectrum of this material indicated that it was almost entirely cis 1-benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6).

Reduction of the Enamine of N-Benzoyl-3-ethyl-4-piperidone (13) with Formic Acid Followed by Reduction with LAH. A mixture of 1.2 g (5.0 mmol) of 13, 0.1 g of p-toluenesulfonic acid, 1.5 g (21 mmol) of pyrrolidine and 35 ml of benzene was placed in a 100 ml round-bottom flask. The flask was fitted with a Dean-Stark trap and condenser, and the mixture was heated under reflux for 2 hr. Evaporation of the solvent afforded 1.4 g (100%) of a yellow oil. This
oil was treated with 0.30 g (5.5 mmol) of 88% formic acid and this mixture was heated neat at 60-70° for 12 hr. The mixture was cooled and dissolved in 30 ml of 6N hydrochloric acid. The acid solution was washed with ether, then made basic with 10% NaOH. The aqueous solution was extracted four times with a total of 40 ml of chloroform. The combined chloroform extracts were dried (Na$_2$SO$_4$), filtered, and evaporated leaving 1.3 g of an oil. This oil was dissolved in 35 ml of anhydrous ether and 250 mg of LAH was slowly added. The mixture was heated under reflux for 8 hr. After cooling, 10% NaOH was added dropwise until all the excess LAH had reacted. The ether solution was filtered, dried over Na$_2$SO$_4$, filtered and evaporated leaving 1.0 g (77%) of a liquid. The nmr spectrum of this material (see appendix) showed it to be a mixture of cis- and trans-1-benzyl-3-ethyl-4-(N-pyrrolidino)-piperidine (8 and 8a).
SUMMARY

The "Three-Axial Alkyl Effect" has been shown to be valid for a series of cis- and trans-3-alkyl-4-alkylamino-1-benzylpiperidines. Thus, non-equivalence of the benzyl protons is observed for a three-axial substituent. Non-equivalence is also observed for a three-equatorial substituent provided that a pseudo-axial rotomeric form can be assumed. The non-equivalent N-benzyl protons for conformers possessing a three-axial substituent have a larger $\Delta \nu$ value compared to those conformers possessing a pseudo-axial substituent.
REFERENCES


PART II

APPENDIX
cis-4-Amylaminol-benzyl-3-methylpiperidine (5).
A-2. cis-1-Benzyl-3-methyl-4-(N-pyrrolidino)-piperidine (6).
A-3. *cis*-4-Amylamino-1-benzyl-3-ethylpiperidine (7).
A-4. cis-1-Benzyl-3-ethyl-4-(N-pyrroldino)-piperidine (8).
A-5. cis and trans-4-Amino-1-benzyl-3-methylpiperidine (4 and 4a).
A-6, cis and trans-1-Benzyl-3-ethyl-4-(N-pyrrolidino)-piperidine (8 and 8a).
BIOGRAPHICAL DATA

NMAE: John Lawrence LaMattina

DATE OF BIRTH: January 22, 1950

PLACE OF BIRTH: Brooklyn, New York

SECONDARY EDUCATION: Brooklyn Preparatory School
Brooklyn, New York

COLLEGIATE EDUCATION:

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HONORS: Boston College Scholarship, 1967-1971
B.S. Cum Laude, 1971
UNH Summer Fellowship, 1972, 1973, 1974

PUBLICATIONS: