THE STUDY OF THE MANNICH CONDENSATION OF COMPOUNDS CONTAINING THE ACIDIC –NH– GROUP

Caurino Cesar Bombardieri
THE STUDY OF THE MANNICH CONDENSATION OF COMPOUNDS CONTAINING THE ACIDIC -NH GROUP

A Thesis

by

Caurino Cesar Bombardieri, M.Sc. (Alberta)

Submitted to the Faculty of Graduate Studies and Research of McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

McGill University, Montreal, Canada. September, 1954
ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks and appreciation to Dr. Alfred Taurins for guidance, encouragement and general interest during the course of this investigation.

Grateful acknowledgement is made to the National Research Council of Canada for a summer grant (1953) and for a Studentship (1953-54); and to the Department of Veterans' Affairs for assistance during the past seven years.
TABLE OF CONTENTS

GENERAL INTRODUCTION

HISTORICAL INTRODUCTION

I. MANNICH CONDENSATION ........................................ 1
   (a) Mechanism .................................................. 1
   (b) Active Hydrogen on Carbon ................................. 5
   (c) Active Hydrogen on Nitrogen .............................. 23
   (d) The Rôle of Mannich Condensation in the
        Biogenesis of Alkaloids ................................. 26

II. SUBSTITUTION REACTIONS OF THE -NH- GROUP IN
    IMINES AND IMIDES .......................................... 29
    Succinimide and Phthalimide ................................. 30
    Hydantoin and Substituted Hydantoin ....................... 31
    Uracil and Hydouracil ....................................... 32
    Carbazole .................................................... 33
    2-Pyrrolidone ................................................ 34
    2,4-Thiazolidinedione ....................................... 35
    AlkylNitramines .............................................. 36

III. ULTRAVIOLET ABSORPTION SPECTRA OF ALKYLNITR-
     AMINES .......................................................... 36

DISCUSSION OF RESULTS ............................................ 38

1. General Method and Conditions of Mannich
   Reactions ...................................................... 42
2. Condensation of 2-Pyrrolidone with Formaldehyde
   and Secondary Amines ....................................... 43
   (a) Reaction with Morpholine ................................. 43
   (b) Reaction with Piperidine ................................ 44
   (c) Reaction with Dimethylamine Hydrochloride .......... 44
3. Condensation of Hydantoin with Formaldehyde
   and Morpholine .............................................. 45
4. Condensation of 5,5-Dimethylhydantoin with
   Formaldehyde and Morpholine .............................. 47
5. Condensation of 2,4-Thiazolidinedione with
   Formaldehyde and Secondary Amines ....................... 49
   (a) Reaction with Piperidine ................................ 49
   (b) Reaction with Morpholine ............................... 50
   (c) Reaction with Dimethylamine ........................... 50
   (d) Reaction with Methylamine ............................. 51
TABLE OF CONTENTS (cont'd.)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6.</td>
<td>Condensation of Uracil with Formaldehyde and Morpholine</td>
<td>52</td>
</tr>
<tr>
<td>7.</td>
<td>Attempted Condensation of Hydouracil with Formaldehyde and Secondary Amines</td>
<td>54</td>
</tr>
<tr>
<td>8.</td>
<td>Condensation of Succinimide with Formaldehyde and Morpholine</td>
<td>55</td>
</tr>
<tr>
<td>9.</td>
<td>Condensation of Phthalimide with Formaldehyde and Morpholine</td>
<td>57</td>
</tr>
<tr>
<td>10.</td>
<td>Attempted Condensation of 1,8-Naphthalimide with Formaldehyde and Secondary Amines</td>
<td>57</td>
</tr>
<tr>
<td>11.</td>
<td>Condensation of Carbazole with Formaldehyde and Piperidine</td>
<td>58</td>
</tr>
<tr>
<td>12.</td>
<td>Condensation of Alkynitramines with Formaldehyde and Secondary Amines</td>
<td>60</td>
</tr>
<tr>
<td>13.</td>
<td>Condensation of n-Butynitramine with Formaldehyde and Secondary Amines</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>(a) Reaction with Piperidine</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>(b) Reaction with Morpholine</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>(c) Reaction with Diethylamine</td>
<td>63</td>
</tr>
<tr>
<td>14.</td>
<td>Condensation of Ethynitramine with Formaldehyde and Secondary Amines</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>(a) Reaction with Piperidine</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>(b) Reaction with Morpholine</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>(c) Reaction with Dimethylamine</td>
<td>65</td>
</tr>
<tr>
<td>15.</td>
<td>Attempted Condensation of Methylnitramine with Formaldehyde and Secondary Amines</td>
<td>65</td>
</tr>
<tr>
<td>16.</td>
<td>Colour Test of the Alkynitramines</td>
<td>65</td>
</tr>
<tr>
<td>17.</td>
<td>Ultraviolet Absorption Spectra of Alkynitramines and their Mannich Products</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>EXPERIMENTAL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Starting Materials</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Picrates of the Mannich Bases</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Methyl Iodide Derivatives</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Analyses</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Ultraviolet Absorption Spectra Determinations</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>The Preparation of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydantoin</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>5,5-Dimethylhydantoin</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>1,8-Naphthalimide</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Uracil</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Hydouracil</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Methyl-, Ethyl- and n-Butynitramines</td>
<td>75</td>
</tr>
</tbody>
</table>
### TABLE OF CONTENTS (cont'd.)

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannich Condensations</td>
<td>79</td>
</tr>
<tr>
<td>1. Reactions of 2-pyrrolidone</td>
<td>79</td>
</tr>
<tr>
<td>1-(Morpholinomethyl)-2-pyrrolidone</td>
<td>79</td>
</tr>
<tr>
<td>1-(Piperidinomethyl)-2-pyrrolidone</td>
<td>80</td>
</tr>
<tr>
<td>1-(Dimethylaminomethyl)-2-pyrrolidone</td>
<td>81</td>
</tr>
<tr>
<td>Attempted Condensation of 2-Pyrrolidone with Formaldehyde and Pyrrolidine</td>
<td>81</td>
</tr>
<tr>
<td>2. Reactions of Hydantoin</td>
<td>82</td>
</tr>
<tr>
<td>1,3-Di(morpholinomethyl)hydantoin</td>
<td>82</td>
</tr>
<tr>
<td>Acid Hydrolysis of 1,3-Di(morpholinomethyl)-hydantoin</td>
<td>83</td>
</tr>
<tr>
<td>Attempted Condensations of Hydantoin with Formaldehyde and the following Secondary Amines:</td>
<td></td>
</tr>
<tr>
<td>(a) Diethylamine</td>
<td>83</td>
</tr>
<tr>
<td>(b) Di-n-butylamine</td>
<td>84</td>
</tr>
<tr>
<td>(c) Piperidine</td>
<td>84</td>
</tr>
<tr>
<td>3. Reactions of 5,5-Dimethylhydantoin</td>
<td>84</td>
</tr>
<tr>
<td>1,3-Di(morpholinomethyl)-5,5-dimethylhydantoin</td>
<td>84</td>
</tr>
<tr>
<td>Attempted Condensations of 5,5-Dimethylhydantoin with Formaldehyde and the following Secondary Amines:</td>
<td></td>
</tr>
<tr>
<td>(a) Diethylamine</td>
<td>85</td>
</tr>
<tr>
<td>(b) Piperidine</td>
<td>85</td>
</tr>
<tr>
<td>(c) Dimethylamine Hydrochloride</td>
<td>86</td>
</tr>
<tr>
<td>4. Reactions of 2,4-Thiazolidinedione</td>
<td>86</td>
</tr>
<tr>
<td>3-(Piperidinomethyl)-2,4-thiazolidinedione</td>
<td>86</td>
</tr>
<tr>
<td>3-(Morpholinomethyl)-2,4-thiazolidinedione</td>
<td>87</td>
</tr>
<tr>
<td>3-(Dimethylaminomethyl)-2,4-thiazolidinedione</td>
<td>88</td>
</tr>
<tr>
<td>N-Methyl-N,N-bis(2,4-thiazolidinedione)amile</td>
<td>88</td>
</tr>
<tr>
<td>5. Reactions of Uracil</td>
<td>89</td>
</tr>
<tr>
<td>3-(Morpholinomethyl)uracil</td>
<td>89</td>
</tr>
<tr>
<td>Attempted Condensation of Uracil with Formaldehyde and Piperidine</td>
<td>90</td>
</tr>
<tr>
<td>6. Reactions of Hydouracil</td>
<td>90</td>
</tr>
<tr>
<td>Attempted Condensations of Hydouracil with Formaldehyde and the following Secondary Amines:</td>
<td></td>
</tr>
<tr>
<td>(a) Morpholine</td>
<td>90</td>
</tr>
<tr>
<td>(b) Piperidine</td>
<td>91</td>
</tr>
<tr>
<td>7. Reactions of Succinimide</td>
<td>91</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)succinimide</td>
<td>91</td>
</tr>
<tr>
<td>Attempted Condensation of Succinimide with Formaldehyde and Pyrrolidine</td>
<td>92</td>
</tr>
<tr>
<td>8. Reactions of Phthalimide</td>
<td>92</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)phthalimide</td>
<td>92</td>
</tr>
<tr>
<td>TABLE OF CONTENTS (cont'd.)</td>
<td>page</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Acid Hydrolysis of N-(Morpholino-methyl)phthalimide</td>
<td>93</td>
</tr>
<tr>
<td>Attempted Condensation of Phthalimide with Formaldehyde and Diethylamine</td>
<td>93</td>
</tr>
<tr>
<td><strong>9. Reactions of 1,8-Naphthalimide</strong></td>
<td>94</td>
</tr>
<tr>
<td>Attempted Condensations of 1,8-Naphthalimide with Formaldehyde and the following Secondary Amines:</td>
<td>94</td>
</tr>
<tr>
<td>(a) Morpholine</td>
<td>94</td>
</tr>
<tr>
<td>(b) Piperidine</td>
<td>94</td>
</tr>
<tr>
<td><strong>10. Reactions of Carbazole</strong></td>
<td>94</td>
</tr>
<tr>
<td>N-(Piperidinomethyl)carbazole</td>
<td>94</td>
</tr>
<tr>
<td>Attempted Condensations of Carbazole with Formaldehyde and the following Secondary Amines:</td>
<td>95</td>
</tr>
<tr>
<td>(a) Morpholine</td>
<td>95</td>
</tr>
<tr>
<td>(b) Dimethylamine</td>
<td>96</td>
</tr>
<tr>
<td>(c) Dimethylamine Hydrochloride</td>
<td>96</td>
</tr>
<tr>
<td><strong>11. Reactions of n-Butynitramine</strong></td>
<td>96</td>
</tr>
<tr>
<td>N-(Piperidinomethyl)-n-butylnitramine</td>
<td>96</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)-n-butylnitramine</td>
<td>97</td>
</tr>
<tr>
<td>Attempted Condensation of n-Butynitramine with Formaldehyde and Diethylamine</td>
<td>97</td>
</tr>
<tr>
<td><strong>12. Reactions of Ethylnitramine</strong></td>
<td>98</td>
</tr>
<tr>
<td>N-(Piperidinomethyl)-α-(piperidinomethyl)ethylnitramine</td>
<td>98</td>
</tr>
<tr>
<td>N-Morpholinomethyl)ethylnitramine</td>
<td>98</td>
</tr>
<tr>
<td>Attempted Condensation of Ethylnitramine with Formaldehyde and Diethylamine</td>
<td>99</td>
</tr>
<tr>
<td><strong>13. Attempted Condensations of MethylNitramine with Formaldehyde and Secondary Amines</strong></td>
<td>99</td>
</tr>
<tr>
<td>Colour Test of AlkylNitramines</td>
<td>100</td>
</tr>
<tr>
<td>Ultraviolet Absorption Spectra Determinations</td>
<td>100</td>
</tr>
<tr>
<td><strong>SUMMARY AND CLAIMS TO ORIGINAL RESEARCH</strong></td>
<td>111</td>
</tr>
<tr>
<td><strong>REFERENCES</strong></td>
<td>114</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Molecular Extinction Coefficients of Alkylnitramines</td>
<td>66</td>
</tr>
<tr>
<td>II</td>
<td>Concentrations of Solutions of Alkylnitramines and their Mannich Products</td>
<td>101</td>
</tr>
<tr>
<td>III</td>
<td>The Absorption Spectra Data and the Corresponding Graphs</td>
<td>101</td>
</tr>
<tr>
<td>IV</td>
<td>Ultraviolet Absorption Spectrum of Methylnitramine in Absolute Alcohol</td>
<td>102</td>
</tr>
<tr>
<td>V</td>
<td>Ultraviolet Absorption Spectrum of Ethylnitramine in Absolute Alcohol</td>
<td>104</td>
</tr>
<tr>
<td>VI</td>
<td>Ultraviolet Absorption Spectrum of N-(Morpholinomethyl)ethylnitramine in Absolute Ethanol</td>
<td>106</td>
</tr>
<tr>
<td>VII</td>
<td>Ultraviolet Absorption Spectrum of n-Butylnitramine in Absolute Ethanol</td>
<td>108</td>
</tr>
<tr>
<td>VIII</td>
<td>Ultraviolet Absorption Spectrum of N-(Morpholinomethyl)-n-butylnitramine</td>
<td>109</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>The Course of the Mannich Reaction According to Lieberman and Wagner</td>
<td>3</td>
</tr>
<tr>
<td>2.</td>
<td>Ultraviolet Absorption Spectrum of Methylnitramine</td>
<td>103</td>
</tr>
<tr>
<td>3.</td>
<td>Ultraviolet Absorption Spectrum of Ethyl-nitramine</td>
<td>105</td>
</tr>
<tr>
<td>4.</td>
<td>Ultraviolet Absorption Spectrum of N-(Morpholinomethyl)ethylnitramine</td>
<td>107</td>
</tr>
<tr>
<td>5.</td>
<td>Ultraviolet Absorption Spectra of n-Butynitramine and N-(Morpholinomethyl)-n-butynitramine</td>
<td>110</td>
</tr>
</tbody>
</table>
GENERAL INTRODUCTION

In most studies of the Mannich condensation, compounds containing active hydrogens on carbon were used. Only a few reactions using compounds possessing active hydrogens on nitrogen have been reported in the literature. The objective of this work was to carry out a systematic study of the Mannich condensation of secondary amines and formaldehyde with compounds containing one or two imino groups in which the hydrogens were activated for this type of reaction by the presence of carbonyl groups. In addition to this group of compounds the Mannich reaction of alkynitramines was investigated. The hydrogen of these nitramines was activated by the presence of the adjacent nitro group. This work would mean the extension of the scope of the classical Mannich condensation and give a series of new functional derivatives of the starting materials.

In this study the following substances were investigated: 2-pyrrolidone, hydantoin, 5,5-dimethylhydantoin, uracil, hydouracil, succinimide, phthalimide, 1,8-naphthalimide, 2,4-thiazolidinedione, carbazole and a few alkynitramines.

The ultraviolet absorption spectra of methyl-, ethyl- and n-butynitramines and the Mannich bases of ethyl- and n-butynitramines were determined.
Mannich Condensation

(a) Mechanism

The Mannich reaction involves the condensation of formaldehyde and a primary or secondary amine with a compound possessing one or more active hydrogens. Blicke (1) in 1942 published an extensive review of the literature on the Mannich reaction. A subsequent account of Mannich's own investigations in this field can be found in a paper by Karbe (2). This reaction can be represented by the following equations:

\[
\begin{align*}
Z\text{CH} + \text{HCHO} + \text{HNR}_2 & \rightarrow Z\text{C}^{-\text{C}}-\text{NR}_2 + \text{H}_2\text{O} \\
Z\text{NH} + \text{HCHO} + \text{HNR}_2 & \rightarrow Z\text{N}^{-\text{C}}-\text{NR}_2 + \text{H}_2\text{O}
\end{align*}
\]

(Z is the activating group)

The Mannich reaction occurs with different classes of compounds possessing acidic hydrogen atoms. The characteristic feature of this reaction is its great velocity under mild conditions. According to the current views there is no single mechanism of the Mannich condensation which would be valid for all of the large variety of acidic substances. However, there is an agreement that the initial step of the condensation involves the primary reaction between formaldehyde and amine.
In 1949 a mechanism was suggested for the Mannich reaction by Lieberman and Wagner (3). They believed that a primary condensation occurs between the formaldehyde and amine to form either the dialkylaminomethanol $R-N-CH_2OH$ or the methylene-bis-amine $R-N=CH-N-R'$.

In their study of the kinetics of the reaction of ethylmalonic acid with formaldehyde and dimethylamine, Alexander and Underhill (4) concluded that in this condensation the product of the primary reaction was dialkylaminomethanol whereas Lieberman and Wagner (3) assumed that it was very probable that the first product was methylene-bis-amine. According to their views the following steps are taking place in the further course of the reaction. The primary product accepts a proton either from the acidic substance or from the acid which has been added as a catalyst. In this step either oxonium- or ammonium-cation is formed. These cations lose a molecule of water to form a carbonium cation which reacts further with the carbanion formed from the $\overset{\text{C-H}}{\text{acidic substance}}$ to produce the Mannich base. The scheme for the mechanism as suggested by Lieberman and Wagner (3) is more fully illustrated in Figure 1.
The Course of the Mannich Reaction
According to Liebermann and Wagner (3)

Amine + Formaldehyde → \( \text{-}^+\text{C-H} \) acidic substance

\[ \begin{align*}
R_2\text{NH} + \text{CH}_2\text{O} + Z\text{CH} \quad \text{(dialkylaminomethanol)} \quad \text{(methylene-bis-amine)} \quad \text{(Carbanion)}
\end{align*} \]

\[ \begin{align*}
\text{H}^+ \\
R_2\text{NCH}_2\text{NR}_2 \\
\text{(carbonium ion)}
\end{align*} \]

\[ \text{R}_2\text{NCH}_2\text{OH} \quad \text{(ammonium ion)} \]

or

\[ \begin{align*}
\text{R}_2\text{NCH}_2\text{OH} \quad \text{(oxonium ion)}
\end{align*} \]

\[ \text{R}_2\text{NCH}_2\text{NR}_2 \quad \text{R}_2\text{NH} \]

Mannich base.

Figure 1
Alexander and Underhill (4) suggested the following ionic mechanism which appeared consistent with their kinetic results:

\[
\text{CH}_2\text{O} + (\text{CH}_3)_2\text{NH} \quad \overset{H}{\longrightarrow} \quad (\text{CH}_3)_2\text{NCH}_2\text{OH} \quad (\text{dialkylaminomethanol})
\]

\[
(\text{CH}_3)_2\text{NCH}_2\cdot\text{O} + \text{HA} \quad \overset{H}{\longrightarrow} \quad (\text{CH}_3)_2\text{NCH}_2\cdot\text{O} \quad \cdots \quad \text{HA}
\]

In the same year Dewar (5) postulated that since acid was required as a catalyst, the aminomethanol group was probably first converted into a reactive methyleneammonium salt. This salt condensed either with the ketone itself, or with the enol form of the ketone formed catalytically by the acid present.

\[
R_2\text{NH} + \text{CH}_2\text{O} \quad \overset{H^+}{\longrightarrow} \quad R_2\text{NCH}_2\text{OH} \quad \overset{H^+}{\longrightarrow} \quad R_2\text{N}=\text{CH}_2 \quad (\text{methyleneammonium salt})
\]

\[
R_2\text{N} = \text{CH}_2 + \text{CR}_2\cdot\text{H} \quad \overset{H^+}{\longrightarrow} \quad R_2\text{N} \cdot \text{CH}_2 \cdot \text{CR}_2 \cdot \text{H}^+ \quad \overset{\text{COR}}{\longrightarrow} \quad \text{COR}
\]

\[
R_2\text{N} = \text{CH}_2 + (\text{RC}-\text{O}-\text{H}) \quad \overset{\text{COR}}{\longrightarrow} \quad R_2\text{N} \cdot \text{CH}_2 \cdot \text{CR}_2 \cdot \text{H}^+ \quad \overset{\text{RC}=\text{O}}{\longrightarrow} \quad \text{RC}=\text{O}
\]
Dewar (5) also stated that an acid-base relationship existed in the Mannich reaction and that an excess of one or the other could cause a hindrance to the formation of the product.

(b) Active hydrogens on carbon

Early investigators first used malonic acid as the acidic reagent in Mannich reactions. In 1920 Mannich and Kather (6) prepared amino acids from malonic acid, amine and formaldehyde. This reaction was extended further by Mannich and his co-workers (7,8) to include alkyl and aryl derivatives of malonic acid. Later, Mannich and Ritsert (9) formed a condensation product with malonic ester, diethylamine and formaldehyde. Recently, Vystrcil and Dasek (10) studied this condensation using acyl-malonic ester. One of a series of tertiary ester bases prepared by Butenandt and Hellman (11) from secondary amines, formaldehyde and an acylaminomalonic ester (I) was dimethyl formamino-N-piperidinomethylmalonate (II).

\[
\begin{align*}
\text{I} & \quad \text{II} \\
\text{COOCH}_3 & \quad \text{COOCH}_3 \\
\text{COOCH}_3 & \quad \text{COOCH}_3
\end{align*}
\]

Other acids possessing strongly active hydrogens on carbon were also employed in the Mannich condensations by the early workers. Mannich and Bauroth (12) investigated the condensation of pyruvic acid and levulinic acid with
formaldehyde and amines. Further work on the $\beta$-keto acids was carried out by Mannich and Curtaz (13). In 1925 Mannich and Stein (14) used substituted arylacetic acids in their condensation studies.

Although Mannich and Heilner (15) were considered among the first to investigate the reaction of acetophenone, formaldehyde and methylamine hydrochloride, Schaefer and Tollens (16) in 1906 formed a condensation product from acetophenone, formaldehyde and ammonium chloride. In more recent years Blicke and Burckhalter (17) prepared $\beta$-keto amines by the condensation of acetophenone with formaldehyde and methylamine hydrochloride and this reaction was given further study by Platé and Wenner (18) in 1949.

Mannich and Schutz (19) in 1927 described the condensation of aryldene ketones (III) with formaldehyde and a secondary base hydrochloride as a method of preparing $\beta$-amino ketones.

$$\text{RCH}=\text{C}-\overset{\circ}{\text{C}}-\text{CH}_3 + \text{CH}_2\text{O} + \text{HNR}_2\cdot\text{HCl} \rightarrow \text{RCH}=\text{C}-\overset{\circ}{\text{C}}-\text{CH}_2-\text{CH}_2-\text{NR}_2\cdot\text{HCl} + \text{H}_2\text{O}$$

III

IV

In an analogous manner Nisbet and Gray (20) allowed furfurylidene acetone to react with formaldehyde and methylamine hydrochloride. This work was extended further by Levy and Nisbet (21) to synthesize $\beta$-amino ketones from 2-acetylthiophene, 2-acetyl-4-phenylthiazole and
2-acetylfuran. In 1938 Mannich and Dannehl (22) obtained condensation products using substituted acetophenone compounds.

Mannich (23) was one of the earliest workers to use aliphatic ketones to synthesize β-keto bases. In 1926 Mannich and Ball (24) obtained 1,4-dimethyl-3-acetotetrahydro-pyridine (VI) by allowing acetone to condense with formaldehyde and methylamine hydrochloride followed by reduction of the unsaturated base (V).

![Chemical structure image]

Aliphatic aromatic ketones (VII) were also used by Mannich and Lammering (25) to synthesize β-keto bases (VIII).

![Chemical structure image]

The condensations of 2-R-5-acetyl-4-methylpyrimidines (IX) with formaldehyde and amine hydrochlorides were studied by Graham and his co-workers (26) for the preparation of amino alcohols with a pyrimidine nucleus.
This Mannich condensation of pyrimidines was expanded further by Christensen, Graham and Griffith (27) to substituted quinazolines (XI).

Bailey, Nowlin and Bost (28), using morpholine, formaldehyde and 1,2-dibenzoylethane, observed the formation of 2,3-dibenzoyl-1-(4-morpholinol)-propane (XIV). They believed that the first step of this condensation involves a reaction between formaldehyde and the amine hydrochloride followed by reaction of this intermediate with 1,2-dibenzoylethane (XIII).

\[
\begin{align*}
\text{CH}_2\text{O} + \text{HCl}\cdot\text{NCH}_2\text{CH}_2\cdot\text{CH}_3 & \rightarrow \text{OH}_2\text{C}_4\text{NCH}_2\text{OH}\cdot\text{HCl} \\
\text{OH}_2\text{C}_4\text{NCH}_2\text{OH}\cdot\text{HCl} & \rightarrow \text{XIII} + \text{H}_2\text{O}
\end{align*}
\]
These authors favored the mechanisms suggested by Lieberman and Wagner (3) and by Alexander and Underhill (4); that a primary condensation occurs between formaldehyde and amine followed by the reaction of this intermediate with the acidic substance.

Noller and Baliah (29) synthesized a large variety of 4-piperidones (XV) with different substituents in the 1-, 2-, 3-, 5- and 6-positions by modification of the Mannich reaction of simple piperidones.

Cyclic ketones were also known to possess active hydrogen. A report on the synthesis of β-keto bases using cyclohexanone was submitted by Mannich and Braun (30) in 1920. Further reactions with cycloketones were investigated by Mannich and Hieronimus (31). In 1919 Mannich and Kather (32) obtained condensation products from amine salts, formaldehyde and antipyrine (XVI).
The participation of lawsone (2-hydroxy-1,4-naphthoquinone) in the Mannich reaction was reported by Leffler and Hathaway (33). The Mannich base was represented by the general formula (XVIII).

(XVIII)

(Where R is hydrogen or alkyl and R' is alkyl, alicyclic or aralkyl or where NRR' make up a heterocyclic ring).

Dalgliesh (34) expanded this reaction to prepare Mannich bases by using higher aliphatic amines and either acetaldehyde or benzaldehyde as the aldehyde component.

Recently, Hellman and Renze (35) stated that 0,N-diacyl-dioxindoles (XIX) readily gave tertiary bases (XX) with formaldehyde and amines.
In 1930 Mannich and Muck (36) succeeded in synthesizing a new bicyclic compound named "pydin", containing the fused rings of both pyran and piperidine and possessing three carbon atoms common to the both rings. Such pydin derivative was 1,5-dicarbomethoxy-3,6,8-trimethyl-9-oxopydin (XXII) formed by the condensation of 3,5-dicarbomethoxy tetrahydro-γ-pyron (XXI) with formaldehyde and methylamine. The reaction occurred in alcohol and water solution at ordinary temperatures and methylamine was used in the form of its hydrochloride.
This reaction was extended also to the condensation of substituted \( \gamma \)-piperidone-dicarboxylic esters (XXIII) and bicyclic piperidine derivatives to form a bispidin (XXIV) in excellent yield (37).

\[
\begin{align*}
\text{XXIII} & \\
\text{(1-Methyl-3,5-dicarbethoxy-2,6-diphenyl-4-piperidone)} & \\
\text{XXIV} & \\
\text{(1,5-Dicarbethoxy-9-oxo-3,7-dimethyl-6,8-diphenyl-bispidin)}
\end{align*}
\]

In the above reactions the hydrogen atoms were highly activated because of the presence of the adjacent carbonyl groups.

Other cyclic ketone compounds containing active ring hydrogens were used in the Mannich reaction.
Robertson and Link (38) prepared a series of 3-substituted-aminomethyl-4-hydroxy coumarins (XXVI)(A) from 4-hydroxy coumarin (XXV), formaldehyde and secondary amines.

\[
\text{XXV} \quad \text{CH}_2\text{O} + \text{HNRR}' \rightarrow \quad \text{XXVI (A)}
\]

(Where R is hydrogen or alkyl, R' is alkyl or alalkyl or where -NRR' makes up a heterocyclic ring)

In their study of ketosteroids, Julian, Meyer and Printy (39) obtained 16-dimethylaminomethyldehydroepiandrosterone (XXVII) from dehydroepiandrosterone (XXVI)(B), dimethylamine and paraformaldehyde.
Nitrile groups were known to activate adjacent hydrogen on carbon. Zaugg, Horrom and Vernsten (40) prepared Mannich type products by the reaction of diphenylacetonitrile (XXVIII) and formaldehyde with secondary amines.

\[
(C_6H_5)_2CH-C\equiv N + CH_2O + R_2NH \rightarrow (C_6H_5)_2C\equiv N \biggm\uparrow \biggm\downarrow CH_2 \biggm\uparrow NR_2 + H_2O
\]

XXVIII XXIX

The Mannich reaction of primary acetylenic compounds with formaldehyde and secondary aliphatic amines was shown by Mannich and Chang (41) to give good yields of aminomethyl derivatives having the formula RC=CCH_2NR_2, (R= phenyl or substituted phenyl and R_2= diethyl). This reaction was applied by Coffman (42) to vinyl acetylene (XXX)

\[
CH_2=C-C\equiv CH + HCHO + HNR_2 \rightarrow CH_2=C-C\equiv C-CH_2NR_2 + H_2O
\]

XXX XXXI

Jones, Marszak and Bader (43) enlarged the scope of this reaction to mono-substituted acetylenic compounds which included alkylacetylenes and several types of acetylenic alcohols.
Active ring hydrogens were believed to be present in cyclic compounds containing other activating groups than the carbonyl. Decombe (44) was among the first workers to use phenols in the Mannich condensation. Subsequent studies were later carried out on substituted phenols (45, 46, 47, 48). The general formulae for these products were:

![Chemical structures](image)

XXXII  XXXIII  XXXIV

More recently, Burke, Murdock and Grace (49) obtained the condensation of hydroxyaromatic compounds with formaldehyde and primary aromatic amines. The preparation of a compound (XXXVI), with a basic side chain, from a phenolic product (XXXV) obtained by Hantzsch synthesis has been described by Phillips (50) in 1951.
Stempel and Buzzi (51) have found that 3-hydroxypyridine (XXXVII) reacted rapidly with formaldehyde and dialkylamine, alkarylamines, and heterocyclic amines to give 2-substituted aminomethyl-3-pyridols (XXXVIII) in good yields.

Toluene containing nitro substituents were found to react with formaldehyde and amine (52, 53).
When the Mannich condensation was applied to heterocyclic compounds which did not contain carbonyl groups, two types of active hydrogen were involved: (1) those directly attached to the nucleus, (2) those attached to the α-carbon of alkyl substituent attached to the ring.

Among the compounds of type (1) that were used in the Mannich reaction was pyrrole. Bachman and Heisey (54) carried out an extensive investigation of the condensation of pyrroles (XLI) with formaldehyde and secondary amines.

Further studies of this reaction were continued by Herz, Dittmer and Cristol (55). More recently, Burke and Hammer (56) extended the condensation reaction to include primary amines.
The condensations of furan and substituted furan with formaldehyde and amines were investigated by Mooney (57) and by Holdren and Hixon (58).

Hartough and his co-workers (59) obtained 2-aminomethyl-thiophene (XLVI) by treating thiophene (XLV) with formaldehyde and ammonium chloride. In their subsequent studies, they suggested a mechanism which involved a primary condensation of the formaldehyde and ammonium chloride to form a formaldimine (XLIV).

\[ \text{CH}_2\text{O} + \text{NH}_4\text{Cl} \rightleftharpoons \text{CH}_2\text{=NH} + \text{HCl} + \text{H}_2\text{O} \]

XLIV

which further reacted rapidly with thiophene to form the Mannich base (XLVI).

\[ \text{CH}_2\text{=NH} + \text{S} \rightleftharpoons \text{CH}_2\text{-NH}_2\text{.HCl} \]

XLV

XLVI

This suggestion could appear as additional support to the mechanism as given by Dewar (5).

It has been found (60) that indole (XLVII) reacted readily with formaldehyde and secondary amines to form gramine (XLVIII).
This reaction was investigated further by Snyder, Smith and Stewart (61) and later by Snyder, Meyers and Kellom (62) for the synthesis of the essential amino acid tryptophan. Bell and Lindwall (63) and Brehm and Lindwall (64) used indole derivatives to prepare a series of compounds resembling gramine. More recently, Cornforth and his co-workers (65) continued the study of this reaction.

In their investigation of benzene and benzene derivatives of thiophene, Burger and Bryant (66) obtained tertiary dibenzothiophenyl-β amino ketones (L) from 2- and 4-acetyldibenzothiophene (XLIX) by the Mannich reaction.
The condensations of pyrazoles with formaldehyde and amines were studied by Bachman and Heisey (54). Heath, Lawson and Rimington (67) obtained 5(4)-dimethylaminomethyl-2-mercapto-4(5)-methylglyoxaline (LII) from 2-mercapto-4(5)-methylglyoxaline (LI), formaldehyde and dimethylamine.

\[
\begin{align*}
\text{CH}_3\text{-}\text{C}=\text{C}\text{-}\text{N}\text{-}\text{NH} + (\text{CH}_3)_2\text{NH} & \rightarrow \text{CH}_3\text{-}\text{C}=\text{C}\text{-}\text{CH}_2\text{-N}\text{CH}_3 + \text{H}_2\text{O} \\
\text{LI} & \rightarrow \text{LII}
\end{align*}
\]

Methyl-pyridine, -quinoline and -pyrimidine were examples of heterocyclic compounds which were used in the Mannich condensation. In these compounds the active hydrogen is attached to the methyl substituent. Applications of the Mannich reaction to 2-methylpyridine and 2-methylquinoline have been reported by Heou-Feo and Delepine (68,69) and by Kermack and Muir (70).

Recently, Boekelheide and Marinetti (71) obtained 2-(β-dimethylaminoethyl)-quinoline (LIII) and 1,3-(dimethylamino)-2-(2-quinolyl)-propane (LIV) by treating 2-methylquinoline with formaldehyde and dimethylamine.

\[
\begin{align*}
\text{LIII} & \quad \text{LIV}
\end{align*}
\]
The most recent studies on 4-methylpyridine (LV) were carried out by Matuszko and Taurins (72).

Just recently, Snyder and Foster (73) have shown that 2,6-dimethyl-4-hydroxypyrimidine (LVII) reacted with formaldehyde and secondary amine to yield 2-bis-(1-piperidino-methyl) (LVIII) and 2-bis-(1-piperidinomethyl)-methyl-4-(1-piperidinoethyl)-6-hydroxypyrimidine (LIX).

Further work on these pyrimidine derivatives have been described by Snyder, Foster and Nussberger (74).
Acidic hydrogen was known to be present in compounds containing nitro groups. Senkus (75) showed that amines reacted with formaldehyde and nitroparaffins or with nitroalcohols, derived from formaldehyde and nitroparaffins, to yield 2-nitroalkylamines (LX).

\[
\begin{align*}
R_2NH + CH_2O + H-C-NO_2 & \rightarrow R_2NCH_2CH_2C-NO_2 + H_2O \\
\text{LX}
\end{align*}
\]

Before any definite mechanism was proposed for the Mannich condensation (3,4,5) Senkus had stated that a reaction occurred between the formaldehyde and amine to form a \( N \)-hydroxyethylalkylamine (LXI)

\[
R_2NH + CH_2O \rightarrow R_2NCH_2OH
\]

LXI

which reacted with the nitroparaffin to form the Mannich base (LX). He also claimed that a reaction occurred between the formaldehyde and nitroparaffin to form the nitroalcohol (LXII)

\[
\begin{align*}
O_2N-C-H + CH_2O & \rightarrow HOCH_2C-NO_2 \\
\text{LXII}
\end{align*}
\]

which reacted further with the primary alkylamines.
In the same year, Johnson (76) had reported that although the same end-products resulted in either case, he believed that the nitroalcohol or nitrodiol first decomposed into the nitroparaffin and formaldehyde before reacting with the amine.

Recently, Senkus (77) has described further work on the study of the Mannich condensations of 2-nitroalkylamines.

In their study of the preparation of 2-nitro-1-alkenes from nitro amines, Blomquist and Shelley (78) have shown that the initial step of the Mannich reaction was the addition of formaldehyde to the amine to form the 2-nitroalkylamine.

(c) Active hydrogen on nitrogen

The most commonly known compounds possessing acidic hydrogen on nitrogen were succinimide and phthalimide. In 1942 Feldman and Wagner (79) obtained N-(piperidinomethyl)succinimide (LXIII), N-(piperidinomethyl)phthalimide (LXIV), and N-(piperidinomethyl)carbazole (LXV) by the Mannich reaction.

![Diagram of LXIII and LXIV molecules]
In their study of morpholinomethyl derivatives of urea and substituted urea, Weaver, Simons and Baldwin (80) condensed morpholinomethanol with phthalimide and succinimide to form the N-(morpholinomethyl)-derivatives.

N-(morpholinomethyl)phthalimide and N-(piperidinomethyl)phthalimide were readily synthesized by Moore and Rapala (81) in 1946 by the Mannich reaction.

A number of condensations were carried out by Bogemann and Zaucker (82) to prepare Mannich bases from benzothiazole-2-thione, benzimidazole-2-thione and benzoxazole-2-thione.

Bachman and Heisey (54) also obtained condensation products by treating benzimidazole (LXVI) and benzotriazole (LXVII) with formaldehyde and secondary amines.
Baker, Querry, Kadish and Williams (83) allowed 4-quinazolone (LXVIII) to react with formaldehyde and heterocyclic amines to form 3-(piperidinomethyl)-4-quinazolone (LXIX) and 3-(morpholinomethyl)-4-quinazolone (LXIX).

Huttel and Jochum (84) found that when pyrazole condensed with formaldehyde and secondary amines, in a neutral solution, N-substituted derivatives were formed.

Recently, Butenandt and Hellman (11) obtained a condensation product from hydantoin, formaldehyde and piperidine. They stated that the reaction could not occur without the addition of acetic acid. This condensation was not investigated further and it was only reported that an intermediate compound was formed in the course of the reaction.

In 1910 Franchimont (85) prepared N-(piperidinomethyl)-methylnitramine (LXXI) by condensing piperidinomethanol (LXX) with the nitramine.
He also claimed that butylnitramine reacted with piperidinomethanol (LXX) to give N-(piperidinomethyl) butylnitramine (LXXII).

\[
\text{N-CH}_2\text{OH} + \text{C}_4\text{H}_9\text{N}_3\text{O}_2 \rightarrow \text{N-CH}_2\text{N-C}_4\text{H}_9 + \text{H}_2\text{O}
\]

Franchimont did not report any analysis or properties of N-(piperidinomethyl)butylnitramine.

(d) The rôle of Mannich condensation in the biogenésis of alkaloids

The Mannich reaction has acquired great interest with the growing realization that it may well be the characteristic step in alkaloid biogenesis. Among the first to introduce and develop this conception were Robinson (86), Mannich (24) and Schöpf (87).

In a particular application of this idea Hahn and his co-workers (88, 89, 90) have reported that in the biogenesis of alkaloids of the yohimbe group, tryptamine and 3-hydroxyphenylacetaldehyde (formed by the deamination of 3-hydroxyphenylalanine) condensed to give LXXIV and from LXXIV, by a similar reaction, which involves the condensation of formaldehyde, an amino group with a nucleophilic centre, LXXV was produced. The latter contains the complete ring skeleton of yohimbine (LXXVI).
In 1948 Woodward (91) had claimed that the formation of strychnine (LXXVII) can be based upon the condensation of the amino acid tryptophan with 3,4-dioxophenylalanine and formaldehyde.
Goutarel, Janot, Prelog and Taylor (92) have also shown that the Mannich condensation plays an important role in the formation of cinchonine (LXXXI) and cinchonamine (LXXXII).
Only recently the condensation of an oxidized 5-hydroxytryptophan, acetone dicarboxylic acid and formaldehyde has been described by Harley-Mason (93) as the initial reaction in the formation of lysergic acid (LXXXIII).

Substitution reactions of the -NH- group in imines and imides

One of the characteristic properties of acidic compounds used in the Mannich reaction was the ability of the active hydrogen to be replaced either by a metal or by a halogen or by both.

In the extension of this idea to compounds containing the -NH- group, the following substances were observed to undergo substitution reactions involving the active hydrogen on nitrogen.
I. Succinimide and phthalimide

In 1882 Landsberg (94) had obtained the potassium, barium, and silver salts of succinimide and phthalimide. The sodium salts of these compounds were prepared by Blacher (95) in 1895.

Ziegler and his co-workers (96) prepared N-bromo­succinimide (LXXXIV) in 75 - 81 per cent yield by brominating an alkaline solution of succinimide.

\[
\begin{align*}
\text{CH}_2 & \quad \text{NH} + \text{BR}_2 \quad \xrightarrow{\text{alkali}} \\
\text{CH}_2 & \quad \text{N-Br} + \text{NaBr}
\end{align*}
\]

N-Bromophthalimide was synthesized by a nearly identical method (97) from phthalimide.

Djerassi and Lenk (98) prepared N-silversuccinimide (LXXXV) as an intermediate product for the synthesis of N-iodosuccinimide (LXXXVI).
II. Hydantoin and substituted hydantoin \([2,4(3H,5H)-\text{imidazoles}dione]\\n
As early as 1903 Harris and Weiss (99) prepared a \n1,3-dichlor-derivative of hydantoin.\\n
Just recently Orazi and Meseri (100) readily \nsynthesized 3-bromo-5,5-dimethylhydantoin (LXXXVIII) by \nbrominating an alkaline solution of 5,5-dimethylhydantoin.
In 1864 silver hydantoin was prepared by Baeyer (101). Harris and Weiss (99) also obtained 3-methylhydantoin (LXXXIX) by allowing 3-silverhydantoin to react with methyl iodide.

III. Uracil and hydouracil \( \{2,4(1H,3H)\text{-pyrimidinedione}\} \)

Johnson and Clapp (102) had prepared the potassium salt of uracil (XC) by allowing uracil to react with potassium hydroxide in absolute alcohol.

In 1893 Lengfeld and Stieglitz (103) had synthesized 3-silverhydouracil (XCI).
IV. Carbazole

The substitution of the hydrogen atom on nitrogen in carbazole was described by Campbell and Barclay (104) in 1947. They stated that N-alkyl, -aryl or -acyl derivatives have been obtained by the action of the appropriate reagents on carbazole, potassium carbazole and carbazole magnesium iodide. For example, N-potassium carbazole reacted with p-chlorobromobenzene to yield 9-p-chlorophenylcarbazole (XCII).

\[
\text{Br} \quad \text{Cl} \quad \rightarrow \quad \text{XCII}
\]

Graebe (105) had obtained 9-potassiumcarbazole (XCIII) from carbazole and potassium hydroxide and this product (XCIII) reacted further with methyl or ethyl iodide to give the N-alkyl derivatives (XCIV, XCV).
V. 2-Pyrrolidone

In 1907 Tafel and Wassmuth (106) prepared the sodium salt of 2-pyrrolidone (XCVI) and this product (XCVI) was allowed to react with methyl iodide in benzene solution to yield the 1-methyl-2-pyrrolidone (XCVII).
N-Bromopyrrolidone was obtained by brominating an alkaline solution of 2-pyrrolidone (107).

VI. 2,4-Thiazolidinedione

In 1877 Claesson (108) prepared the potassium, sodium, barium, silver and mercury salts of 2,4-thiazolidinedione. A typical formula for one of the salts was given as

$$\text{Ba}(\text{OCOCH}_2\text{NCS})_2$$

Thus no indication was given as to which hydrogen was displaced by the metals.

The silver salt of 2,4-thiazolidinedione (XCVIII) was prepared by Whealer and Barnes (109) in 1900 by reacting the alkaline solution of the above compound with silver nitrate.

$$\text{H}_2\text{C}==\text{CH}_2\text{C}==\text{O} + \text{AgNO}_3 \rightarrow \text{H}_2\text{C}==\text{CH}_2\text{C}==\text{O}$$

This product (XCVIII) further reacted with methyl iodide to form 3-methyl-2,4-thiazolidinedione (XCIX).
In 1894 Franchimont (110) had obtained the copper, silver, barium, zinc, cadmium, and mercuric salts of methylnitramine. Later, Umbgrove and Franchimont (111) prepared the potassium salt of methylnitramine.

In their studies on nitramines Lamberton, Lindley and Speakman (112) obtained a potassium salt of the higher nitramino-methylene homologue.

\[
\begin{align*}
\text{CH}_2-\text{C}^\text{\textregistered}_0^\text{NCH}_2-\text{NCH}_2-\text{NCH}_2-\text{N}_2\text{O}_2
\end{align*}
\]

Table: \(\text{XCIX}\)

**Ultraviolet Absorption Spectra of Alkylnitramines**

The spectrometric literature, before 1949, contained only meager references to aliphatic nitramines. Baly and Desch (113) and Hedley (114) in 1908 described the spectra of some aliphatic nitro-compounds. Hantzch and Hein (115) reported on the spectra of several nitro-compounds and their alkali salts in 1919 and, more recently, Kortum has discussed the spectra of several aliphatic nitrogen containing compounds (116, 117, 118) including a few simple nitramines (118).
In 1949 Jones and Thorn (119) have made a comprehensive study of the ultraviolet absorption of nitramines. In their paper, they have summarized all previous spectra data and investigated the spectrum of n-butyl nitramine in ethanol and alkaline solutions.

Only recently, Curry and Mason (120) reported in their ultraviolet absorption studies that nitramines and nitramine salts have absorption maxima in the range of 232 - 235 m\(\mu\).
DISCUSSION

A review of the literature showed that the acidic reagents used in the Mannich condensations by the early workers had active hydrogen on carbon. Among the compounds used were: malonic acid (6), alkyl and aryl derivatives of malonic acid (7) and hydroxymalonic acid (8). Other substances used in the Mannich reactions which contained less reactive hydrogens were: acetone (23), antipyrine (32), cyclohexanone (30) and pyruvic acid (12).

This review also showed that the ease of condensation of a substance with formaldehyde and an amine was directly related to the activity that the acidic compound shows in substitution reactions involving its active hydrogen. It has been known that the acidic hydrogen of the above compounds could be replaced either by a halogen or by a metal or by both.

The replacement reactions of this active hydrogen were considered to be the result of the influence of the adjacent activating group. Lapworth (121) in 1904 had discussed the cases of substitution in the group of compounds containing the carbonyl substituent, such as ketones, aldehydes, carboxylic acids and their derivatives. This work showed that the characteristic replaceability of the α-hydrogen atom may not be a direct process, but one due to the initial formation of the enolic form. His basic
discovery was that the rate of bromination of acetone in acidic aqueous solutions was proportional to the concentration of acetone and to that of the hydrogen ions, but was independent of the concentration of bromine. The interpretation of these facts was that the measured process was the acid-catalyzed enolization of acetone.

Other investigators (122, 123, 124) have confirmed the essential correctness of Lapworth's interpretation with the modification that in basic catalysis, enolization itself is a composite process, rate-controlled by ionization, which is equally rate-controlling for halogenation (125).

The acid-catalyzed enolization of cyclohexanone can be considered as the essential step in the chlorination of cyclohexanone (126) (CII).
Recently, Cardwell and Kilner (127) have studied the acid-catalyzed enolization and substitution reactions of saturated aliphatic and monocyclic ketones and found that alkyl substituents will stabilize the enol in a hyperconjugative manner. Thus in reactions where enolization is not rate-controlling, orientation of substitution will be influenced by relative concentrations of the isomeric enol at equilibrium. For instance, 1-methyl-2-cyclohexanone would enolize in either direction,

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} \\
\quad & \leftrightarrow \\
\text{H} & \quad \text{H}
\end{align*}
\]

but the formation of 1-chloro-1-methyl-2-cyclohexanone (128) (CIII) showed that the methyl group has a greater effect on acid-catalyzed enolization by stabilizing the transition state in a hyperconjugative manner.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Cl} \\
\quad & \leftrightarrow \\
\text{Cl} & \quad \text{HCl}
\end{align*}
\]
The electron attraction (-I) by the nitrile group was known to be of the same order of intensity as the carbonyl group (125) and this inductive effect would be responsible for the shift of electrons towards the nitrogen atom thus increasing the electropositivity of the α-carbon. The carbon-hydrogen bond of this atom would be subsequently weakened and the proton readily displaced. An example of this effect was noted in the bromination of phenylacetanilide (129).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{C}≡\text{N} & \quad \text{H}_2\text{C}-\text{Br} \\
\text{C}_6\text{H}_5 & \quad + \quad \text{HBr}
\end{align*}
\]

The reactivity of the methyl groups in heterocyclic bases was studied by Mills and Smith (130) and they suggested that the marked power of the methyl groups must be due to the presence, under conditions of the reaction, of a small quantity of a reactive tautomeric isomer with which it exists in equilibrium, and which corresponds closely to that of the enolic modification of methyl ketone.

\[
\begin{align*}
\text{N} \quad \text{CH}_3 & \quad \rightleftharpoons \quad \text{N} \quad \text{CH}_2
\end{align*}
\]
This imide modification would explain the reactivity of the methyl groups in such compounds as quinaldine, lepidine, 1-methylisoquinoline and 4-phenyl-2-methylthiazole. Since the replaceable hydrogen atom on carbon of the above compounds was observed to be involved in Mannich condensations, it was considered that other acidic substances possessing reactive hydrogen on nitrogen, which were known to undergo substitution reactions, would probably condense with formaldehyde and an amine to form a Mannich base.

**General Method and Conditions of Mannich Reactions**

The general procedure of the present research involved the heating of the reaction mixture at reflux temperature of the solvent for various time intervals. The product was extracted with an appropriate solvent and usually was recrystallized from alcohol. In some cases, (2,4-thiazolidinedione, alkynitrarnines and uracil), the reaction was observed to occur at low temperatures. For these experiments the reagents were added in the cold and the reaction mixture was allowed to stand at 4°C for a minimum of twelve hours. The product was filtered from the solution and was recrystallized. Most of the reactions were carried out in a neutral medium, since it was known that the \( \text{-N}_1\text{-C}_1\text{-N}_1 \) grouping of the Mannich bases was susceptible to acid hydrolysis (3, 83).
Condensation of 2-pyrrolidone with formaldehyde and secondary amines.

One of the simplest heterocyclic compounds containing a carbonyl group in the $\alpha$-position to -NH- group is 2-pyrrolidone (CIV).

Substitution reactions involving the active hydrogen of CIV (106, 107) indicated that this compound would probably condense with formaldehyde and secondary amines.

(a) Reaction with morpholine

The condensation reaction of 2-pyrrolidone with formaldehyde and morpholine was expected to yield 1-(morpholinomethyl)-2-pyrrolidone (CV).

The yield of the product (CV) was 27.15 per cent but it was found that the extension of the reflux time increased the yield to 37.8 per cent.
(b) Reaction with piperidine

A similar Mannich reaction of 2-pyrrolidone occurred with piperidine to form 1-(piperidinomethyl)-2-pyrrolidone (CVI).

The product obtained melted at 47.5 - 49° and readily formed a picrate. However, the yield of CVI was decreased when the reflux time was extended an additional thirty minutes. 1-(Piperidinomethyl)-2-pyrrolidone (CVI) readily formed the methyl iodide salt (CVII) which melted at 153.5 - 154°.

(c) Reaction with dimethylamine hydrochloride

When the Mannich condensation of 2-pyrrolidone was extended to dimethylamine, no product was obtained. However,
when the hydrochloride was used, a reaction occurred to form 1-(dimethylaminomethyl)-2-pyrrolidone (CVIII).

\[
\text{H}_2\text{C} - \bigg\| - \text{CH}_2\text{NH} + \text{CH}_2\text{O} + \text{HN(CH}_3\text{)}_2 \rightarrow \text{H}_2\text{C} - \bigg\| - \text{NCH}_2 - \text{NCH}_3
\]

CVIII

The attempted condensation of 2-pyrrolidone with formaldehyde and pyrrolidine failed to yield any product.

**Condensation of hydantoin with formaldehyde and morpholine**

Hydantoin (CIX) is a heterocyclic five-membered compound which is related to 2-pyrrolidone by the replacement of the CH\(_2\) groups with a carbonyl and with a \(-\text{N-N-}\) group. Thus the structure of CIX shows two carbonyl and two imino groups.

\[
\text{HN} = \text{C} = \text{O} \\
\text{O} = \text{C} \\
\text{CH}_2 \\
\text{N} \\
\text{H}
\]

CIX

The method used for the synthesis of hydantoin involved the reaction of glycine ethyl ester hydrochloride with potassium cyanate (131). The first product of the reaction was the formation of ethyl ester of hydantoic acid (CX).
The cyclic anhydride of the hydantoic acid or hydantoin (CIX) was obtained by heating CX with 25 per cent hydrochloric acid. The hydrogen atoms of the imino groups of hydantoin can be replaced by halogens and metals (99). Thus 1,3-di(morpholinomethyl) hydantoin (CXI) was expected to be formed by condensing hydantoin with morpholine and formaldehyde.

\[
\begin{align*}
\text{H}_2\text{C}_8 & \quad \text{C}=\text{O} \\
\text{H}-\text{N} & \quad \text{N-H} \\
\end{align*}
\quad + \quad 2\text{CH}_2\text{O} + 2 \begin{array}{c} \\
\text{N} \quad \text{O} \\
\end{array}
\rightarrow
\begin{align*}
\text{H}_2\text{C} & \quad \text{C}=\text{O} \\
\text{N}-\text{CH}_2\text{N} & \quad \text{N}-\text{CH}_2\text{N} \\
\end{align*}
\]

The yield of the product (CXI) was 22.3\% per cent and evidence was obtained that 1,3-di(morpholinomethyl) hydantoin was formed by the reaction of both imino groups. This evidence was supported by analysis and by the increased yield (49.27\%).
when the mole ratio of hydantoin, formaldehyde and morpholine
was changed to 1:2:2 respectively. The reaction time was
extended to thirty, forty-five and sixty minutes, however,
the best yield was realized when the experiment was carried
out for fifteen minutes. The cleavage of the $\text{N}^\text{R}_1\text{C}^\text{R}_2\text{N}^\text{R}_3$ grouping
of CXI by acid hydrolysis yielded quantitative amounts of
hydantoin. All further attempts of obtaining condensation
products using other secondary amines with hydantoin and
formaldehyde were unsuccessful.

Condensation of $5,5$-dimethylhydantoin with formaldehyde
and morpholine

Since $5,5$-dimethylhydantoin and hydantoin possesses
the same reactivity toward halogens and metals, it was
expected that the first compound would react in the Mannich
condensation. The method of preparation of $5,5$-dimethyl-
hydantoin (CXII) was first described by Bucherer and his
associates (132,133). They allowed acetone to react in a
dilute alcoholic solution with potassium cyanide and ammonium
carbonate for two hours. The hydantoin was isolated on
cooling of the solution.

\[
\begin{align*}
\text{CH}_3\text{C}=\text{O} & \xrightarrow{\text{KCN}} \text{CH}_3\text{C}^\text{\text{OH}} \quad \text{CH}_3\text{C}^\text{\text{OH}} \\
\text{CH}_3 & \quad \text{CH}_3\text{C}^\text{\text{OH}} \quad \text{(NH}_4\text{)}_2\text{CO}_3 \\
& \quad \text{HN} \quad \text{C}=\text{O} \\
\text{CH}_3 & \quad \text{O}=\text{C} \quad \text{N} \quad \text{CH}_3 \\
& \quad \text{N} \quad \text{CH}_3
\end{align*}
\]

CXII
When CXII was treated with formaldehyde and morpholine, 1,3-di(morpholinomethyl)-5,5-dimethylhydantoin (CXIII) was obtained in 39.8 per cent yield.

\[
\begin{align*}
\text{CH}_3 & \quad \text{C-CH}_3 + 2\text{CH}_2\text{O} + 2 \quad \overset{\text{N}}{\text{N-CH}_2\text{-N}} \quad \overset{\text{O}}{\text{O}} \\
\text{H} & \quad \text{N} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{N} & \quad \text{H} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

CXIII

The reflux time of the reaction was varied to determine its effect on the yield, which was found to be reduced on prolonged heating. Further attempts to use other secondary amines or their hydrochlorides were unsuccessful and the separation of the reaction mixture by fractional distillation at reduced pressure yielded nearly quantitative amounts of the starting materials. The preparation for 1,3-di(morpholinomethyl)-5,5-dimethylhydantoin (CXIII) was modified when piperidine was used. This modification involved the addition of acetic acid to the reaction mixture of formaldehyde, piperidine and 5,5-dimethylhydantoin (11) but all experiments failed to form any condensation product.
Condensation of 2,4-thiazolidinedione with formaldehyde and secondary amines

2,4-Thiazolidinedione (CXIV), a heterocyclic azole compound, related to hydantoin, contains a sulphur atom in addition to the carbonyl and imino groups.

\[
\begin{align*}
&\text{S}\quad\text{C} \quad\text{NH} \\
&\text{H}_2\text{C} \quad \text{C} = \text{O}
\end{align*}
\]

CXIV

The active hydrogen of this compound (CXIV) was shown to be replaced by halogens and metals (108, 109). Consequently, it was thought that CXIV would also react with formaldehyde and an amine to form a Mannich base. The subsequent experiments proved that 2,4-thiazolidinedione was considerably reactive.

(a) Reaction with piperidine

The initial condensation was investigated with piperidine and the reaction was expected to form 3-(piperidino-methyl)-2,4-thiazolidinedione (CXV).

\[
\begin{align*}
&\text{S}\quad\text{C} \quad\text{NH} + \text{CH}_2\text{O} + \text{N} \\
&\text{H}_2\text{C} \quad \text{C} \quad \text{CH}_2\text{N} \quad \xrightarrow{\text{CXV}} \quad \text{S}\quad\text{C} \quad\text{NHCH}_2\text{N}
\end{align*}
\]
When the experiment was performed under reflux a resin was produced. Subsequent attempts showed that condensation products could be obtained when the reaction mixture was kept at 0°, and a nearly quantitative yield of 3-(piperidinomethyl)-2,4-thiazolidinedione (CXV) was thus obtained. Analysis of CXV for carbon, hydrogen and nitrogen agreed closely with theory. However, a decreased yield (52.2%) was obtained when the reaction mixture was heated at 40° for one-half hour.

(b) Reaction with morpholine

A further Mannich condensation was carried out with morpholine to form 3-(morpholinomethyl)-2,4-thiazolidinedione (CXVI).

\[
\begin{align*}
\text{S} & \quad \text{C}^\ominus \\
\text{C} & \quad \text{NH} + \text{CH}_2\text{O} + \text{N} & \quad \text{O} & \quad \text{S} & \quad \text{C}^\ominus \\
\text{H}_2 & \quad \text{C} & \quad \text{O} & \quad \text{N-CH}_2\text{-N} & \quad \text{O}
\end{align*}
\]

CXVI

A quantitative yield of CXVI was formed and this product readily formed a picrate which melted at 150.5 - 151°.

(c) Reaction with dimethylamine

The reaction with dimethylamine readily yielded 3-(dimethylaminomethyl)-2,4-thiazolidinedione (CXVII).
The product was obtained in a yield of 71.5 per cent, but a dark resin was formed when the reaction was repeated with the application of heat. 3-(Dimethylaminomethyl)-2,4-thiazolidinedione formed a methyl iodide salt (CXVIII) which melted at 176.5 - 177° (decomposed).

(d) Reaction with methylamine

3-(Methylaminomethyl)-2,4-thiazolidinedione was expected to form when 2,4-thiazolidinedione was allowed to react with methylamine and formaldehyde, but the nitrogen value found for the product did not agree with the calculated value. A possible explanation was that the nitrogen atom of the methylamine acted as a basic amine for a further reaction with formaldehyde and 2,4-thiazolidinedione to yield N-methyl-N,N-bis(2,4-thiazolidinedionomethyl)amine (CXIX).
This assumption was supported by the increased yield (83%) when the experiment was repeated using a 2:2:1 mole ratio of 2,4-thiazolidinedione, formaldehyde and methylamine respectively, and by the nitrogen analyses of CXIX.

Condensation of uracil with formaldehyde and morpholine

In comparing uracil (CXX), a six-membered heterocyclic compound which contained two imino and two carbonyl groups, with hydantoin, it was noted that one of the CH$_2$ groups of the latter was replaced by an unsaturated carbon-carbon bond.
The imino groups of CXX were considered to be activated by the presence of the adjacent carbonyl groups whose inductive effect greatly increases the electropositivity of the nitrogen atom.

Since the acidity of the reactive hydrogen of uracil was shown by its substitution reactions with metals (102), it was believed that the above compound (CXX) would probably react in the Mannich condensation. Chen (134) prepared uracil by modifying the method of Davidson and Baudisch (135). The synthesis essentially involved the reaction between urea (CXXIII) and the intermediate hydroxymethylene acetic acid (CXXII) which was formed on treating malic acid (CXXI) with concentrated sulphuric acid.
The formation of 3-(morpholinomethyl) uracil (CXXIV) was expected to occur when morpholine was used as the secondary amine.

The product (CXXIV) was obtained when the reaction mixture was immediately cooled after the addition of all the reagents and the yield was 56.1 per cent. The attempted condensation of uracil with formaldehyde and piperidine at various time intervals failed to yield any reaction product.

Attempted condensation of hydouracil with formaldehyde and secondary amines

As uracil formed a Mannich product (CXXIV), it was thought that hydouracil (CXXV) would probably react with
formaldehyde and morpholine, and it was assumed further that the hydrogenation of uracil would not fundamentally change the reactivity of the hydrogen atom on nitrogen. The preparation of CXXV was carried out by adopting the method of Brown and Johnson (136) in which they used colloidal platinum as the catalyst.

\[
\begin{align*}
\text{HC} & \text{C=O} \\
\text{C} & \text{N} \\
\text{H} & \text{H} \\
\text{Pt} & \\
\hline
\text{H}_2 & \text{C} \xrightarrow{\text{H}_2} \text{H}_2\text{C} \\
\text{C} & \text{N} \\
\text{O} & \text{H} \\
\text{CXXV}
\end{align*}
\]

All attempts at condensing hydouracil with formaldehyde and secondary amines were unsuccessful and the unreacted hydouracil was always quantitatively recovered from the reaction mixture. It was concluded that the hydrogen on nitrogen in CXXV was not as reactive as the acidic hydrogen in CXX. Possibly the saturated structure of CXXV increases the electron stability in the molecule.

**Condensation of succinimide with formaldehyde and morpholine**

The reactivity of the hydrogen atom on nitrogen in succinimide was noted by its replacement reactions with halogens and metals (94, 95, 96, 98). Consequently, it was believed that succinimide would also react in the Mannich condensation. In the reaction of succinimide, formaldehyde and morpholine, N-(morpholinomethyl)succinimide (CXXVI) was expected to form.
This product (CXXVI) was obtained in a yield of 43.3 per cent and it readily formed a picrate which melted at 181 - 182°. An identical product was obtained by Weaver, Simons and Baldwin (80) by condensing morpholinomethanol (CXXVII) with succinimide.

Since both reactions produced CXXVI, it was thought that the first reaction offered additional support to the mechanism of the Mannich condensation suggested by Alexander and Underhill (4) in which they postulated that the amine-methanol group was the primary reaction product of the Mannich condensation. Since no product was obtained when this reaction was extended to use pyrrolidine as the secondary amine, it was assumed that the strongly basic character of pyrrolidine interfered in the acid-base relationship of the Mannich condensation (3,5) by checking the formation of the carbonium ion \( R_2\text{NCH}_2^+ \).
Condensation of phthalimide with formaldehyde and morpholine

A reaction product similar to CXXVI occurred when phthalimide was used as the imide compound and the yield of N-(morpholinomethyl)phthalimide (CXXVIII) was 25.7 per cent.

\[
\text{NH} + \text{CH}_2\text{O} + \text{N} \xrightarrow{\text{O}} \text{C} \xrightarrow{\text{O}} \\
\text{CXXVIII}
\]

When the product (CXXVIII) was hydrolyzed by dry hydrogen chloride, the phthalimide component was quantitatively recovered. N-(Morpholinomethyl)phthalimide was also obtained by allowing morpholinomethanol to react with phthalimide (80). The attempts to use diethylamine in the condensation with phthalimide and formaldehyde proved to be unsuccessful.

Attempted condensation of 1,8-naphthalimide with formaldehyde and secondary amines

With the idea of pursuing the application of the Mannich reaction to other imides, 1,8-naphthalimide (CXXXII) was considered for investigation. This compound (CXXXII) was prepared by Graebe and Gfeller (137) in 1892 from acenaphthene (CXXIX) which was oxidized to 1,8-naphthalic acid (CXXX) and the latter converted to the anhydride (CXXXI). 1,8-Naphthalimide was obtained by the ammonolysis of CXXXI.
All attempts to condense 1,8-naphthalimide with formaldehyde and secondary amines failed. Possibly the hydrogen atom on nitrogen is not as reactive as the acidic hydrogen in succinimide and phthalimide.

**Condensation of carbazole with formaldehyde and piperidine**

Although the molecular structure of carbazole (CXXXIII) does not show any activating substituent, it is known that the acidic hydrogen is capable of being replaced by metals (104). A possible explanation of this reactive hydrogen atom would be the presence of benzene rings which would facilitate the flow of electrons away from the nitrogen atom.
N-(Piperidinomethyl)carbazole (CXXXIV) was expected to form by the reaction of CXXXIII with formaldehyde and piperidine.

The product (CXXXIV) was obtained in a quantitative yield and it readily formed a picrate which melted at 242 - 243°. An identical product was also obtained by Feldman and Wagner (79) but they did not report any further reactions of carbazole with other secondary amines. However, the attempted condensations using either morpholine or dimethylamine failed to yield any reaction product.
Condensation of alkylnitramines with formaldehyde and secondary amines.

The acidic hydrogen atom on nitrogen in alkylnitramines was known to be activated by the adjacent nitro group. Lindley and Speakman (138) have measured the thermodynamic dissociation constants for the series of primary dibasic nitramines, \( \text{NO}_2\text{NH(CH}_2\text{)}_n\text{NHNO}_2 \), in which \( n = 1, 2, 3 \) and 4 and they have compared the resulting values of \( pK_1 \), \( pK_2 \) and \( \Delta pK \) with those for corresponding members of the series of dicarboxylic acids, \( \text{CO}_2\text{H(CH}_2\text{)}_n\text{COOH} \). Since the hydrogen atom in nitramines was also known to be replaced by metals and halogens (110, 111), it was assumed that the alkylnitramines would probably condense with formaldehyde and an amine to form a Mannich base. The general procedure for the preparation of nitramines involved the formation, nitration, and ammonolysis of the carbamate (CXXXV) followed by acidification of the ammonium salt.

\[
\begin{array}{c}
\text{R}_2\text{N} + \text{Cl-C-OC}_2\text{H}_5 \rightarrow \text{R}_2\text{-N-C-OC}_2\text{H}_5 \\
\text{H} \quad \text{H} \\
\text{H} \quad \text{H}
\end{array}
\]

Aliphatic and alicyclic carbamates were found to be nitrated smoothly and in excellent yields with fuming nitric acid and acetic anhydride to form N-nitrocarbamates (139)(CXXXVI).
The N-nitro derivatives of primary amines have been prepared by the ammonolysis of N-nitrocarbamates (CXXXVI) using aqueous or alcoholic ammonia or dry ammonia gas (139).

Condensation of n-butynitramine with formaldehyde and secondary amines.

(a) Reaction with piperidine.

The initial condensations of n-butynitramine with formaldehyde and piperidine formed a product whose nitrogen analysis failed to support the structure. Further reactions were carried out using either the hydrochloride or acetate of piperidine but this method also proved to be unsuccessful. It was finally decided to keep the reaction mixture below 0° and maintain this temperature for twelve hours. When n-butynitramine was allowed to react with formaldehyde and piperidine in this manner, N-(piperidinomethyl)-n-butynitramine (CXXXVII) was obtained which showed a boiling range of 97 - 100° at 1 mm. pressure.
The carbon, hydrogen and nitrogen analyses of this product gave excellent agreements with theory. Franchimont (85) obtained CXXXVII by reacting piperidinomethanol (CXXXVIII) with n-butylnitramine but did not report any analysis or properties of this compound (CXXXVII).

(b) Reaction with morpholine

When morpholine was used as the secondary amine, the reaction was expected to form N-(morpholinomethyl)-n-butylnitramine (CXXXIX). The product (CXXXIX) was re-crystallized from petroleum ether (yield 97.6 per cent).
(c) Reaction with diethylamine

When n-butylnitramine was treated with formaldehyde and diethylamine, a liquid product was obtained. The nitrogen analysis of this substance gave values which agreed with the calculated values for the salt of n-butylnitramine and diethylamine. This liquid product failed to form a picrate.

Condensation of ethylnitramine with formaldehyde and secondary amines

(a) Reaction with piperidine

The product obtained by allowing piperidine to react with formaldehyde and ethylnitramine did not correspond to the structure CXL which would be formed in the normal course of the reaction.

\[
\text{CH}_3\text{CH}_2\text{-NH} + \text{CH}_2\text{O} + \text{N} \rightarrow \text{CH}_3\text{CH}_2\text{-NCH}_2\text{-N} \]

\[
\text{NO}_2 \quad \text{NO}_2
\]

CXL

The analysis showed excellent agreement with the structure which could be formed in a further condensation at the \(\alpha\)-carbon of the ethyl group of CXL to form \(N\)-(piperidinomethyl)-\(\alpha\)-(piperidinomethyl)ethylnitramine (CXLII).
The formation of the product CXLI appears to be a significant reaction because it is the first time a beta hydrogen of an acidic compound containing an activating group is known to be sufficiently reactive to undergo a further condensation.

(b) Reaction with morpholine

\[
\text{N-(Morpholinomethyl)ethylnitramine (CXLII) was obtained when ethylnitramine was allowed to react with formaldehyde and morpholine.}
\]

\[
\text{The carbon, hydrogen and nitrogen analyses showed close agreement to the calculated values.}
\]
(c) Reaction with dimethylamine.

The attempted condensation of ethylnitramine with formaldehyde and dimethylamine failed to yield any product.

 Attempted condensations of methylnitramine with formaldehyde and secondary amines.

All attempts to form a Mannich base using methylnitramine with formaldehyde and secondary amines were unsuccessful.

Color test of the alkylnitramines

Franchimont (140) noted that nitramines in glacial acetic acid gave a pink color with α-naphthalamine and a green color with dimethylaniline on the addition of zinc dust. This test was applied by McKay (141) who also presented further references of its use by other investigators. When dimethylaniline was used as the aromatic amine, the prepared alkylnitramines showed a green color.

Ultraviolet absorption spectra of alkylnitramines and their Mannich products

The absorption maxima of the alkylnitramines were found to occur between 227 - 234 μ. Although the observed values of λ_max, are in agreement with the reported absorption spectra (119), it was noted that the values of the molecular extinction coefficient are considerably higher. Table 1 shows a comparison of the observed molecular
extinctions of methyl-, and n-butylnitramines with the reported values (119).

**TABLE 1**

**Molecular Extinction Coefficients of Alkynitramines**

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>FOUND</th>
<th>REPORTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnitramine</td>
<td>14,010</td>
<td>7,200 (a)</td>
</tr>
<tr>
<td>Ethynitramine</td>
<td>28,230</td>
<td></td>
</tr>
<tr>
<td>n-Butynitramine</td>
<td>9,727</td>
<td>7,200 (b)</td>
</tr>
</tbody>
</table>

(a) = $5 \times 10^{-3}$ N HCl solvent  
(b) = ethanol solvent

The absorption maxima values for the Mannich products of ethyl- and n-butylnitramines with morpholine were also found to occur between 227 - 234 m\(\mu\) but with decreased molecular extinction coefficients.
EXPERIMENTAL

Starting Materials

Dimethylamine, diethylamine, n-butylamine, di-n-butylamine, pyrrolidine, morpholine, succinimide, phthalimide, acenaphthene, ethyl chloroformate, carbazole, 2,4-thiazolidinedione and glycine ethyl ester hydrochloride were obtained from Eastman Kodak Company. A generous sample of 2-pyrrolidone was supplied by General Aniline and Film Corporation. Urea, malic acid, methylamine and platinic chloride were obtained from Fischer Scientific Company and piperidine was obtained from Brickman and Company. Methylamine and dimethylamine were used in the form of a 25 per cent solution in water; formaldehyde was used in the form of a 35 per cent solution in water.

The hydrochlorides of the secondary amines were prepared by the addition of dilute hydrochloric acid to the amine in a three-necked flask equipped with a mechanical stirrer, condenser and dropping funnel. The mixture was kept cool during the addition of the acid by placing the flask in an ice bath. Upon completion of addition of the acid, the solution was evaporated to dryness on the water bath under reduced pressure leaving the salt residue as a solid compact mass of crystals. The solid amine hydrochlor-
ide was recrystallized from absolute ethanol and dried in a vacuum dessicator over anhydrous calcium chloride. The acetates of morpholine and piperidine were prepared by adopting the same procedure for the preparation of the amine hydrochlorides.

**Picrates of the Mannich Bases**

A sample of the compound (0.3 to 0.5 grams) was dissolved in 10 ml. of 95 per cent ethanol. An excess (20-25 ml.) of a saturated solution of picric acid in 95 per cent ethanol was added to the solution. The mixture was allowed to stand at room temperature with occasional stirring until crystals precipitated out of the solution. The salt was removed by filtration and recrystallized from an appropriate solvent.

**Methyl Iodide Derivatives**

A slight excess of methyl iodide was added to a small (0.3-0.4 grams) amount of the Mannich base in a three-necked flask fitted with a dropping funnel and a condenser. The readily formed salt was collected on a filter in quantitative yields.

**Analyses**

All solid materials to be analyzed were recrystallized two to four times from an appropriate solvent and dried in vacuo over phosphorus pentoxide for a period of twenty-
four hours. Liquid to be analyzed were redistilled one or more times.

The nitrogen analyses of the solid substances were performed by the author. The analyses were carried out in duplicate on a micro-scale following the Kjeldahl method as modified by Gunning (142).

Carbon, hydrogen and other nitrogen analyses were performed on a micro-scale in single determinations by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Ultraviolet Absorption Spectra Determinations

Solutions of the alkynitramines and their Mannich condensation products with morpholine were prepared in absolute ethanol. The absorption spectra of the solutions were determined between 212 and 270 millimicrons using a Beckman DU Quartz Spectrophotometer and were performed in the Organic Laboratory, Chemistry Department, McGill University by the author.

Preparation of Hydantoin

(a) Preparation of ethyl ester of hydantoic acid

In a 100 ml. flask a concentrated solution of 17.85 grams (0.22 M) of potassium cyanate was placed. To this solution 51.9 grams (0.3 M) of glycine ethyl ester hydrochloride was added. After a short time and accompanied by a
slight increase in heat, the hydantoin ester precipitated as a solid mass of white crystals. This ester was washed with four 10 ml. portions of absolute alcohol to remove small amounts of potassium chloride. The yield of the compound when recrystallized from hot water was nearly quantitative and the white crystals melted at 135°.

(b) Preparation of Hydantoin

An excess of 25 per cent hydrochloric acid solution was added to the ester in a large round bottom flask. The mixture was evaporated at reduced pressure until a solid residue of hydantoin remained. The product (CIX) which was recrystallized from hot absolute alcohol in a nearly quantitative yield (30 grams), formed white crystals which melted at 215-216°.

Preparation of 5,5-Dimethylhydantoin

(a) Preparation of acetone cyanohydrin

A solution of 124 grams (2.7 M) of potassium cyanide in 400 ml. of water was placed in a two-litre three-necked flask equipped with a mechanical stirrer, dropping funnel and thermometer. To this solution 146 ml. of pure acetone (3.1 M) was added. Following the introduction of the acetone 668 grams (550 ml.) of 30 per cent sulphuric acid (by weight) was slowly added from the dropping funnel with constant stirring.
The temperature was not allowed to rise above $20^\circ$ and this was accomplished by adding crushed ice to the reaction mixture. After the acid was added, the solution was stirred for an additional fifteen minutes. The reaction mixture was extracted with three 100 ml. portions of ether and the combined extract was dried with anhydrous sodium sulphate. The ether was evaporated by distillation on the water bath and the product was distilled rapidly under reduced pressure. The acetone cyanohydrin passed over at 85-90$^\circ$ at 20 mm. pressure in a quantitative yield of 100 grams.

(b) Preparation of 5,5-dimethylhydantoin

In a large evaporating dish 85 grams (1 M) of acetone cyanohydrin was placed. To this compound 150 grams (1.5 M) of freshly powdered ammonium carbonate was added. The reagents were mixed thoroughly and placed on a water bath. The reaction was kept at 70-80$^\circ$ with constant stirring for three hours and was finally brought to completion by raising the temperature to 90$^\circ$ and maintaining it until the mixture became quiescent. Upon completion of reaction (about half-hour) the mixture was dissolved in 100 ml. of hot water to which decolourizing carbon was added, and the solution was rapidly filtered through a pre-heated Büchner funnel. The filtrate was evaporated until crystals appeared
on the surface and the flask was then placed on an ice bath. The white crystals were filtered with a suction and washed twice with 8 ml. portions of ether. The mother liquor was concentrated by evaporation and the second crop of crystals was collected by the same procedure. The product was dissolved in a minute volume of water (60 ml.) and digested with a little decolourizing carbon. The hot solution was filtered through a pre-heated Büchner funnel and the filtrate was cooled to room temperature. The recrystallized product (CXII) which was collected on a filter as fine white crystals weighed 51.5 grams. The melting point of the product was 174-175°C, (yield 40%).

Preparation of 1,8-Naphthalimide

In a large three-necked flask which contained 600 ml. of glacial acetic acid, 50 grams (0.32 M) of acenaphthene was added. The mixture was heated until all the compound was dissolved. To this mixture, 350 grams of sodium dichromate was introduced. During the addition of the salt, the temperature was kept below 80°C but upon completion of the addition, the mixture was heated to 80°C and maintained at that temperature for one hour. The reaction mixture was heated further for two hours at reflux temperature of acetic acid. Upon completion of reaction, the contents of the flask was poured into a beaker which contained 500 ml. of
warm water. The formed granular precipitate was collected on a filter, dissolved in 400 ml. of 5 per cent sodium hydroxide and heated for an additional five minutes. The solution was filtered. The white precipitate of naphthalic acid was formed when 200 ml. of 2 N sulphuric acid was added to the filtrate. After the product was collected on a filter and allowed to dry overnight at room temperature, it was recrystallized from concentrated nitric acid. The 1,8-naphthalic acid appeared as long yellow needles which melted at 270° (decomp.). The total yield was 52.8 grams (75.3%). The 1,8-naphthalic anhydride was obtained by heating the naphthalic acid in a drying oven at 145° for twenty-four hours. The product appeared as yellow crystals which melted at 275°. This anhydride was converted to 1,8-naphthalimide by heating the anhydride with concentrated ammonia in the fume cupboard for three hours, adding smaller amounts of ammonia as the solution evaporated. Upon completion of the cooling of the reaction mixture, the product (CXXXII) was collected on a filter, washed with several portions of water and dried overnight at room temperature. The total yield before sublimation of the product under reduced pressure was 24.5 grams (83.9%). The white crystals melted at 305°.

**Preparation of Uracil**

Into a one-litre three-necked flask which contained
400 ml. of fuming sulphuric acid (15 per cent sulphur trioxide) and fitted with a mechanical stirrer and thermometer, 100 grams (1.6 M) of urea was added with stirring. During the addition of urea, the temperature was maintained below 0°C. After all of the urea had been introduced, 100 grams (0.74 M) of malic acid was added to the solution. The mixture was heated to 85°C with stirring and finally poured into a beaker filled with cracked ice. The product precipitated (CXX) as a voluminous mass of crystals and was recrystallized from 1250 ml. of water. The final yield was 59 grams (71%). The small white crystals of uracid melted at 336-337°C.

Preparation of Hydouracil

In the reduction flask 6 grams of pure uracil was placed and to this compound 2 grams of gum arabic dissolved in 50 ml. of hot water, 10 ml. of 10 per cent chloroplatinic acid solution, and 150 ml. of water was added. Before placing the reduction flask in position on the hydrogenating apparatus, the catalyst was seeded by adopting a method reported by Lochte, Bailey and Noyes (143). In a small beaker which contained 10 ml. of water and a few drops of gum arabic solution, 5 ml. of 10 per cent chloroplatinic acid was added. To this solution 0.5 ml. of 30 per cent sodium hydroxide was introduced followed by a few crystals of symmetrical di-iso-propyl-hydrazine. The mixture was heated and the reduction
of the platinum occurred instantly. This black liquid was poured into the reduction flask which was then placed in position on the hydrogenation apparatus and connected with a cylinder of hydrogen. After removal of air, hydrogen was introduced until 30 lbs./in\(^2\) was obtained. The shaking apparatus was started and the electric current was applied to the hot plate placed underneath the shaker. Within a short time the reaction mixture turned completely black and the temperature was increased to and maintained at 75\(^\circ\) by proper regulation of the current. The total decrease of hydrogen pressure was 5 lbs./in\(^2\) (theoretical 5.6 lbs./in\(^2\)) and the reduction was completed in six and one-half hours. The reduction solution was poured into an equal volume of acetone (210 ml.) and the precipitated colloid was allowed to settle. The clear solution was decanted and filtered. Upon removal of the acetone by distillation of the filtrate, the aqueous portion was evaporated to a small volume on the water bath. On standing at room temperature, crystals of hydrouracil formed in the solution. The product (CXXV) was recrystallized from water as small white crystals which melted at 282-284\(^\circ\). The yield of hydrouracil was 4.5 grams (65%).

**Preparation of Methyl-, Ethyl- and n-Butylnitramines**

(a) Preparation of the ethyl N-alkylcarbamate

In a one-litre three-necked flask fitted with a
mechanical stirrer, dropping funnel and thermometer, 73.5 grams (1.84 M) of sodium hydroxide dissolved in 100 ml. of water was placed. The mixture was cooled to 0° by means of an ice bath and 1.6 M of the amine was added. Into this solution 163.5 grams (1.5 M) of ethyl chloroformate was introduced at such a rate that the temperature did not rise above 20°. When addition was complete, the stirring was continued for a few minutes. The ethyl N-alkylcarbamate was extracted with ether and the ether solution dried over anhydrous potassium carbonate. The dried ether solution was distilled on a water bath and the product was distilled further under reduced pressure. The following products were prepared: (1) 143.5 grams of ethyl N-methylcarbamate boiling at 51° and 2 mm. pressure; (2) 155.4 grams of ethyl N-ethylcarbamate boiling at 54° and 3 mm. pressure; (3) 213.3 grams of ethyl N-n-butylcarbamate boiling at 67° and 1 mm. pressure.

(b) Preparation of ethyl N-nitro-N-alkylcarbamate

In a two-litre three-necked flask equipped with a mechanical stirrer, dropping funnel and thermometer, 318 grams (2.12 M) of acetic anhydride was placed. The flask was cooled by means of an ice bath and 162.5 grams (2.25 M) (109 ml.) of fuming nitric acid (sp. gr. 1.49) was added from the dropping funnel at such a rate that the temperature did not rise above 10°. When addition of the acid was completed, 1.5 M of ethyl N-alkylcarbamate was introduced from the drop-
ping funnel. The rate of addition was controlled so that the temperature was maintained in the range 20-30°. After all the carbamate was added, the temperature was allowed to fall to 0° and the mixture was poured into a large beaker partially filled with ice and water. The nitrocarbamate water mixture was extracted with ether and the ether layer was repeatedly washed with water and 10 per cent potassium carbonate until the solution was alkaline (litmus test). The ether solution was dried over anhydrous magnesium sulphate and the product was distilled at reduced pressures after removal of the ether. The following products were prepared: (1) ethyl N-nitro-N-methylcarbamate, 117.2 grams (0.78 M), boiling at 75° and 3 mm. pressure; (2) ethyl N-nitro-N-ethylcarbamate, 168.7 grams (1.03 M), boiling at 64° and 2 mm. pressure; (3) ethyl N-nitro-N-butylcarbamate, 190 grams (1 M) boiling at 85° and 1 mm. pressure.

(c) Ammonolysis of the ethyl N-nitro-N-alkylcarbamate

The nitrocarbamate was placed in a two-litre round-bottom flask containing one litre of anhydrous ether. Dry ammonia was allowed to bubble through the solution with the excess gas absorbed by a water trap. Within one hour the ammonium salt of the nitramine started to precipitate from the solution. Upon completion of reaction (about four hours) the salt was collected on a filter and washed with two 25 ml. portions of anhydrous ether.
(d) Acidification of the ammonium nitramine

Dilute hydrochloric acid was added to the salt until the solution was acidic (litmus test). The nitramine was extracted with ether and distilled under reduced pressure after removal of the ether.

When methylnitramine was distilled after removal of the ether portion, the product did not give a correct carbon and hydrogen analysis and showed a melting point of 52° (Lit. 32°) (144). A modification was employed by which the methylnitramine was obtained from the extracted ether portion of the acidified solution. The ether was removed by distillation on a water bath and the product which remained in the distilling flask as white solid crystals was recrystallized from petroleum ether (boiling range 30-60°). The following alkyl nitramines were prepared: (1) methylnitramine, m.p. 32-33.5°, yield 7-9 grams (10-12%); (2) ethyl nitramine, yield 75.8 grams (84%), b.p. 77°, at 3 mm. pressure; (3) n-butylnitramine, b.p. 82-84° at 2 mm. pressure, yield 67.5 grams (60%).
1. Reactions of 2-pyrrolidone

(a) Condensation of 2-pyrrolidone with formaldehyde and morpholine

1-(Morpholinomethyl)-2-pyrrolidone (CV)

In a 50 ml. three-necked flask fitted with a mechanical stirrer, reflux condenser, dropping funnel and thermometer, a solution containing 2.55 grams (0.03 M) of 2-pyrrolidone in 20 ml. of water and 2.8 grams (0.03 M) of morpholine was placed. The mixture was stirred and 2.7 ml. (0.03 M) of 35 per cent formaldehyde was added slowly. The reaction mixture was refluxed at 100° for one hour. Upon cooling the solution was extracted with chloroform and the chloroform portion was concentrated by distillation on a water bath. To this residue 25 ml. of alcohol was added and the solution was concentrated by further distillation. After twelve hours, hard white crystals of CV appeared in the residue which after several crystallizations melted at 68.5-69.5°. The total yield was 1.5 grams (27.15%).

Anal. Calcd. for C₉H₁₆N₂O₂: N, 15.26%

Found: N, 15.12; 15.48%

The readily formed picrate of CV was recrystallized from ethanol to yield fine yellow needles which melted at 156.5-158°.

The yield of CV was increased to 2.1 grams (37.8%) when the above experiment was repeated with the reaction time extended to two hours.
(b) Condensation of 2-pyrrolidone with formaldehyde and piperidine

1-(Piperidinomethyl)-2-pyrrolidone (CVI)

This product (CVI) was prepared by refluxing the mixture of 2.55 grams (0.03 M) of 2-pyrrolidone, 2.7 ml. (0.03 M) of 35 per cent formaldehyde, 2.7 ml. (0.03 M) of piperidine and 20 ml. of water at 100° for one-half hour. When the solution was cooled, the product (CVI) was extracted in the same manner as described for the above experiment. A precipitate (CVI) formed in the residue was recrystallized from alcohol and yielded 1.5 grams (27.4%) of white crystals which melted at 47.5-49°.

Anal. Calcd. for C_{10}H_{18}N_{2}O: N, 15.37%

Found: N, 15.22; 15.25%

The picrate of CVI was prepared and recrystallized from ethanol to yield soft white crystals which melted at 155.5°.

The methyl iodide salt (CVII) was readily formed to yield soft white crystals which melted at 153.5-154°.

When the experiment was repeated with the reaction time extended to one hour, the yield was decreased to 0.5 grams (9.1%).
(c) Condensation of 2-pyrrolidone with formaldehyde and dimethylamine hydrochloride

1-(Dimethylaminomethyl)-2-pyrrolidone (CVIII)

The reaction mixture of 2.55 grams (0.03 M) of 2-pyrrolidone, 2.7 ml. (0.03 M) of 35 per cent formaldehyde, 2.45 grams (0.03 M) of dimethylamine hydrochloride and 20 ml. of water was heated at 68° for one half-hour with constant stirring. An excess of 20 per cent aqueous solution of potassium carbonate was introduced into the cold solution and the reaction was stirred vigorously. The alkaline portion was extracted with chloroform layer and concentrated by distillation on a water bath. The residue was fractionally distilled to yield 1.5 grams (37.4%) of a liquid product (CVIII) with a boiling range of 64-67° at 1 mm. pressure.

Anal. Calcd. for C_{7}H_{14}N_{2}O: N, 19.7%

Found: N, 18.72%

Yellow needles, which melted at 168-169°, were formed when the picrate of CVIII was recrystallized from 95% ethyl alcohol.

(d) Attempted condensation of 2-pyrrolidone with formaldehyde and pyrrolidone

In a 50 ml. flask containing equimolecular amounts of 2-pyrrolidone, formaldehyde and 20 ml. of water, 2.5 ml. of pyrrolidone was added. The solution was stirred at 90° for thirty minutes. The reaction mixture was extracted in the same manner as experiment (a) but no condensation product
was isolated.

2. Reactions of Hydantoin

(a) Condensation of hydantoin with formaldehyde and morpholine

1,3-Di(morpholinomethyl) hydantoin (CXI)

Hydantoin (3 g., 0.03 M) dissolved in 20 ml. of hot water was placed in a reaction flask fitted with a mechanical stirrer, reflux condenser, dropping funnel and thermometer. To this heated solution, 2.8 ml. (0.03 M) of morpholine was added. The mixture was stirred and 2.7 ml. (0.03 M) of 35 per cent formaldehyde was introduced dropwise from the dropping funnel. The reaction mixture was heated at 85° for fifteen minutes. The product was extracted from the cold solution with chloroform and the chloroform portion was concentrated by distillation on water bath. Twenty-five ml. of alcohol was added to the residue and this solution was concentrated by further distillation. The residue was cooled at 4° for twelve hours. The product (CXI) after filtration and recrystallization from ethanol yielded 2 grams (22.34%) of hard white crystals which melted at 144.5-145.5°.

Anal. Calcd. for C_{13}H_{22}N_{4}O_{4}; N, 18.84%

Found: N, 18.73; 18.76; 19.03; 18.71%

When the picrate of CXI was recrystallized from ethanol, it yielded short yellow needles which melted at 149.5-150.5°.

The experiment was repeated using 1:2:2 mole ratio
of hydantoin, formaldehyde and morpholine respectively and this condensation reaction yielded 4.3 grams (49.2%) of CXI.

The above experiment, using the 1:2:2 mole ratio, was also repeated with the extension of the reaction time to thirty, forty-five and sixty minutes. These reactions gave yields of 4 grams (44.9%), 3.8 grams (42.6%) and 3.8 grams respectively.

Acid hydrolysis of 1,3-di(morpholinomethyl) hydantoin

In a 50 ml. flask a sample (0.3 g.) of CXI was placed. To this compound 25 ml. of absolute alcohol was added and dry hydrogen chloride was allowed to bubble through the solution. A white precipitate appeared which melted at 213-215°C after several crystallizations from hot water. This product mixed with hydantoin melted at 215-216°C. It was assumed that the precipitate was hydantoin (lit. m.p. 220°C) (145).

(b) Attempted condensation of hydantoin with formaldehyde and diethylamine

A water solution containing equimolecular amounts of hydantoin, formaldehyde and diethylamine was refluxed at 100°C for thirty minutes. No condensation product was observed to occur from the extracted portion of the cooled mixture.

The experiment was repeated with the reaction time extended to forty-five and sixty minutes but in both cases no product was isolated.
(c) Attempted condensation of hydantoin with formaldehyde and di-n-butylamine

An equimolecular mixture of hydantoin, formaldehyde and di-n-butylamine was heated at 100° in a 50 ml. round-bottom flask for fifteen minutes with stirring. The extracted portion of the cooled mixture yielded unreacted hydantoin.

The above experiment was repeated with the reaction time extended to one-half hour but no condensation product was obtained.

(d) Attempted condensation of hydantoin with formaldehyde and piperidine

All attempts to form a condensation product using piperidine as the secondary amine were unsuccessful.

3. Reactions of 5,5-dimethylhydantoin

(a) Condensation of 5,5-dimethylhydantoin with formaldehyde and morpholine

1,3-Di(morpholinomethyl)-5,5-dimethylhydantoin (CXIII)

A 50 ml. flask was fitted with a mechanical stirrer, reflux condenser, dropping funnel and thermometer. Into this flask 3.8 grams (0.03 M) of 5,5-dimethylhydantoin dissolved in 20 ml. of water and 5.4 ml. (0.06 M) of 35 per cent formaldehyde was placed. To this mixture 5.6 ml. (0.06 M) of morpholine was introduced. The reaction solution was stirred at 90° for thirty minutes. When the solution was cooled, the product was extracted by the method described for the preparation of 1,3-di(morpholinomethyl)hydantoin.
After twelve hours at 4°C a precipitate formed in the alcohol residue. This product (CXIII) was collected on a filter and recrystallized from alcohol to yield 3.9 grams (39.8%) of white crystals which melted at 134-134.5°C.

Anal. Calcd. for C15H26N4O4: N, 17.1%

Found: N, 17.02; 17.1; 16.97; 17.05%

When the readily formed picrate of CXIII was recrystallized from ethanol, it yielded small yellow prisms which melted at 146-147.5°C.

The above experiment was repeated with the reaction time extended to one hour and one hour and thirty minutes. The yields obtained from these reactions were 2.9 grams (29.6%) and 2.69 grams (26.5%) respectively.

(b) Attempted condensation of 5,5-dimethylhydantoin with formaldehyde and diethylamine

A condensation reaction was attempted by heating a water mixture of 5,5-dimethylhydantoin, formaldehyde and diethylamine at 90°C for thirty minutes but no product was observed to occur. The experiment was repeated with the reaction time extended to one hour. However, fractional distillation of the reaction mixture yielded nearly quantitative amounts of diethylamine.

(c) Attempted condensation of 5,5-dimethylhydantoin with formaldehyde and piperidine

To a solution containing 3.8 grams (0.03 M) of 5,5-dimethylhydantoin dissolved in 20 ml. of water and 5.4
ml. (0.06 M) of 35 per cent formaldehyde, 5.4 ml. (0.06 M) of piperidine was added. The mixture was heated at 90° for one hour. All attempts to isolate a reaction product from the cooled solution proved unsuccessful.

The experiment was modified by adding 4 ml. of acetic acid to the reaction mixture but this reaction yielded only a resin product.

(d) Attempted condensation of 5,5-dimethylhydantoin with formaldehyde and dimethylamine hydrochloride

A reaction mixture of 5,5-dimethylhydantoin, formaldehyde and dimethylamine hydrochloride was refluxed at 100° for thirty minutes. When the solution was cooled, an excess of 20 per cent aqueous solution of potassium carbonate was added to the mixture. No condensation product was obtained from the extracted alkaline portion.

4. Reactions of 2,4-thiazolidinedione

(a) Condensation of 2,4-thiazolidinedione with formaldehyde and piperidine

3-(Piperidinomethyl)-2,4-thiazolidinedione (CXV)

In a 50 ml. flask 3.5 grams (0.03 M) of 2,4-thiazolidinedione dissolved in 15 ml. of alcohol was placed. The solution was cooled to 0° and 2.7 ml. (0.03 M) of 35 per cent formaldehyde was added. To this cold mixture 2.7 ml. (0.03 M) of piperidine was slowly introduced with the temperature maintained at 0°. In a short time crystals (CXV) appeared in
the reaction flask and after several crystallizations from absolute alcohol yielded 6.17 grams (95.9%) of white crystals which melted at 76-77°.

Anal. Calcd. for C₉H₁₄N₂O₂S: C, 50.44; H, 6.58; N, 13.02%

Found: C, 50.69; H, 6.55; N, 13.04%

The picrate of CXV was recrystallized from alcohol to yield small yellow needles which melted at 151-152°.

A decreased yield (3.42 g.) (52.2%) was obtained when the experiment was repeated and the reaction mixture heated at 40° for one-half hour. A resin was formed when the reaction mixture was heated at 80° for one-half hour.

(b) Condensation of 2,4-thiazolidinedione with formaldehyde and morpholine

3-\{(Morpholinomethyl)-2,4-thiazolidinedione (CXVI)

To a cold solution containing 3.5 grams (0.03 M) of 2,4-thiazolidinedione dissolved in 15 ml. of alcohol and 2.7 ml. (0.03 M) of 35 per cent formaldehyde, 218 ml. (0.03 M) of morpholine was added. The formed precipitate (CXVI) was collected on a filter and recrystallized from absolute ethanol to yield 6.48 grams (100%) of white crystals which melted at 147°.

Anal. Calcd. for C₈H₁₂N₂O₃S: N, 12.95%

Found: N, 13.05; 13.03%

Small yellow needles which melted at 150.5-151° were formed when the picrate of CXVI was recrystallized from alcohol.
(c) Condensation of 2,4-thiazolidinedione with formaldehyde and dimethylamine

3-(Dimethylaminomethyl)-2,4-thiazolidinedione (CXVII)

This condensation product (CXVII) was obtained by slowly adding 5.5 ml. (0.03 M) of 25 per cent dimethylamine to a cold solution of 3.5 grams (0.03 M) of 2,4-thiazolidinedione dissolved in 15 ml. of alcohol and 2.7 ml. (0.03 M) of 35 per cent formaldehyde. The filtered precipitate (CXVII) which was recrystallized from absolute alcohol yielded 3.74 grams (71.5%) of white crystals which melted at 82°.

Anal. Calcd. for C₆H₁₀N₂O₂S: C, 41.36; H, 51.78; N, 16.08%  
Found: C, 41.60; H, 5.92; N, 16.05%

The picrate of CXVII was recrystallized from ethanol to yield small yellow plates which melted at 159.5-160°.

A dark resin was formed when the condensation reaction was repeated with the application of heat.

The methyl iodide salt (CXVIII) which formed in a quantitative yield, melted at 176.5-177° (decomposed).

(d) Condensation of 2,4-thiazolidinedione with formaldehyde and methylamine

N-Methyl-N,N-bis(2,4-thiazolidinedionomethyl)amine (CXIX)

A mixture of 3.5 grams (0.03 M) of 2,4-thiazolidinedione dissolved in 15 ml. of alcohol and 2.7 ml. of (0.03 M) of 35 per cent formaldehyde was cooled to 0°. The flask was maintained in the ice bath while 0.93 grams (4.84 ml.) (0.03 M) of 25 per cent methylamine was added dropwise. The reaction
product (CXIX) was recrystallized from absolute alcohol to yield 4.34 grams (50.1%) of soft white crystals which melted at 144-145°.

Anal. Calcd. for C$_9$H$_{11}$N$_3$O$_4$S$_2$: N, 14.52%
Found: N, 14.59; 14.42%

When the picrate was recrystallized from ethanol, it yielded yellow needles which melted at 207-207.5°.

The above experiment was repeated using a 2:2:1 mole ratio of 2,4-thiazolidinedione, formaldehyde and methylamine respectively. The obtained yield of CXIX was 7.1 grams (83%).

5. Reactions of uracil
   (a) Condensation of uracil with formaldehyde and morpholine

   3-(Morpholinomethyl)uracil (CXXIV)

   Uracil (3.36 g.) (0.03 M) dissolved in 40 ml. of water and morpholine (2.8 ml.) (0.03 M) were introduced in a 50 ml. round-bottom flask. The mixture was stirred while 2.7 ml. (0.03 M) of 35 per cent formaldehyde was slowly added. The solution was immediately cooled after the addition of formaldehyde. A precipitate (CXXIV) was formed from the reduced volume of the solvent which after filtration and recrystallization from alcohol formed 2.16 grams (56.1%) of white crystals which melted at 208.5-209°.

   Anal. Calcd. for C$_9$H$_{13}$N$_3$O$_2$: N, 19.89%
   Found: N, 19.7; 19.92%

   The picrate of CXXIV was recrystallized from acetone
to yield yellow prisms which melted at 234°.

The above experiment was repeated with the reaction time extended to one-half hour and one hour but in these cases no identifiable product could be isolated.

(b) Attempted condensation of uracil with formaldehyde and piperidine

No apparent reaction took place when the above procedure was repeated using piperidine as the secondary amine. The experiment was repeated with the application of heat and the extension of the reaction time to fifteen and thirty minutes. In both attempts unreacted uracil was recovered from the reaction solution.

6. Reactions of hydouracil

(a) Attempted condensation of hydouracil with formaldehyde and morpholine

To a solution of 3.42 grams (0.03 M) of hydouracil dissolved in 40 ml. of water and 2.8 ml. (0.03 M) of morpholine, 2.7 ml. (0.03 M) of 35 per cent formaldehyde was added dropwise. After cooling of the reaction mixture and reduction of the volume of solvent, no precipitate was observed to occur.

The application of heat and the extension of the reaction time failed to form any reaction product. The experiment was modified by separating the reaction mixture with chloroform and adding the alcohol to the concentrated chloroform solution, but no product could be isolated. In
all of the attempts hydouracil was quantitatively recovered from the reaction solution.

(b) Attempted condensation of hydouracil with formaldehyde and piperidine

In a 50 ml. round-bottom flask, a mixture of hydouracil, formaldehyde and piperidine in water was immediately cooled but this experiment failed to yield any condensation product. No reaction took place when the experiment was repeated with the application of heat and the extension of the reaction time.

7. Reactions of succinimide

(a) Condensation of succinimide with formaldehyde and morpholine

\[ \text{N-(Morpholinomethyl)succinimide (CXXVI)} \]

A mixture containing 2.9 grams (0.03 M) of succinimide dissolved in 20 ml. of water and 2.7 ml. (0.03 M) of 35 per cent formaldehyde was placed in a 50 ml. three-necked flask equipped with a mechanical stirrer, reflux condenser, dropping funnel and thermometer. The solution was stirred while 2.8 ml. (0.03 M) of morpholine was added dropwise. The reaction mixture was heated at 95° for one-half hour. When the solution was cooled, the product was extracted with three 10 ml. portions of chloroform. The combined chloroform extracts were evaporated by distillation under reduced pressure at room temperature until a minimum volume of solvent was retained in the distilling flask. To the residue, 25 ml.
of ethanol was added and this solution was distilled further at reduced pressure until all traces of the chloroform was removed and only a small volume of ethanol solvent remained. Upon standing at 40 for twelve hours a precipitate (CXXVI) was formed, which after several crystallizations from alcohol yielded 2.6 grams (43.3%) of hard white crystals which melted at 112.5-113.50.


Found: N, 14.06; 14.26%

The picrate of CXXVI was prepared and recrystallized from ethanol. It formed yellow needles which melted at 181-1820.

(b) Attempted condensation of succinimide with formaldehyde and pyrrolidine

The above procedure was repeated using pyrrolidine as the secondary amine but no reaction was observed to occur. No product was obtained when the reaction time was extended to one hour.

8. Reactions of phthalimide

(a) Condensation of phthalimide with formaldehyde and morpholine

N-(Morpholinomethyl)phthalimide (CXXVIII)

This product (CXXVIII) was prepared by adding 2.7 ml. (0.03 M) of 35 per cent formaldehyde to a solution containing 4.4 grams (0.03 M) of phthalimide dissolved in 20 ml. of ethanol and 2.8 ml. (0.03 M) of morpholine. The reaction
mixture was stirred at 90° for one hour. A solid precipitate formed in the reaction flask when the solution was cooled to room temperature. The product (CXXVIII) was collected on a filter and after repeated crystallizations from alcohol gave 2.9 grams (25.7%) of white crystals which melted at 117.5-119°.

Anal. Calcd. for C_{13}H_{14}N_{2}O_{3}: N, 11.37%
Found: N, 11.30; 11.25%

The crystals of the picrate of CXXVIII, which was recrystallized from ethanol, were short yellow needles which melted at 194-195°.

Acid hydrolysis of N-(morpholinomethyl)phthalimide (CXXVIII)

Dry hydrogen chloride was allowed to bubble through a solution containing a sample (0.3 g.) of CXXVIII dissolved in 50 ml. of absolute alcohol. A white precipitate formed accompanied by a slight warming of the solution. After several crystallizations from absolute alcohol, this precipitate formed soft white needles which melted at 229°. The mixed melting point of this product with phthalimide was 230° (m.p. of phthalimide 238°) (145). The precipitate was assumed to be phthalimide.

(b) Attempted condensation of phthalimide with formaldehyde and diethylamine

An alcoholic solution of phthalimide, formaldehyde and diethylamine was heated for one-half hour at 90°. No product was isolated from the cold solution.
The attempt failed to yield any condensation product when the reaction time was extended to one hour. In both cases nearly quantitative amounts of phthalimide were recovered from the reaction.

9. Reactions of 1,8-naphthalimide

(a) Attempted condensation of 1,8-naphthalimide with formaldehyde and morpholine

No reaction took place when a water mixture of 1,8-naphthalimide, morpholine and formaldehyde was refluxed at 100°C for five hours. Nearly quantitative amounts of 1,8-naphthalimide was recovered from the cooled reaction solution. When alcohol was used as the solvent and the reaction time extended to six, sixteen, twenty-four and forty-four hours, no condensation product was obtained.

(b) Attempted condensation of 1,8-naphthalimide with formaldehyde and piperidine

A similar attempt was performed with piperidine as the secondary amine but this experiment also failed to yield any reaction product.

10. Reactions of carbazole

(a) Condensation of carbazole with formaldehyde and piperidine

\[ \text{N-\{Piperidinomethyl\}carbazole (CXXXIV)} \]

In a 50 ml. flask equipped with a mechanical stirrer, reflux condenser, dropping funnel and thermometer, 5 grams (0.03 M) of carbazole dissolved in 50 ml. of acetone
was added. To this solution, 2.7 ml. (0.03 M) of 35 per cent formaldehyde was added. The reaction mixture was cooled to room temperature and 2.7 ml. (0.03 M) of piperidine was slowly introduced. The reaction solution was heated for one-half hour at reflux temperature of solvent and upon completion, the excess solvent was evaporated by distillation. A white precipitate (CXXXIV) formed in the flask which after several crystallizations from acetone yielded 7.64 grams (96.3%) of white crystals which melted at 99.5-100°.

Anal. Calcd. for C_{13}H_{20}N_{2}: C, 81.77; H, 7.62; N, 10.59%

Found: C, 81.83; H, 7.68; N, 10.75%

The picrate of CXXXIV was crystallized from alcohol and it yielded small yellow plates which melted at 242-243°.

(b) Attempted condensation of carbazole with formaldehyde and morpholine

A reaction mixture which contained 0.03 equimolecular amounts of carbazole, formaldehyde, morpholine and 100 ml. of acetone was refluxed for one-half hour. The solution was allowed to cool and the amount of solvent was reduced but no reaction product was isolated.

The experiment was repeated with the reaction time extended to one and four hours but in both cases nearly quantitative amounts of carbazole were recovered from the reaction solution.
(c) Attempted condensation of carbazole with formaldehyde and dimethylamine

No condensation product was obtained when an equimolecular mixture of carbazole, formaldehyde and dimethylamine was allowed to reflux for one-half hour.

(d) Attempted condensation of carbazole with formaldehyde and dimethylamine hydrochloride

Quantitative amounts of carbazole were recovered from the acetone portion when the hydrochloride of dimethylamine was used in the reaction mixture carbazole and formaldehyde and acetone.

11. Reactions of n-butylnitramine

(a) Condensation of n-butylnitramine with formaldehyde and piperidine

N-(Piperidinomethyl)-n-butylnitramine (CXXXVII)

A mixture containing 7.08 grams (0.06 M) of n-butylnitramine dissolved in 20 ml. of alcohol was placed in a 50 ml. round-bottom flask fitted with a thermometer and dropping funnel. The solution was cooled to 0° and 5.4 ml. (0.06 M) of 35 per cent formaldehyde was added dropwise. To this mixture, 5.4 ml. (0.06 M) of piperidine was slowly introduced with the temperature of the reaction mixture maintained at 0°. After twelve hours at 4° the alcohol was evaporated by distillation and the residue was fractionally distilled at reduced pressure. The total yield of the condensation product (CXXXVII) was 4.61 grams (35.7%) and the boiling point was 97-100° at 1 mm. pressure.
Small yellow needles which melted at 148-149° were obtained when the picrate of CXXXVII was recrystallized from alcohol.

(b) Condensation of n-butylnitramine with formaldehyde and morpholine

N-(Morpholinomethyl)-n-butylnitramine (CXXXIX)

The product (CXXXIX) was prepared by the method described in the above procedure with the exception that a precipitate was formed by allowing the reaction mixture to stand for twelve hours at 4°. This precipitate (CXXXIX) which was crystallized from petroleum ether (boiling range 30-60°) yielded 12.7 grams (97.6%) of white crystals which melted at 53-53.5°.

Anal. Calcd. for C_{9}H_{19}N_{3}O_{3}: N, 19.34%

Found: N, 19.62%

The picrate was recrystallized from alcohol to yield small yellow crystals which melted at 148-149°.

(c) Attempted condensation of n-butylnitramine with formaldehyde and diethylamine

The reaction mixture which contained 0.06 equimolecular amounts of n-butylnitramine, formaldehyde, diethylamine and 20 ml. of ethanol was allowed to stand at 4° for twenty-four hours but no condensation product was obtained.
12. Reactions of ethylnitramine

(a) Condensation of ethylnitramine with formaldehyde and piperidine

\[ \text{N-}(\text{Piperidinomethyl})-\alpha-(\text{piperidinomethyl})\text{ethylnitramine (CXLI)} \]

A reaction occurred when 5.4 grams (0.06 M) of ethylnitramine dissolved in 20 ml. of alcohol was added to a cold solution of 5.4 ml. (0.06 M) of 35 per cent formaldehyde and 5.4 ml. (0.06 M) of piperidine. During the addition of the ethylnitramine, the temperature of the reaction mixture was maintained at 0\(^\circ\). The solution was allowed to stand for twelve hours at 4\(^\circ\). A white precipitate (CXLI) formed in the flask, which after filtration and several crystallizations from petroleum ether (boiling range 30-60\(^\circ\)), yielded 8.3 grams (48.8\%) of soft white crystals which melted at 57.5-58\(^\circ\).

Anal. Calcd. for \( \text{C}_{14}\text{H}_{28}\text{N}_{4}\text{O}_{2} \): C, 59.12; H, 9.92\%

Found: C, H,

When the difficultly formed picrate of CXLI was recrystallized from ethanol it yielded yellow crystals which melted at 215.5\(^\circ\) (decomposed).

Anal. Calcd. for \( \text{C}_{20}\text{H}_{31}\text{N}_{7}\text{O}_{9} \): N, 19.09\%

Found: N, 19.06\%

(b) Condensation of ethylnitramine with formaldehyde and morpholine

\[ \text{N-}(\text{Morpholinomethyl})\text{ethylnitramine (CXLI\text{I}))} \]

In a 50 ml. round-bottom flask immersed in an ice bath, 5.4 grams (0.06 M) of ethylnitramine dissolved in 20 ml.
of alcohol and 5.4 ml. (0.06 M) of 35 per cent formaldehyde was added. To this cold solution 5.6 ml. (0.06 M) of morpholine was added dropwise with the reaction mixture kept at 0°. After twelve hours at 4° a precipitate (CXLII) appeared which, after several crystallizations from petroleum ether (boiling range 65-110°), yielded 10.5 grams (92%) of soft white plates which melted at 86-87°.

Anal. Calcd. for C7H15N3O3: C, 44.43; H, 7.99
N, 22.2%

Found: C, 44.61; H, 8.0; N, 21.97%

Yellow crystals which melted at 149.5-150° were obtained when the picrate of CXLII was recrystallized from alcohol.

(c) Attempted condensation of ethylnitramine with formaldehyde and diethylamine

The attempt to form a reaction product when a reaction mixture, which contained 0.06 equimolecular amounts of ethylnitramine, formaldehyde, diethylamine and 20 ml. of ethanol, was allowed to stand at 4° for forty hours failed.

Attempted condensations of methyl nitramine with formaldehyde and secondary amines

All attempts to form reaction products using methyl nitramine, with formaldehyde and secondary amines were unsuccessful.
Colour test for alkylnitramines

This test was performed by adding to a few crystals of the compound several drops of glacial acetic acid. To this mixture, several drops of a 1 per cent solution of dimethylaniline in glacial acetic acid and a pinch of zinc dust were added.

Methyl-, ethyl- and n-butylnitramine showed the characteristic green colour.

Ultraviolet absorption spectra determinations

The value of the molecular extinction coefficient was calculated by the equation

\[ \varepsilon = \frac{A}{cb} \]

In this equation \( \varepsilon \) = the molar extinction coefficient, \( A \) = the observed optical density, \( c \) = molar concentration (moles/litre) and \( b \) = width of absorption cell in cm.

The concentrations of the solutions of alkylnitramines and the Mannich products of ethyl- and n-butylnitramine with morpholine in absolute ethanol are shown in Table II.

The cell width (b) was 1.002 cm. (No. 21628 S).
TABLE II

Concentrations of Solutions of Alkylnitramines and their Mannich Products

<table>
<thead>
<tr>
<th>Compound</th>
<th>Moles/litre of solvent</th>
<th>Grams/1000 g. of solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnitramine</td>
<td>0.000144</td>
<td>0.0011</td>
</tr>
<tr>
<td>Ethylnitramine</td>
<td>0.000099</td>
<td>0.0009</td>
</tr>
<tr>
<td>n-Butylnitramine</td>
<td>0.000118</td>
<td>0.0014</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)ethylnitramine</td>
<td>0.0000845</td>
<td>0.0016</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)-n-butylnitramine</td>
<td>0.0000828</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

The absorption spectra data and the corresponding graphs are shown in Table III.

TABLE III

Absorption Spectra Data and the Corresponding Graphs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Table</th>
<th>Graphs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylnitramine</td>
<td>IV</td>
<td>Figure 2</td>
</tr>
<tr>
<td>Ethylnitramine</td>
<td>V</td>
<td>Figure 3</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)ethylnitramine</td>
<td>VI</td>
<td>Figure 4</td>
</tr>
<tr>
<td>n-Butylnitramine</td>
<td>VII</td>
<td>Figure 5</td>
</tr>
<tr>
<td>N-(Morpholinomethyl)-n-butylnitramine</td>
<td>VIII</td>
<td>Figure 5</td>
</tr>
</tbody>
</table>
TABLE IV

Ultraviolet Absorption Spectrum of Methylnitramine in Absolute Alcohol
<table>
<thead>
<tr>
<th>Wavelength (mμ)</th>
<th>Optical Density</th>
<th>Molar Extinction Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>1.480</td>
<td>10,230</td>
</tr>
<tr>
<td>214</td>
<td>1.542</td>
<td>10,690</td>
</tr>
<tr>
<td>216</td>
<td>1.605</td>
<td>11,130</td>
</tr>
<tr>
<td>218</td>
<td>1.680</td>
<td>11,650</td>
</tr>
<tr>
<td>220</td>
<td>1.760</td>
<td>12,200</td>
</tr>
<tr>
<td>222</td>
<td>1.825</td>
<td>12,660</td>
</tr>
<tr>
<td>224</td>
<td>1.915</td>
<td>13,270</td>
</tr>
<tr>
<td>226</td>
<td>1.965</td>
<td>13,620</td>
</tr>
<tr>
<td>228</td>
<td>2.000</td>
<td>13,870</td>
</tr>
<tr>
<td>230</td>
<td>2.020</td>
<td>14,010</td>
</tr>
<tr>
<td>232</td>
<td>1.98</td>
<td>13,730</td>
</tr>
<tr>
<td>234</td>
<td>1.92</td>
<td>13,310</td>
</tr>
<tr>
<td>236</td>
<td>1.838</td>
<td>12,750</td>
</tr>
<tr>
<td>238</td>
<td>1.72</td>
<td>11,920</td>
</tr>
<tr>
<td>240</td>
<td>1.57</td>
<td>10,880</td>
</tr>
<tr>
<td>242</td>
<td>1.409</td>
<td>9,766</td>
</tr>
<tr>
<td>244</td>
<td>1.233</td>
<td>8,547</td>
</tr>
<tr>
<td>246</td>
<td>1.062</td>
<td>7,362</td>
</tr>
<tr>
<td>248</td>
<td>0.895</td>
<td>6,204</td>
</tr>
<tr>
<td>250</td>
<td>0.732</td>
<td>5,075</td>
</tr>
<tr>
<td>252</td>
<td>0.598</td>
<td>4,146</td>
</tr>
<tr>
<td>254</td>
<td>0.475</td>
<td>3,294</td>
</tr>
<tr>
<td>256</td>
<td>0.376</td>
<td>2,607</td>
</tr>
<tr>
<td>260</td>
<td>0.235</td>
<td>1,629</td>
</tr>
<tr>
<td>270</td>
<td>0.075</td>
<td>520</td>
</tr>
</tbody>
</table>
ULTRAVIOLET ABSORPTION SPECTRUM
OF METHYLNITRAMINE

CONC. - 0.000144 MOLAR IN ABS. ETHANOL

MOLAR EXTINCTION COEFFICIENT X 10^-3

WAVELENGTH - m\mu.

FIGURE 2
<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Absorbance (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>250</td>
<td>1.0</td>
</tr>
<tr>
<td>300</td>
<td>1.5</td>
</tr>
<tr>
<td>350</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**TABLE V**

Ultraviolet Absorption Spectrum of Ethylnitramine in Absolute Ethanol
<table>
<thead>
<tr>
<th>Wavelength</th>
<th>Optical Density</th>
<th>Molar Extinction Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>2.1</td>
<td>21,160</td>
</tr>
<tr>
<td>213</td>
<td>2.08</td>
<td>20,960</td>
</tr>
<tr>
<td>214</td>
<td>2.1</td>
<td>21,160</td>
</tr>
<tr>
<td>215</td>
<td>2.14</td>
<td>21,570</td>
</tr>
<tr>
<td>216</td>
<td>2.2</td>
<td>22,180</td>
</tr>
<tr>
<td>217</td>
<td>2.22</td>
<td>22,390</td>
</tr>
<tr>
<td>218</td>
<td>2.33</td>
<td>23,490</td>
</tr>
<tr>
<td>219</td>
<td>2.37</td>
<td>23,890</td>
</tr>
<tr>
<td>220</td>
<td>2.43</td>
<td>24,500</td>
</tr>
<tr>
<td>221</td>
<td>2.49</td>
<td>25,100</td>
</tr>
<tr>
<td>222</td>
<td>2.58</td>
<td>26,010</td>
</tr>
<tr>
<td>223</td>
<td>2.6</td>
<td>26,210</td>
</tr>
<tr>
<td>224</td>
<td>2.66</td>
<td>26,810</td>
</tr>
<tr>
<td>225</td>
<td>2.68</td>
<td>27,020</td>
</tr>
<tr>
<td>226</td>
<td>2.70</td>
<td>27,220</td>
</tr>
<tr>
<td>227</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>228</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>229</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>230</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>231</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>232</td>
<td>2.8</td>
<td>28,230</td>
</tr>
<tr>
<td>233</td>
<td>2.70</td>
<td>27,220</td>
</tr>
<tr>
<td>234</td>
<td>2.62</td>
<td>26,310</td>
</tr>
<tr>
<td>235</td>
<td>2.58</td>
<td>26,010</td>
</tr>
<tr>
<td>236</td>
<td>2.45</td>
<td>24,700</td>
</tr>
<tr>
<td>237</td>
<td>2.33</td>
<td>22,980</td>
</tr>
<tr>
<td>238</td>
<td>2.08</td>
<td>20,960</td>
</tr>
<tr>
<td>239</td>
<td>1.84</td>
<td>18,550</td>
</tr>
<tr>
<td>240</td>
<td>1.602</td>
<td>16,140</td>
</tr>
<tr>
<td>241</td>
<td>1.355</td>
<td>13,660</td>
</tr>
<tr>
<td>242</td>
<td>1.132</td>
<td>11,410</td>
</tr>
<tr>
<td>243</td>
<td>0.92</td>
<td>9,274</td>
</tr>
<tr>
<td>244</td>
<td>0.75</td>
<td>7,561</td>
</tr>
<tr>
<td>245</td>
<td>0.602</td>
<td>6,068</td>
</tr>
<tr>
<td>246</td>
<td>0.482</td>
<td>4,859</td>
</tr>
<tr>
<td>247</td>
<td>0.384</td>
<td>3,871</td>
</tr>
<tr>
<td>248</td>
<td>0.315</td>
<td>3,176</td>
</tr>
<tr>
<td>249</td>
<td>0.253</td>
<td>2,551</td>
</tr>
<tr>
<td>250</td>
<td>0.208</td>
<td>2,097</td>
</tr>
<tr>
<td>251</td>
<td>0.171</td>
<td>1,724</td>
</tr>
<tr>
<td>252</td>
<td>0.070</td>
<td>705</td>
</tr>
</tbody>
</table>
ULTRAVIOLET ABSORPTION SPECTRUM OF ETHYLNITRAMINE

CONC. - 0.000099 MOLAR IN ABSOLUTE ETHANOL

MOLAR EXTINCTION COEFFICIENT X 10^{-3}

WAVELENGTH - μm.

FIGURE 3
TABLE VI

Ultraviolet Absorption Spectrum of N-(Morpholinomethyl)ethynitramine in Absolute Ethanol
<table>
<thead>
<tr>
<th>Wavelength ((m\mu))</th>
<th>Optical Density</th>
<th>Molar Extinction Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>.406</td>
<td>4,795</td>
</tr>
<tr>
<td>214</td>
<td>.400</td>
<td>4,725</td>
</tr>
<tr>
<td>216</td>
<td>.402</td>
<td>4,747</td>
</tr>
<tr>
<td>218</td>
<td>.414</td>
<td>4,890</td>
</tr>
<tr>
<td>220</td>
<td>.432</td>
<td>5,102</td>
</tr>
<tr>
<td>222</td>
<td>.456</td>
<td>5,392</td>
</tr>
<tr>
<td>224</td>
<td>.484</td>
<td>5,716</td>
</tr>
<tr>
<td>226</td>
<td>.510</td>
<td>6,024</td>
</tr>
<tr>
<td>228</td>
<td>.535</td>
<td>6,320</td>
</tr>
<tr>
<td>230</td>
<td>.550</td>
<td>6,497</td>
</tr>
<tr>
<td>232</td>
<td>.559</td>
<td>6,603</td>
</tr>
<tr>
<td>234</td>
<td>.550</td>
<td>6,497</td>
</tr>
<tr>
<td>236</td>
<td>.532</td>
<td>6,284</td>
</tr>
<tr>
<td>238</td>
<td>.502</td>
<td>5,929</td>
</tr>
<tr>
<td>240</td>
<td>.462</td>
<td>5,456</td>
</tr>
<tr>
<td>242</td>
<td>.416</td>
<td>4,914</td>
</tr>
<tr>
<td>244</td>
<td>.361</td>
<td>4,264</td>
</tr>
<tr>
<td>246</td>
<td>.305</td>
<td>3,644</td>
</tr>
<tr>
<td>248</td>
<td>.247</td>
<td>2,917</td>
</tr>
<tr>
<td>250</td>
<td>.193</td>
<td>2,280</td>
</tr>
<tr>
<td>252</td>
<td>.140</td>
<td>1,654</td>
</tr>
<tr>
<td>254</td>
<td>.091</td>
<td>1,075</td>
</tr>
<tr>
<td>256</td>
<td>.048</td>
<td>566</td>
</tr>
<tr>
<td>258</td>
<td>.011</td>
<td>129</td>
</tr>
</tbody>
</table>
ULTRAVIOLET ABSORPTION SPECTRUM OF N-(MORPHOLINOMETHYL)ETHYL NITRAMINE

CONC. - 0.0000845 MOLAR IN ABS. ETHANOL

MOLAR EXTINCTION COEFFICIENT X 10^3

WAVELENGTH - mμ.

FIGURE 4
TABLE VII

Ultraviolet Absorption Spectrum of n-Butylnitramine in Absolute Ethanol
### TABLE VII

<table>
<thead>
<tr>
<th>Wavelength (m(\mu))</th>
<th>Optical Density</th>
<th>Molar Extinction Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>.82</td>
<td>6,935</td>
</tr>
<tr>
<td>215</td>
<td>.82</td>
<td>6,935</td>
</tr>
<tr>
<td>217</td>
<td>.84</td>
<td>7,106</td>
</tr>
<tr>
<td>219</td>
<td>.88</td>
<td>7,444</td>
</tr>
<tr>
<td>221</td>
<td>.938</td>
<td>7,934</td>
</tr>
<tr>
<td>223</td>
<td>.99</td>
<td>8,363</td>
</tr>
<tr>
<td>225</td>
<td>1.05</td>
<td>8,882</td>
</tr>
<tr>
<td>227</td>
<td>1.08</td>
<td>9,135</td>
</tr>
<tr>
<td>229</td>
<td>1.125</td>
<td>9,493</td>
</tr>
<tr>
<td>231</td>
<td>1.15</td>
<td>9,727</td>
</tr>
<tr>
<td>232</td>
<td>1.15</td>
<td>9,727</td>
</tr>
<tr>
<td>233</td>
<td>1.15</td>
<td>9,727</td>
</tr>
<tr>
<td>235</td>
<td>1.125</td>
<td>9,493</td>
</tr>
<tr>
<td>237</td>
<td>1.08</td>
<td>9,135</td>
</tr>
<tr>
<td>239</td>
<td>1.03</td>
<td>8,712</td>
</tr>
<tr>
<td>241</td>
<td>.96</td>
<td>8,121</td>
</tr>
<tr>
<td>243</td>
<td>.878</td>
<td>7,427</td>
</tr>
<tr>
<td>245</td>
<td>.785</td>
<td>6,639</td>
</tr>
<tr>
<td>247</td>
<td>.69</td>
<td>5,835</td>
</tr>
<tr>
<td>249</td>
<td>.60</td>
<td>5,076</td>
</tr>
<tr>
<td>251</td>
<td>.505</td>
<td>4,272</td>
</tr>
<tr>
<td>253</td>
<td>.424</td>
<td>3,581</td>
</tr>
<tr>
<td>255</td>
<td>.351</td>
<td>2,969</td>
</tr>
<tr>
<td>257</td>
<td>.288</td>
<td>2,436</td>
</tr>
<tr>
<td>259</td>
<td>.237</td>
<td>2,004</td>
</tr>
<tr>
<td>260</td>
<td>.215</td>
<td>1,819</td>
</tr>
<tr>
<td>270</td>
<td>.085</td>
<td>719</td>
</tr>
</tbody>
</table>
TABLE VIII

Ultraviolet Absorption Spectrum of N-(Morpholinomethyl)-n-Butynitramine in Absolute Ethanol
<table>
<thead>
<tr>
<th>Wavelength ((\mu))</th>
<th>Optical Density</th>
<th>Molar Extinction Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>212</td>
<td>0.159</td>
<td>1,916</td>
</tr>
<tr>
<td>214</td>
<td>0.152</td>
<td>1,831</td>
</tr>
<tr>
<td>216</td>
<td>0.154</td>
<td>1,857</td>
</tr>
<tr>
<td>218</td>
<td>0.154</td>
<td>1,857</td>
</tr>
<tr>
<td>220</td>
<td>0.154</td>
<td>1,857</td>
</tr>
<tr>
<td>222</td>
<td>0.167</td>
<td>2,012</td>
</tr>
<tr>
<td>224</td>
<td>0.184</td>
<td>2,217</td>
</tr>
<tr>
<td>226</td>
<td>0.202</td>
<td>2,430</td>
</tr>
<tr>
<td>228</td>
<td>0.220</td>
<td>2,651</td>
</tr>
<tr>
<td>230</td>
<td>0.237</td>
<td>2,856</td>
</tr>
<tr>
<td>232</td>
<td>0.243</td>
<td>2,928</td>
</tr>
<tr>
<td>234</td>
<td>0.244</td>
<td>2,931</td>
</tr>
<tr>
<td>236</td>
<td>0.237</td>
<td>2,856</td>
</tr>
<tr>
<td>238</td>
<td>0.225</td>
<td>2,711</td>
</tr>
<tr>
<td>240</td>
<td>0.208</td>
<td>2,507</td>
</tr>
<tr>
<td>242</td>
<td>0.182</td>
<td>2,194</td>
</tr>
<tr>
<td>244</td>
<td>0.157</td>
<td>1,892</td>
</tr>
<tr>
<td>246</td>
<td>0.126</td>
<td>1,518</td>
</tr>
<tr>
<td>248</td>
<td>0.096</td>
<td>1,157</td>
</tr>
<tr>
<td>250</td>
<td>0.065</td>
<td>783</td>
</tr>
<tr>
<td>252</td>
<td>0.033</td>
<td>397</td>
</tr>
<tr>
<td>254</td>
<td>0.005</td>
<td>60</td>
</tr>
</tbody>
</table>
ULTRAVIOLET ABSORPTION SPECTRA

(A) \( \eta \)-BUTYLNITRAMINE
CONC. - 0.000118 MOLAR
IN ABSOLUTE ETHANOL

(B) N-(MORPHOLINOMETHYL)-\( \eta \)-BUTYLNITRAMINE
CONC. - 0.0000828 MOLAR
IN ABSOLUTE ETHANOL

MOLAR EXTINCTION COEFFICIENT \( \times 10^{-3} \)

WAVELENGTH - \( \text{m} \mu \).

FIGURE 5
SUMMARY AND CLAIMS TO ORIGINAL RESEARCH

1. The following literature has been reviewed: (1) the Mannich condensation; (2) the rôle of the Mannich condensation in the biogenesis of alkaloids; (3) substitution reactions of the -NH- group in imines and imides; (4) ultraviolet absorption spectra of alkynitramines.

2. The scope of the Mannich condensation was extended to acidic compounds containing the -NH- group. Additional information on the reactivity of -NH- groups has been obtained and a series of new functional derivatives containing the group \( \text{N-CH}_2\text{-N} \) has been prepared.

3. A principle has been applied by which a compound can be considered to undergo Mannich reactions. The characteristic feature of this principle is the ability of the active hydrogen of the acidic compounds to be replaced either by a metal or by a halogen or by both.

4. The activating influence of the carbonyl and nitro substituent on the -NH- group was established in the Mannich condensation.

5. The synthesis of Mannich bases was accomplished by the condensation of secondary amines and formaldehyde with the following compounds: (1) 2-pyrrolidone; (2) hydantoin; (3) 5,5-dimethylhydantoin; (4) 2,4-thiazolidinedione; (5) uracil; (6) succinimide; (7) phthalimide; (8) carbaz-
ole; (9) ethyl nitramine; (10) n-butylnitramine.

6. Hydrouracil, 1,8-naphthalimide and methylnitramine failed to form Mannich bases.

7. The synthesis of N-(morpholinomethyl)succinimide (CXXVI), N-(morpholinomethyl)-phthalimide (CXXVIII) and N-(piperidinomethyl)-n-butylnitramine (CXXXVII) by the Mannich condensation offered additional support to the mechanism favoured by Alexander and Underhill (4) in which they postulated that the formation of aminomethanol compound was the primary reaction of the Mannich condensation.

8. The cleavage of the -N-\textsuperscript{\textdagger}C-N- grouping of N-(morpholinomethyl)phthalimide (CXXVIII) and 1,3-di(morpholinomethyl)hydantoin (CXI) was observed by acid hydrolysis.

9. The ultraviolet absorption spectra of methylnitramine, ethyl nitramine, n-butylnitramine, N-(morpholinomethyl)ethyl nitramine (CXLII) and N-(morpholinomethyl)-n-butylnitramine (CXXXIX) have been investigated between 212 and 270 m\textmu. The following absorption maxima were found:

- methylnitramine, \( \lambda_{\text{max}} \). 230 m\textmu
- ethyl nitramine, \( \lambda_{\text{max}} \). 227-232 m\textmu
- N-(morpholinomethyl)ethyl nitramine, \( \lambda_{\text{max}} \). 232 m\textmu
- n-butylnitramine, \( \lambda_{\text{max}} \). 231-233 m\textmu
- N-(morpholinomethyl)-n-butylnitramine, \( \lambda_{\text{max}} \). 234 m\textmu

10. The following compounds have been contributed to the
literature:

(1) 1,3-di(morpholinomethyl)hydantoin  
(2) 1,3-di(morpholinomethyl)-5,5-dimethylhydantoin  
(3) 3-(morpholinomethyl)uracil  
(4) 1-(dimethylaminomethyl)-2-pyrrolidone  
(5) 1-(morpholinomethyl)-2-pyrrolidone  
(6) 1-(piperidinomethyl)-2-pyrrolidone  
(7) 3-(morpholinomethyl)-2,4-thiazolidinedione  
(8) 3-(piperidinomethyl)-2,4-thiazolidinedione  
(9) 3-(dimethylaminomethyl)-2,4-thiazolidinedione  
(10) N-methyl-N,N-bis(2,4-thiazolidinedionomethyl)-amine  
(11) N-(morpholinomethyl)ethylnitramine  
(12) N-(piperidinomethyl)-α-(piperidinomethyl)-ethylnitramine  
(13) N-(morpholinomethyl)-n-butylnitramine

11. Picric acid derivatives were prepared with all the reaction products and the methyl iodide derivatives of N-(piperidinomethyl)-2-pyrrolidone and N-(dimethylaminomethyl)-2,4-thiazolidinedione were prepared in quantitative yields.
REFERENCES

1. Blicke, F.F. Organic Reactions 1, 303 (1942); John Wiley and Sons, New York, N.Y.


8. Mannich, C. and Bauroth, M. Ber. 55, 3504 (1922).


23. Mannich, C. Arch. Pharm. 255, 261 (1917).
24. Mannich, C. and Ball, B. Arch. Pharm. 264, 65 (1926).
31. Mannich, C. and Hieronimus, O. Ber. 75, 49 (1942).
37. Mannich, C. Arch. Pharm. 272, 323 (1934).
44. Decombe, J. Compt. rend. 196, 866; 197, 258 (1933).


60. Kuhn, H. and Stein, O. Ber. 70, 567 (1937).


88. Hahn, G. and Ludewig, H. Ber. 67, 2031 (1934).
90. Hahn, G. and Hansel, A. Ber. 71, 2192 (1938).
95. Blacher, C. Ber. 28, 2353 (1895).
97. Bredt, J. and Hof, H. Ber. 23, 21 (1900).
106. Tafel, J. and Wassmuth, O. Ber. 40, 2831 (1907).
107. Tafel, J. and Stern, M. Ber. 33, 2224 (1900).
110. Franchimont, M.A.P.N. Rec. trav. chim. 12, 308 (1894).
131. Harries, C. and Weiss, M. Ber. 33, 3418 (1900).
140. Franchimont, M.A.P.N. Rec. trav. chim. 16, 213 (1897).
144. Franchimont, M.A.P.N. Rec. trav. chim. 7, 359 (1888).