THE REACTION OF HYDRAZOIC ACID WITH SUBSTITUTED CYANAMIDES: THE SYNTHESIS AND PROPERTIES OF VARIOUS DERIVATIVES OF 5-AMINOTETRAZOLE

By

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Department of Chemistry

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INTRODUCTION

While 5-aminotetrazole has been known for many years (1), its derivatives in which amino hydrogens are replaced by alkyl groups are not, in general, known.

A study of this class of compounds, the 5-di- and mono-alkylaminotetrazoles, is of interest for several reasons. The parent substance, 5-aminotetrazole, possessing both an acidic and a basic function, leads one to speculate concerning the effect of substituents on these functions. Further, since alkylation of 5-aminotetrazole leads to a mixture of materials (2), there is need for a direct, unequivocal synthesis of these derivatives. Also, the possibility that this class of compounds might have useful physiological activity seemed attractive.

5-Substituted tetrazoles have long been obtained through the action of hydrazoic acid on the carbon-nitrogen triple bond. Recently, for example, acyl nitriles were shown to yield the corresponding 5-alkyl- and 5-aryltetrazoles (3). Hantzsch and Vagt (4), some fifty years ago, prepared 5-aminotetrazole by the interaction of hydrazoic acid and cyanamide. Similarly, Oliveri-
Mandalà (5) prepared 5-bromo-, 5-cyano-, and 5-carbethoxytetrazole from cyanogen bromide, cyanogen, and ethyl cyanoformate, respectively.

The only 5-disubstituted aminotetrazoles recorded in the literature are 5-phenylmethyl-, 5-phenylethyl, and 5-phenylbenzylaminotetrazole. These were prepared by Stollé, who heated the corresponding disubstituted cyanamides in a benzene solution of hydrazoic acid under pressure (6).

The reaction of hydrazoic acid with variously substituted cyanamides appeared to constitute a promising method for the direct and relatively unequivocal synthesis of the desired compounds. The results of these investigations are described in the following under the headings:

Part I. The Action of Hydrazoic Acid on Dialkylcyanamides.

Part II. The Action of Hydrazoic Acid on Monoalkylcyanamides.

Part III. The Synthesis of 5-Monoalkylaminotetrazoles.

Part IV. The Rearrangement of Certain Aminotetrazole Derivatives.

Part V. The Effect of Substituents on the Acidity of Certain Tetrazole Derivatives.
PART I

THE ACTION OF HYDRAZOIC ACID ON DIALKYL CYANAMIDES

Discussion

The synthesis of 5-aminotetrazole and some of its substituted derivatives has been accomplished by a number of methods. The parent compound was first obtained by Thiele (1) through the action of nitrous acid on aminoguanidine. The reaction involved the initial formation of guanyl azide which readily cyclized with the formation of 5-aminotetrazole.

\[
\begin{align*}
\text{H}_2\text{N-C}=-\text{NH} \quad & \xrightarrow{\text{HONO}} \quad \text{H}_2\text{N-C}=-\text{NH} \quad & \rightarrow \quad \text{H}_2\text{N-C}=-\text{N-H} \\
\text{NH}_2 & \quad & \text{N}_3 & \quad & \text{N}' \\
\end{align*}
\]

Busch and Bauer (7) have applied an analogous reaction to N,N'-diaryl-N''-aminoguanidines and have reported the formation of 1-aryl-5-arylaminotetrazoles. Recently a similar sequence of reactions has been applied to N-nitro-N'-aminoguanidine and the formation of 5-nitroaminotetrazole reported (8).

The direct formation of 5-aminotetrazole by the addition of hydrazoic acid to cyanamide was observed by Hantzsch and
Vagt (4). It has been suggested that the reaction involves the formation of a guanyl azide through addition of hydrazoic acid to the cyanide group followed almost immediately by cyclization of the intermediate.

\[ \text{HN}_3 \rightarrow \left[H_2\text{N-C} \equiv \text{NH}\right] \rightarrow \text{H}_2\text{N-C} \equiv \text{N-H} \]

Stollé (6) has applied the same type of reaction to several phenylalkylcyanamides and has described the formation of the corresponding 5-aminotetrazoles in which the hydrogens of the amino group were replaced by a phenyl group and an alkyl group.

The formation of 5-substituted tetrazole derivatives by the addition of hydrazoic acid to the cyanide group of nitriles has become recognized as a general procedure through the studies of Dimroth and Fester with hydrocyanic acid (9), Oliveri-Mandála with cyanogen, cyanogen bromide, and ethyl cyanoformate (5), and Mihina and Herbst with an extensive group of alkyl and aryl cyanides (3).

Substituted derivatives of 5-aminotetrazole have been prepared by the action of sodium azide on thiourea derivatives in a carbon dioxide atmosphere in the presence of lead oxide or lead
carbonate. This reaction has been studied extensively by Stollé and his co-workers (10), who suggested that the reaction proceeded with the initial formation of carbodiimide derivatives followed by addition of hydrazoic acid to the carbon-nitrogen unsaturation and cyclization to the tetrazole.

\[
RNH-CS-NHR \rightarrow [R-N=C=N-R] \rightarrow [R-NH-C=N-R] \rightarrow R-NH-C=N-R
\]

When a monosubstituted thiourea derivative was used in this reaction, the product was a 1-alkyl- or 1-aryl-5-aminotetrazole.

In an attempt to prepare 5-alkyltetrazoles from nitriles by interaction with hydrazoic acid in the presence of concentrated sulfuric acid von Braun and Keller (11) observed the formation of 1-alkyl-5-aminotetrazoles. It has been suggested (12) that this reaction involves the intermediate formation of an imide azide which undergoes a Curtius type rearrangement to a carbodiimide derivative and that the latter adds a second molecule of hydrazoic acid and undergoes cyclization to the tetrazole.
Although the above reactions show that it is possible to arrive at the 5-aminotetrazole structure from several different starting points, it is interesting to observe that in each sequence of reactions a guanyl azide structure is proposed as the intermediate which undergoes cyclization to the tetrazole stage.

Of the several procedures available, it appears that only two are suitable for the synthesis of 5-dialkylaminotetrazoles. Such compounds could conceivably be formed by the action of nitrous acid on N,N-dialkyl-N'-aminoguanidines or by the addition of hydrazoic acid to dialkylcyanamides.
In view of the commercial availability of a number of dialkyl-cyanamides, the approach from this group of compounds was selected. Furthermore, the preparation of dialkylcyanamides in a single step from secondary amines by interaction with cyanogen bromide appeared to be much simpler than the preparation of the corresponding dialkylaminoguanidines.

The action of hydrazoic acid on disubstituted cyanamides was studied with the following cyanamide derivatives: dimethyl-, diethyl-, diisopropyl-, di-n-butyl-, diisobutyl-, di-n-amyl-, diisoamyl-, dibenzyl-, benzylmethyl-, and benzylethylcyanamide; also included in this group are cyanomorpholine, cyanopyrrolidine, and cyanopiperidine. These starting materials were all known substances except di-n-amylcyanamide and cyanopyrrolidine, and were prepared by the method of McKee (13) involving the action of potassium cyanide and bromine on an aqueous suspension of the appropriate secondary amine; or, preferably, by the direct action of cyanogen bromide on the amine.

\[
2R_2NH + BrCN \rightarrow R_2N-CN + R_2NH\cdot HBr
\]

Table I summarizes boiling point and refractive index data as well as references to the literature for these materials.
The secondary amines were all commercially available with the exception of benzylmethylamine and benzylethylamine. These two materials were obtained by reductive alkylation of the Schiff's bases resulting from the action of methylamine and ethylamine, respectively, on benzaldehyde (14).

The 5-dialkylaminotetrazoles were obtained in generally excellent yield by heating the appropriate cyanamide derivative with excess hydrazoic acid in either aqueous alcohol, benzene, xylene, or ethyl acetate solution for periods ranging from five to ninety hours. Since there was no effort made to study optimum reaction conditions, the yields cited do not indicate maximum yields possible and different yields obtained by changing solvent are not necessarily significant.

The choice of solvent was dictated by the following considerations. In aqueous media, the cyanamide may undergo hydrolysis to a substituted urea derivative and then to a secondary amine. This side reaction becomes more pronounced as the substituents become more bulky, hindering tetrazole formation. In the case of diisopropylcyanamide and, especially, diisoamylcyanamide nonaqueous media are indicated. Also, when the product is water soluble, as is 5-(N-morpholiny1)-tetrazole, the ease of
isolation is enhanced by carrying out the reaction in nonaqueous solution. Table II summarizes yields, reaction media, melting points, and qualitative solubility data. Table III contains analytical results.

All of the 5-dialkylaminotetrazoles are acidic substances and dissolve readily in dilute, aqueous alkali. They are, in general, little soluble in cold water and readily soluble in alcohol. Their solubility in ether, while very limited with the lower members, becomes more pronounced as the size of substituent increases. The basic function, while not comparable to the acidic function in strength, is sufficiently well expressed to lend acid solubility to most of the tetrazoles studied; the exceptions are those with the largest substituents, i.e., di-n-butyl-, di-n-amyl-, diisoamyl-, and dibenzylaminotetrazole.

All of the 5-dialkylaminotetrazoles form silver salts which are insoluble in water, alcohol, and cold dilute nitric acid. These salts do not appear to be light-sensitive or sensitive to shock, although they decompose with a flash when heated on a spatula. They may be decomposed by boiling in concentrated nitric acid. The silver content of the acid solutions can subsequently be determined by the conventional Volhard technique. Silver salt
formation by those tetrazoles which are not substituted on the ring nitrogens seems to be quite general (3) and could be adapted to a volumetric analytical scheme for these materials.

Hydrochlorides may be prepared under anhydrous conditions, but the resulting salts are of indefinite melting point. The potentiometric titration curves of these 5-dialkylaminotetrazole hydrochlorides, while clearly exhibiting two breaks corresponding roughly to the consumption of two equivalents of standard aqueous potassium hydroxide, were of little quantitative significance. The lack of good correspondence between the found and the calculated equivalence points reflected the difficulty in preparing the pure hydrochlorides. The materials were either partially dissociated or, if crystallized in the presence of excess hydrogen chloride, they contained occluded hydrogen chloride, in most instances. The initial low pH of the solutions of the hydrochlorides indicated that they were largely dissociated in aqueous media. The potentiometric titration of the dialkylaminotetrazoles with standard aqueous hydrochloric acid further substantiated this conclusion, in that the pH observed was approximately that calculated for the corresponding hydrochloric acid concentration. The compounds were too
weak as bases to permit determination of their basic dissociation constants by this technique.

Apparent acidic dissociation constants and equivalent weights of the 5-dialkylaminotetrazoles were determined potentiometrically in approximately fifty per cent aqueous methanol by volume at 25° C. The titration curve for each of the compounds was typical of that for a weak acid; no abnormalities were observed. These results are summarized in Table IV and the data are collected in Appendix I. Representative titration curves are illustrated in Figures 1 and 2. A discussion of the acidic character of these materials is included in Part V of this thesis.

Ultraviolet absorption spectra of 5-aminotetrazole and 5-dimethylaminotetrazole were obtained using a Beckman quartz spectrophotometer, Model DU. These materials are essentially completely transparent throughout the range studied, from 220 to 450 mu., absorption beginning to occur near the lower limit of the instrument. The absorption curves obtained are represented graphically in Figure 3; the data are collected in Appendix II.
Figure 1. Potentiometric titration curves: A, 5-diethylaminotetrazole hydrochloride in water; B, 5-di-n-butylaminotetrazole in 50 per cent aqueous methanol.
Figure 2. Potentiometric titration curve of 5-dimethylaminotetrazole in water.
Figure 3. Ultraviolet absorption curves: A, 5-aminotetrazole; B, 5-dimethylaminotetrazole.
TABLE I
DIALKYL CYANAMIDES

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<th>Cyanamide</th>
<th>B. P. °C.</th>
<th>n_D/°C.</th>
<th>Ref.</th>
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<tr>
<td>Dimethylcyanamide</td>
<td>46/10 mm.</td>
<td>1.4083/25</td>
<td>13</td>
</tr>
<tr>
<td>Diethylcyanamide</td>
<td>64/10 mm.</td>
<td>1.4206/25</td>
<td>13</td>
</tr>
<tr>
<td>Diallyl cyanamide</td>
<td>96/10 mm.</td>
<td>1.4623/25</td>
<td>15</td>
</tr>
<tr>
<td>Diisopropylcyanamide</td>
<td>82/10 mm.</td>
<td>1.4249/25</td>
<td>--</td>
</tr>
<tr>
<td>Di-n-butylcyanamide</td>
<td>147-151/35 mm.</td>
<td>1.4382/20</td>
<td>15</td>
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<tr>
<td>Diisobutylcyanamide</td>
<td>123/25 mm.</td>
<td>1.4346/20</td>
<td>13</td>
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<tr>
<td>Di-n-amylcyanamide</td>
<td>154-158/12 mm.</td>
<td>1.4422/20</td>
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<tr>
<td>Diisoamylcyanamide</td>
<td>134/14 mm.</td>
<td>1.4405/20</td>
<td>13</td>
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<td>Dibenzyl cyanamide</td>
<td>145-148/10 mm.</td>
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<td></td>
<td>M. P. 54° C.</td>
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<tr>
<td>Benzylmethylcyanamide</td>
<td>139-142/12 mm.</td>
<td>1.5297/20</td>
<td>17</td>
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<td>Benzylethylcyanamide</td>
<td>160/12 mm.</td>
<td>1.5223/20</td>
<td>18</td>
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<td>N-cyanopiperidine</td>
<td>102/11 mm.</td>
<td>1.4678/25</td>
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<tr>
<td>N-cyanomorpholine</td>
<td>117-119/15 mm.</td>
<td>1.4708/25</td>
<td>19</td>
</tr>
<tr>
<td>N-cyanopyrrolidine</td>
<td>107-110/17 mm.</td>
<td>1.4670/23</td>
<td>--</td>
</tr>
</tbody>
</table>

1 Obtained from American Cyanamide Corp.

2 Analysis. Calc'd for C_{11}H_{22}N_{2}: N, 15.37. Found: N, 15.38.

3 Analysis. Calc'd for C_{5}H_{8}N_{2}: C, 62.5; H, 8.39; N, 29.2. Found: C, 62.2, 62.1; H, 8.38, 8.21; N, 29.8, 29.9.
# TABLE II

## 5-DIALKYLAMINOTETRAZOLES

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>M.P. °C.</th>
<th>Crystallized From</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Dimethylamino</td>
<td>A, 5.5 hrs.</td>
<td>78</td>
<td>235-236</td>
<td>Water</td>
</tr>
<tr>
<td>5-Diethylamino</td>
<td>A, 6 hrs.</td>
<td>43</td>
<td>124-125</td>
<td>Water</td>
</tr>
<tr>
<td>5-Diisopropylamino</td>
<td>A, 48 hrs. B, 64 hrs.</td>
<td>47</td>
<td>d.184^3</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-Diallylamino</td>
<td>A, 17.5 hrs. B, 20 hrs.</td>
<td>36</td>
<td>96-97</td>
<td>Ethylene dichloride</td>
</tr>
<tr>
<td>5-Di-n-butylamino</td>
<td>A, 15 hrs.</td>
<td>85</td>
<td>132.5-133.5</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-Diisobutylamino</td>
<td>A, 14 hrs.</td>
<td>91</td>
<td>190-191</td>
<td>Aqueous alcohol</td>
</tr>
<tr>
<td>5-Di-n-amylamino</td>
<td>A, 24 hrs.</td>
<td>87</td>
<td>91.5-92.5</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-Diisoamylamino</td>
<td>C^4, D, 90 hrs.</td>
<td>80</td>
<td>100-101</td>
<td>Diisopropyl ether</td>
</tr>
<tr>
<td>5-Dibenzylamino</td>
<td>A, 46 hrs.</td>
<td>91</td>
<td>158-159</td>
<td>Ethyl acetate</td>
</tr>
</tbody>
</table>
### Qualitative Solubility Data

<table>
<thead>
<tr>
<th>Water</th>
<th>Dil. Aq. HCl</th>
<th>Dil. Aq. KOH</th>
<th>Alcohol</th>
<th>Ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod. Sol.</td>
<td></td>
<td></td>
<td></td>
<td>Sl. Sol.</td>
</tr>
</tbody>
</table>
TABLE II (Continued)

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Reaction Conditions</th>
<th>Yield %</th>
<th>M.P. °C.</th>
<th>Crystallized From</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Benzylmethylamino</td>
<td>D, 22 hrs.</td>
<td>89</td>
<td>135.5-136.5</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-Benzylethlamino</td>
<td>D, 57 hrs.</td>
<td>88</td>
<td>134.5-135</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-(N-piperidyl)-</td>
<td>A, 43 hrs.</td>
<td>79</td>
<td>199-199.5</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td></td>
<td>C, 25 hrs.</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-(N-morpholinyl)-</td>
<td>C, 23 hrs.</td>
<td>78</td>
<td>180.5-190</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>5-(N-pyrrolidyl)-</td>
<td>A, 26 hrs.</td>
<td>54</td>
<td>d.231</td>
<td>Absolute alcohol</td>
</tr>
<tr>
<td></td>
<td>C, 23 hrs.</td>
<td>86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Hours indicated are reflux hours. Solvent is designated by capital letter: A, aqueous alcoholic solution of hydrazoic acid; B, ethyl acetate solution of hydrazoic acid; C, benzene solution of hydrazoic acid; D, xylene solution of hydrazoic acid.

2 Melting points were taken in open capillary tubes and were corrected.

3 Exists also in a polymorphic form which melts at 162.5 - 163.5° C.
TABLE II (Continued)

<table>
<thead>
<tr>
<th>Water</th>
<th>Dil. Aq. HCl</th>
<th>Dil. Aq. KOH</th>
<th>Alcohol</th>
<th>Ether</th>
</tr>
</thead>
</table>

4 Reaction carried out in sealed tube at 100° for 55 hours.

5 Recently prepared from the appropriate aminoguanidine (20).
<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Analysis</th>
<th>Silver Salts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calc'd</td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>5-Dimethylamino</td>
<td>C₃H₇N₅</td>
<td>N, 61.9</td>
</tr>
<tr>
<td></td>
<td>C₅H₁₀AgN₅</td>
<td>N, 49.6</td>
</tr>
<tr>
<td></td>
<td>C₇H₁₄AgN₅</td>
<td>C, 49.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H, 8.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N, 41.4</td>
</tr>
<tr>
<td>5-Diethylamino</td>
<td>C₅H₁₁N₅</td>
<td>C, 50.9</td>
</tr>
<tr>
<td></td>
<td>C₇H₁₄AgN₅</td>
<td>H, 6.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N, 42.4</td>
</tr>
<tr>
<td>5-Diisopropylamino</td>
<td>C₇H₁₅N₅</td>
<td>C, 54.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H, 9.7</td>
</tr>
<tr>
<td>5-Diallylamo</td>
<td>C₇H₁₉N₅</td>
<td>C, 54.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H, 9.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N, 35.5</td>
</tr>
<tr>
<td>Tetrazole</td>
<td>Formula</td>
<td>Analysis</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Diisobutylamino</td>
<td>C_{9}H_{19}N_{5}</td>
<td>C, 54.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Di-n-amylamino</td>
<td>C_{11}H_{23}N_{5}</td>
<td>C, 58.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Diisoamylamino</td>
<td>C_{11}H_{23}N_{5}</td>
<td>C, 58.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Dibenzylamino</td>
<td>C_{15}H_{15}N_{5}</td>
<td>C, 67.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Benzylmethylamino</td>
<td>C_{9}H_{11}N_{5}</td>
<td>C, 57.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrazole</td>
<td>Formula</td>
<td>Analysis</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Benzylethlamino</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C, 59.10</td>
</tr>
<tr>
<td>5-(N-piperidyl)-</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C, 47.0</td>
</tr>
<tr>
<td>5-(N-morpholinyl)-</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;N&lt;sub&gt;O&lt;/sub&gt;</td>
<td>C, 38.7</td>
</tr>
<tr>
<td>5-(N-pyrrolidyl)-</td>
<td>C&lt;sub&gt;5&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;</td>
<td>C, 43.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

22
TABLE IV

APPARENT ACIDIC DISSOCIATION CONSTANTS AND EQUIVALENT WEIGHTS OF SOME 5-DIALKYLAMINOTETRAZOLES IN APPROXIMATELY 50% AQUEOUS METHANOL BY VOLUME

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Apparent $pK_a$</th>
<th>Apparent $K_a \times 10^8$</th>
<th>Equivalent Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calc'd</td>
</tr>
<tr>
<td>5-Amino</td>
<td>5.93</td>
<td>120(^\text{2})</td>
<td>85</td>
</tr>
<tr>
<td>5-Amino</td>
<td>6.44</td>
<td>36</td>
<td>85</td>
</tr>
<tr>
<td>5-Dimethylamino</td>
<td>5.92</td>
<td>120</td>
<td>113</td>
</tr>
<tr>
<td>5-Dimethylamino</td>
<td>6.42</td>
<td>38</td>
<td>113</td>
</tr>
<tr>
<td>5-Diethylamino</td>
<td>6.33</td>
<td>47</td>
<td>141</td>
</tr>
<tr>
<td>5-Diethylamino</td>
<td>6.96</td>
<td>11</td>
<td>141</td>
</tr>
<tr>
<td>5-Dibenzylamino</td>
<td>6.45</td>
<td>36</td>
<td>265</td>
</tr>
<tr>
<td>5-Benzylmethylamino</td>
<td>6.42</td>
<td>38</td>
<td>189</td>
</tr>
<tr>
<td>5-Benzylethylamino</td>
<td>6.61</td>
<td>25</td>
<td>203</td>
</tr>
<tr>
<td>5-Diallylamino</td>
<td>6.48</td>
<td>33</td>
<td>165</td>
</tr>
<tr>
<td>5-Diisopropylamino</td>
<td>7.24</td>
<td>5.8</td>
<td>169</td>
</tr>
<tr>
<td>5-Di-n-butylamino</td>
<td>7.00</td>
<td>10</td>
<td>197</td>
</tr>
<tr>
<td>5-Diisobutylamino</td>
<td>7.14</td>
<td>7.2</td>
<td>197</td>
</tr>
<tr>
<td>5-Di-n-amylamino</td>
<td>7.09</td>
<td>8.1</td>
<td>225</td>
</tr>
<tr>
<td>5-Diisoamylamino</td>
<td>7.16</td>
<td>6.9</td>
<td>225</td>
</tr>
<tr>
<td>5-(N-Morpholinyl)-</td>
<td>5.80</td>
<td>160</td>
<td>155</td>
</tr>
<tr>
<td>5-(N-Pyrrolidyl)-</td>
<td>6.88</td>
<td>13</td>
<td>139</td>
</tr>
<tr>
<td>5-(N-Piperidyl)-</td>
<td>6.32</td>
<td>48</td>
<td>153</td>
</tr>
</tbody>
</table>

\(^1\) Determination carried out in water.

\(^2\) The value determined conductometrically was $6.8 \times 10^{-7}$ (21).
Experimental

The Preparation of Dialkylcyanamides

The dialkylcyanamides were prepared by the method of McKee (13), or, preferably, by the direct action of cyanogen bromide on the secondary amine. Typical examples are described below.

**Di-n-butylcyanamide.** To a mixture containing 129 g. (1.0 mole) of di-n-butylamine, 292 g. (4.5 moles) of potassium cyanide, and 1,000 ml. of water was added dropwise with mechanical stirring and cooling in an ice-water bath 56 ml. (2.2 moles) of bromine in 300 ml. of Skellysolve "B." The temperature was maintained below 15° C. during the addition which took about three hours. The dark red reaction mixture was filtered to remove tars. The organic layer was separated, washed with dilute sodium hydroxide solution, then with water, and finally dried over calcium chloride. After removal of the drying agent, the solvent was

---

1 Microanalyses by Micro-Tech Laboratories, Skokie, Illinois.

2 Melting points were taken in open capillary tubes and were corrected.
stripped off, and the residue distilled in vacuo. The product (124 g., 80.5% of theory) was obtained as a faintly yellow liquid boiling at 83-88° C. at 3.0 mm. A sample redistilled for analysis and refractive index determination was colorless.

**Dilsoamylycyanamide.** A mixture containing 78 g. (0.5 mole) of dilsoamylamine, 34 g. (0.6 mole) of potassium hydroxide, 150 ml. of water, and 50 ml. of ethanol was treated dropwise, while mechanically stirred and cooled in an ice-water bath, with 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of ethanol. The addition required about one hour, after which stirring at room temperature was continued for four hours. The organic layer was separated. The aqueous layer was extracted with ether and the ethereal extract and organic layers were combined and dried over anhydrous magnesium sulfate. After removal of ether, the residue was distilled in vacuo to give 70 g. of slightly yellow oil, b.p. 100-102° C. at 0.8 mm. A sample redistilled for analysis and refractive index determination was colorless.

**Cyanopyrroldine.** An ethereal solution of 53 g. (0.5 mole) of cyanogen bromide was added dropwise to a stirred and cooled ether solution of 71 g. (1.0 mole) of pyrrolidine over a period of
two hours. After completing the addition of the cyanogen bromide, the stirring was continued for several hours at room temperature. On removal of the solvent by warming on the steam bath, a brown liquid residue remained from which the product was obtained by distillation as a faint yellow oil weighing 28 g. (58% of theory), b.p. 107°-110° C. at 17 mm. A sample redistilled for analysis and refractive index determination was colorless.

**Di-n-amylcyanamide.** A mixture containing 32 g. (0.2 mole) of di-n-amyamine, .59 g. (0.9 mole) of potassium cyanide, and 60 ml. of water was stirred vigorously and cooled while 12 ml. (0.45 mole) of bromine in 40 ml. of Skellysolve 'B' was added drop-wise. The addition required about one hour after which stirring, while still cooling in the ice-water bath, was continued for one hour. The organic layer was separated, washed with dilute sodium hydroxide solution, then with water, and finally dried over anhydrous sodium sulfate. After removal of the drying agent, the solvent was evaporated and the dark red oily residue was distilled under reduced pressure. The product was obtained as a faint yellow liquid, weighing 31 g. (88% of theory), b.p. 154-158° C. at 12 mm. A sample redistilled for analysis and refractive index determination was colorless.
The Preparation of Hydrazoic Acid Solutions

Aqueous and aqueous-alcoholic solutions of hydrazoic acid are easily prepared by the addition of the calculated amount of hydrochloric acid to the aqueous or aqueous-alcoholic solution of sodium azide. Ethereal and ethyl acetate solutions of hydrazoic acid are best prepared by extraction of aqueous solutions of hydrazoic acid by the desired solvent.

A convenient method for the preparation of stock solutions of hydrazoic acid in benzene or xylene is as follows: a sludge of 520 g. of sodium azide and 500 ml. of water is covered with 1,500 ml. of benzene (or xylene) in a three-liter, round-bottom flask fitted with an efficient stirrer, dropping funnel, and condenser, and cooled in an ice-water bath. Concentrated sulfuric acid (250 ml.) is added dropwise through the dropping funnel, the stem of which should extend slightly below the surface of the benzene, over a period of one and one-half hours. Stirring is continued for several hours, after which the benzene is decanted into a tightly stoppered bottle containing anhydrous sodium sulfate.

The strength of the hydrazoic acid solutions in organic solvents may be readily determined by titration of a small aliquot with standard alkali, using a phenolphthalein indicator. The above
procedure gives solutions of initial strength of 15 to 17 grams of hydrazoic acid per 100 ml. of solution.

The Preparation of 5-Dialkylaminotetrazoles

The dialkylaminotetrazoles were prepared by simply heating the appropriate cyanamide under reflux in a solvent containing hydrazoic acid. Usually an excess of hydrazoic acid was used to provide for an appreciable loss through the condenser. Several typical examples are described below.

5-Di-n-butylaminotetrazole. To a solution of 39 g. (0.25 mole) of di-n-butylcyanamide in 200 ml. of ethanol was added an aqueous solution containing excess hydrazoic acid. The aqueous hydrazoic acid solution was prepared by adding 40 ml. of concentrated hydrochloric acid to an ice-cold solution of 33 g. (0.5 mole) of sodium azide in 100 ml. of water. The reaction mixture was heated under reflux for fifteen hours, then concentrated until turbid. Chilling precipitated 42 g. (85% of theory) of fine, colorless needles which after recrystallization from boiling ethyl acetate weighed 41 g. and melted at 132.5-133.5° C.
5-Benzyilmethyaminotetrazole. A solution of 80 g. (0.55 mole) of benzyilmethylcyanamide in 200 ml. of xylene containing 32 g. of hydrazoic acid was heated under reflux for four and one-half hours. An additional 100 ml. of the xylene solution of hydrazoic acid was added and heating continued for eighteen hours. Chilling precipitated a nearly colorless solid which, after collecting and drying, weighed 92 g. (89% of theory) and melted at 134-136° C. Recrystallization from ethylene dichloride gave fine, colorless needles, m.p. 135.5-136.5° C.

5-Diisoamylaminotetrazole. A solution containing 10 g. (0.06 mole) of diisoamylcyanamide in 35 ml. of xylene containing 4.5 g. of hydrazoic acid was heated under reflux for 22 hours when an additional 35 ml. of the xylene-hydrazoic acid solution was added and heating continued for 67 hours. Removal of most of the solvent in vacuo left a brown oil, which, when treated with dilute aqueous potassium hydroxide, separated into three layers. The intermediate layer was separated and neutralized. The oily solid thus obtained was recrystallized from diisopropyl ether to give 9.8 g. of fine, colorless needles, m.p. 100-101° C.
5-Diisopropylaminotetrazole. A solution containing 6.3 g. (0.05 mole) of diisopropylcyanamide, 4.2 g. (0.1 mole) of hydrazoic acid, 100 ml. of ethanol and 50 ml. of water was heated under reflux for 65 hours. Most of the ethanol was removed by distillation and the residue was made alkaline with 10% aqueous potassium hydroxide. Unreacted cyanamide and amine were extracted with ether. On acidification of the aqueous alkaline solution, a glistening, white solid precipitated, which when collected and dried, weighed 3.3 g. (39% of theory) and melted with decomposition at 184° C. The tetrazole crystallized in fine, colorless needles from boiling ethyl acetate with no change in the melting point.

A subsequent repetition of the above experiment gave a product which melted at 162.5–163.5° C. The low melting form was converted into the high melting form on standing in a stoppered bottle for several months. Furthermore, solutions of the high melting form in ethyl acetate deposited the high melting form spontaneously but when seeded with the low melting form, that form separated.
The Preparation of 5-Dialkylaminotetrazole Hydrochlorides

5-Di-n-butylaminotetrazole hydrochloride. Approximately one gram of 5-di-n-butylaminotetrazole was dissolved in 15 ml. of ether and the minimum amount of absolute alcohol. The cooled solution was treated with an excess of dry, gaseous hydrogen chloride. The colorless plates, which precipitated, were collected and recrystallized from a warm solution of hydrogen chloride in dry ether and the minimum amount of absolute alcohol. The material, when heated in a sealed capillary, decomposed at 183° C. after prior softening and darkening.


5-Benzylmethylaminotetrazole hydrochloride. Approximately one gram of 5-benzylmethylaminotetrazole was dissolved in 15 ml. of absolute ethanol and then treated in the cold with excess dry, gaseous hydrogen chloride. The colorless solid which precipitated was collected and recrystallized from warm alcoholic hydrogen chloride. The fine colorless needles decomposed at 179° C. after prior softening and darkening in a sealed capillary.

Analysis. Calc'd for $\text{C}_9\text{H}_{11}\text{N}_5$: N, 31.03. Found: 31.6, 31.5.
The Preparation of the Silver Salts of the 5-Dialkylaminotetrazoles

Small quantities (0.2-0.5 g.) of the tetrazoles were dissolved in 10 ml. of ethanol and then treated with a slight excess of aqueous silver nitrate solution. The white precipitate of silver salt was digested on the steam bath for fifteen minutes, filtered hot, washed with hot ethanol, and finally dried for several hours at 70° C. Silver analysis was done by boiling carefully weighed samples of the silver salts in approximately 30 ml. of concentrated nitric acid for thirty minutes, cooling, diluting with 15 ml. water, and titrating the silver ion with standard potassium thiocyanate solution using ferric alum indicator (22). The results are tabulated in Table III.

None of the silver salts listed in Table III could be detonated by shock. All of them were stable to sharp blows with a hammer on an anvil. On heating over a flame on a spatula all of them eventually decomposed with a flash. No decomposition of the silver salts was evident after several months' exposure to daylight.
The Determination of Apparent Dissociation Constants of the 5-Dialkylaminotetrazoles

The apparent acidic dissociation constants and equivalent weights of the 5-dialkylaminotetrazoles were determined by titration of weighed samples in aqueous or aqueous-methanolic solution with standard potassium hydroxide solution. The weighed samples were transferred to 250-ml. volumetric flasks and made up to volume with water or methanol as required. One hundred ml. aliquots, diluted with 100 ml. of water, were titrated in a thermostat at 25° ± 1° C. The pH was determined after each addition of alkali with a Beckman pH Meter, Model G. From these data, the region of half neutralization was plotted on a large scale and the best straight line drawn. The pH at half neutralization was determined from the plot and from it was calculated the apparent dissociation constant (23). The titration curves in each instance exhibited the form normally obtained with a weak acid.

In a similar manner, several of the 5-dialkylaminotetrazole hydrochlorides were titrated with standard potassium hydroxide solution. Because of the difficulty in obtaining hydrochlorides of reliable purity, these data were of little quantitative significance.
Potentiometric titrations of the 5-dialkylaminotetrazoles were also carried out using standard hydrochloric acid in an analogous manner.

Typical potentiometric titration curves are presented in Figures 1 and 2; the data are recorded in Appendix I.
PART II

THE ACTION OF HYDRAZOIC ACID ON MONOALKYLCYANAMIDES

Discussion

In Part I of this thesis it was shown that 5-dialkylamino-
tetrazoles could be prepared by interaction of dialkylcyanamides
and hydrazoic acid. As has been noted, Hantzsch and Vagt (4)
had demonstrated that cyanamide would react readily with hydra-
zoic acid to form 5-aminotetrazole. Consequently, it would be
anticipated that the monoalkylcyanamides would also react readily
with hydrazoic acid.

It should be emphasized that the guanyl azide postulated
as an intermediate in the formation of 5-aminotetrazole from
cyanamide and hydrazoic acid could exist in two indistinguishable
tautomeric forms either of which would cyclize to give the same
tetrazole.

\[
\begin{align*}
H_2N-CN & \quad \rightarrow \quad [H_2N-C=NH]_N^3 \\
& \quad \quad \quad \quad \quad \quad \quad \downarrow \\
& \quad \quad \quad \quad \quad \quad \quad [HN=C-NH_2] \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \downarrow \\
& \quad \quad \quad \quad \quad \quad \quad [H_2N-C=NH]_N^3 \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \qua
When the same type of reaction was applied to the dialkyl-cyanamides, tautomerism of the guanyl azide intermediate was precluded by substitution of one of the amino nitrogens with two alkyl groups. Consequently, cyclization could take place in one direction only.

\[
R_2N-CN \quad \rightarrow \quad [R_2-N-C=NH] \quad \rightarrow \quad R_2N-C=\text{N-H}
\]

The addition of hydrazoic acid to a monoalkylcyanamide would be expected to lead to an intermediate guanyl azide which again could exist in two tautomeric modifications. Cyclization in this case could result in two distinctly different 5-aminotetrazole derivatives. If cyclization were to involve the nitrogen carrying the alkyl substituent, a 1-alkyl-5-aminotetrazole would result. On the other hand, involvement of the unsubstituted nitrogen in the cyclization would result in a 5-alkylaminotetrazole.

\[
R-NH-CN \quad \rightarrow \quad [R-NH-C=\text{NH}] \quad \rightarrow \quad R-NH-C=\text{N-H}
\]

\[
[\text{R-N}=\text{C-NH}_2] \quad \rightarrow \quad \text{R-N-}C\text{-NH}_2
\]
Since the formation of two products was to be anticipated in the reaction of monoalkylcyanamides with hydrazoic acid, benzyl cyanamide was selected for the exploratory work. Both 1-benzyl-5-aminotetrazole and 5-benzylaminotetrazole, the probable products of the reaction, were known. 1-Benzyl-5-aminotetrazole had been obtained by von Braun and Keller (11) by interaction of hydrazoic acid and benzyl cyanide in the presence of sulfuric acid and by Thiele and Ingle (2) as a benzylation product of 5-aminotetrazole. 5-Benzylaminotetrazole had also been observed by Thiele and Ingle (2) among the products formed by benzylation of 5-aminotetrazole. These two isomeric products are almost insoluble in water but can be separated easily and quantitatively by virtue of the acidic character of 5-benzylaminotetrazole and its consequent solubility in dilute aqueous alkalies. Treatment of benzylcyanamide with hydrazoic acid in ethereal solution led to the essentially exclusive formation of 1-benzyl-5-aminotetrazole. No alkali-soluble material could be separated from the product.

The formation of a single product from the reaction of benzylcyanamide with hydrazoic acid was rather surprising and suggested that the character of the group substituted on the
cyanamide might influence the nature and distribution of the products. In the reaction of phenylthiourea with sodium azide in the presence of lead oxide, which has also been assumed to involve a guanyl azide as an intermediate, Stolle observed the formation of 1-phenyl-5-aminotetrazole accompanied by a trace of a product which he assumed to be 5-phenylaminotetrazole on the basis of its acidic character and elementary analysis (10).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{NHCSNH}_2 & \longrightarrow [\text{C}_6\text{H}_5-\text{N}=\text{C}=\text{N-H}] & \longrightarrow [\text{C}_6\text{H}_5-\text{N}=\text{C}-\text{NH}_2] \\
[\text{C}_6\text{H}_5-\text{N}=\text{C}-\text{NH}_2] & \downarrow & \text{C}_6\text{H}_5-\text{N}-\text{C}-\text{NH}_2 \\
\text{[C}_6\text{H}_5\text{NH-C}=\text{NH}] & \text{[N}_3 & \longrightarrow \text{C}_6\text{H}_5-\text{NH-C}=\text{N-H} \\
\text{[C}_6\text{H}_5\text{NH-C}=\text{NH}] & \downarrow & \text{C}_6\text{H}_5-\text{NH-C}=\text{N-H}
\end{align*}
\]

Recently the cyclization of a nitroguanyl azide, formed upon treatment of N-nitro-N'-aminoguanidine with nitrous acid, has been described as leading exclusively to the formation of 5-nitroaminotetrazole (8).

\[
\begin{align*}
\text{NO}_2\text{-NH-C}=\text{NH} & \longrightarrow \text{NO}_2\text{-NH-C}=\text{NH} & \longrightarrow \text{NO}_2\text{-NH-C}=\text{NH} \\
\text{NHNNH}_2 & \longrightarrow \text{N}_3 & \longrightarrow \text{N}_3 & \longrightarrow \text{N}_3 & \longrightarrow \text{N}_3
\end{align*}
\]
In order to include a reasonable range of electrical and steric effects, the monosubstituted cyanamides used in this study included methyl-, ethyl-, isobutyl-, n-amyl-, n-hexyl-, n-heptyl-, n-octyl-, benzyl-, phenyl-, and p-nitrophenylcyanamide. The monoalkylcyanamides were prepared by treating the appropriate primary amines with cyanogen bromide, usually in ether, but aqueous alcohol functions as well. The p-nitrophenylcyanamide was prepared according to the method of Pierron (24).

While several of these monoalkylcyanamides have been reported in the older literature (25), their characterization leaves much to be desired. These materials readily polymerize into triazine derivatives and other, less well-defined, polymeric substances. In an effort to place the nature of these intermediates on a firmer basis, in view of the difficulties accompanying attempts to isolate them in pure form, several were converted in excellent yield into the corresponding alkylureas. When a molar equivalent of alkali was used, the reaction did not proceed appreciably; when the amount of alkali was increased to a fivefold excess, the hydrolysis was rapid and nearly complete.

These experimental results are in accord with work on the hydrolysis of the parent substance, cyanamide (26). Cyanamide,
with an acid dissociation constant of $2.1 \times 10^{-9}$, is quantitatively converted to urea in alkaline solutions of pH greater than 12, the reaction is first order in anion concentration. In solutions of lower pH, a second order reaction takes place between the anion and an undissociated molecule yielding dicyandiamide.

All of the monosubstituted cyanamides listed above were treated with hydrazoic acid. Except in the case of p-nitrophenyl-cyanamide which could be isolated in pure form, an ethereal solution of the cyanamide was prepared by adding cyanogen bromide to the appropriate primary amine dissolved in ether. Without separating the amine hydrobromide that precipitated, a solution of hydrazoic acid was added to the ethereal solution of the crude monoalkylcyanamide and the mixture stirred at room temperature for several hours. After evaporation of the solvent and excess hydrazoic acid the product was separated from the residue. The possible presence of alkali-soluble products was investigated in each instance. In every case only the 1-alkyl- or 1-aryl-5-aminotetrazole could be isolated in yields of 50-80% based on the amount of primary amine used for the preparation of the cyanamide. No alkali-soluble products were observed.
The 1-alkyl- and 1-aryl-5-aminotetrazoles were characterized by analysis and comparison with samples obtained by the von Braun technique (12) (see Part I). These data are summarized in Table VI.

Of the compounds described in this Part, only 1-p-nitropheny1-5-aminotetrazole has not been previously described. Structure assignment was based on the analogy of the method of its formation from p-nitrophenylcyanamide and elementary analysis.

To provide an independent synthesis 1-phenyl-5-aminotetrazole was subjected to nitration. The 1-nitrophenyl-5-aminotetrazole obtained in this way was identical in all respects with the product obtained from p-nitrophenylcyanamide. It is interesting to note that the tetrazole ring system when attached to the phenyl group through the nitrogen in position one exerts a para orienting influence. Catalytic reduction of samples of the 1-p-nitrophenyl-5-aminotetrazole prepared by both methods resulted in identical 1-p-aminophenyl-5-aminotetrazoles.
Perhaps the most remarkable feature of the reaction leading to the formation of 1-substituted-5-aminotetrazoles from the monosubstituted cyanamides is the unidirectional character of the cyclization. The nature of the substituent appears to play at best a minor role in directing the course of the reaction. Substituents as different in their electrical effects as the methyl group and the p-nitrophenyl group permit the formation of the same type of compound. Usually the inductive effect of an alkyl group such as methyl is assumed to make the atom to which it is attached more negative. On the other hand, the pronounced resonance effects of the p-nitrophenyl group might be assumed to cause the atom to which it is attached to become more positive.
Since the electrical effects of the alkyl and the aryl substituents would appear to have opposite effects, other factors which overbalance these effects must be operative in determining the course of the reaction.

Also, the nature of the solvent does not seem to be important since 1-n-octyl-5-aminotetrazole could be prepared in equally good yield either in ethereal solution or in aqueous alcoholic solution.

The possibility immediately arises that the guanyl azide structure does not represent the correct intermediate in the reaction. It will be recalled (Part I) that Thiele (1) had succeeded in preparing 5-aminotetrazole by treatment of aminoguanidine with nitrous acid and that it was possible to isolate the guanyl azide formed as an intermediate in this reaction. The application of this sequence of reactions to an N-alkyl-N'-aminoguanidine should help to clarify the question regarding the nature of the intermediate. N-Methyl-N'-aminoguanidine was prepared from N-methyl-
S-methyl isothiourea hydriodide by the method of Kirsten and Smith (27). Treatment of the methylaminoguanidine with nitrous acid gave a product, presumably the guanyl azide, which underwent cyclization to 1-methyl-5-aminotetrazole on warming. No 5-methylaminotetrazole was observed among the products of the reaction.

\[
\begin{align*}
\text{CH}_3\text{NH-C=NH} \quad &\rightarrow\quad \text{CH}_3\text{NH-C=NH} \quad &\rightarrow\quad \text{CH}_3\text{N=N-C=NH}_2 \\
\text{NHNH}_2 \quad &\rightarrow\quad \text{N}_3 \quad &\rightarrow\quad \text{N}_2
\end{align*}
\]

Although this sequence of reactions has not been applied to other compounds, this observation supports the assumption that guanyl azides are also intermediates in the reaction of the monosubstituted cyanamides with hydrazoic acid.

Other effects, such as the relative stability of the two products that might arise through cyclization of the guanyl azides, the relative rates of the two cyclizations, and the stability of the tautomeric forms could profoundly influence the course of the reaction. Unfortunately, the available data do not permit evaluation of these effects.

In general, the ease with which hydrazoic acid is caused to react with a carbon-nitrogen unsaturation to form tetrazole
derivatives varies widely. Negatively substituted cyanides, such as cyanogen bromide, cyanogen, and ethyl cyanoformate, react under mild conditions (5), while the alkyl and aryl cyanides required much more drastic conditions of temperature and longer reaction time (3). These differences may be attributed to the relative electrophilic nature of the carbon, which is enhanced by negative substitution. Enhancement of the electrophilic nature of the cyanide carbon would be expected to facilitate formation of the intermediate imide azide.

\[
\begin{align*}
Y\overset{\text{HN}_3}{\leftarrow}\text{CN} & \quad \overset{\text{[Y-C=N]}_3}{\rightarrow} \quad Y\overset{\text{N}}{\mid}\overset{\text{N}}{\mid}\overset{\text{N}}{\mid}\overset{\text{N}}{\mid}
\end{align*}
\]

The monoalkylamino and dialkylamino cyanides (mono and dialkylcyanamides) also differ greatly in their reactivity toward hydrazoic acid. The monoalkylamino cyanides were found to react readily at room temperature, while the dialkylamino cyanides required more drastic conditions. Also, p-nitrophenylamino cyanide did not react as readily as did the alkylamino cyanides. These differences may be closely related to, and may possibly be explained by, the as yet unknown factors which cause the preferential cyclization.
Experimental

The Conversion of Monoalkyldcyanamides Into the Corresponding Alkylureas

Several alkylcyanamides were converted into the corresponding alkylureas by alkaline hydrolysis. The alkylcyanamides were prepared in ether solution by treating the appropriate primary amine in ether solution with cyanogen bromide. Extracting the ether solution with aqueous alkali and then warming the aqueous alkaline solution of alkylcyanamide on the steam bath sufficed to convert the cyanamide into the urea. Typical examples of this conversion are described below. The reactions carried out are summarized in Table V.

**Benzylurea.** A solution of 21.4 g. (0.2 mole) of benzylamine in ether was treated dropwise, while stirring and cooling in an ice-water bath, with 10.6 g. (0.1 mole) of cyanogen bromide in ether. After removing the benzylamine hydrobromide by filtration, the filtrate was extracted with an aqueous solution containing 28.0 g. (0.5 mole) of potassium hydroxide in 100 ml. of water. The alkaline extract was warmed on the steam bath for three hours and then chilled. The long, lustrous needles were
collected and dried. The crude product weighed 10.2 g., m.p. 148-150° C. The analytical sample, after crystallization from acetone melted at 150-150.5° C.

**Isobutylurea.** A solution of 14.6 g. (0.2 mole) of isobutyl-amine in ether was treated dropwise, while stirring and cooling, with 10.6 g. (0.1 mole) of cyanogen bromide in ether. After removal of the amine salt by filtration, the cyanamide was extracted with 100 ml. of 5N aqueous potassium hydroxide. The alkaline extract was warmed on the steam bath until the urea separated as an immiscible liquid. Chilling produced a colorless, crystalline product which was collected and dried. The crude product weighed 8.9 g., m.p. 135.5-137.5° C. The analytical sample crystallized from acetone as colorless plates, melting at 141.5-142° C.

The Action of Hydrazoic Acid on Monosubstituted Cyanamides

The reaction of hydrazoic acid with the monoalkylcyana- mides and with phenylcyanamide were carried out in essentially the same manner. The appropriate primary amine, usually in ether solution, was treated in the cold with cyanogen bromide
in ether. The resulting ethereal solution of alkylcyanamide was then treated with hydrazoic acid in ether followed by stirring at room temperature for several hours. In the first reactions carried out, the amine hydrobromide was separated before adding the hydrazoic acid but this was found to be unnecessary. The use of ethyl acetate and aqueous alcohol as reaction solvents did not appear to alter the course of the reaction or yield.

Since one of the anticipated products, 5-alkylaminotetrazole, would be expected to possess acidic character, an effort to establish its presence was made by extracting the residue obtained after evaporation of the solvent from the reaction mixture with aqueous alkali. In general, the water-solubility of substituted tetrazoles is low, hence any appreciable amount of 5-alkylaminotetrazole, if formed, would be detected on neutralization of the alkaline extract. The 1-alkyl-5-aminotetrazoles were then isolated from the residue by crystallization from appropriate solvents.

The p-nitrophenylcyanamide was caused to react with hydrazoic acid in boiling xylene-ethanol solution, in sharp contrast to the other reactions which were carried out at room temperature. Several typical examples are described below.
The reaction of hydrazoic acid with methylcyanamide. A solution of 15.5 g. (0.5 mole) of methylamine in 200 ml. of ethyl acetate was treated dropwise, while stirring mechanically and cooling in an ice-water bath, with 26.5 g. (0.25 mole) of cyanogen bromide in 100 ml. dry ether. The amine salt was removed by filtration and the cyanamide solution combined rapidly with an ether solution containing approximately one mole of hydrazoic acid and then stirred at room temperature for one hour. After allowing the solvent to evaporate, 20 g. of crude, colorless product remained from which no acidic material was extracted with aqueous alkali. The crude material yielded 12 g. of fine colorless needles after one crystallization from 100 ml. of boiling water, m.p. 228-229° C. The product was identical in all respects with a sample of 1-methyl-5-aminotetrazole prepared according to the method of von Braun and Keller (12).

The reaction of hydrazoic acid with n-octylcyanamide. To 32.3 g. (0.25 mole) of n-octylamine in 200 ml. of ether was added dropwise, while stirring and cooling, 13 g. (0.12 mole) of cyanogen bromide in 50 ml. of ether. Without removal of the amine salt, an ether solution containing approximately 0.5 mole of hydrazoic acid was added rapidly and the resulting reaction mixture stirred
for several hours at room temperature. On removal of solvent, an almost colorless solid residue remained which was leached with cold water to remove the amine salt, extracted with dilute, aqueous alkali to separate any alkali soluble product, and finally crystallized from ethyl acetate. Twenty grams of colorless needles were thus obtained, m.p. 163.5-164.5°C. The product was identical in all respects with a sample of 1-n-octyl-5-aminotetrazole prepared according to the method of von Braun and Keller (28). No 5-n-octylaminotetrazole was obtained on neutralization of the alkaline extract.

Duplication of the above experiment, except for the use of aqueous ethanol as the solvent, resulted in the formation of 20 g. of 1-n-octyl-5-aminotetrazole, m.p. 163.5-164.5°C. Again, no acidic product was observed.

The reaction of hydrazoic acid with phenylcyanamide. A solution of 93 g. (1.0 mole) of aniline in 200 ml. of dry ether was treated dropwise, while stirring and cooling, with 53 g. (0.5 mole) of cyanogen bromide in 200 ml. of ether over a period of one and one-half hours. An ether solution containing approximately 2.0 moles of hydrazoic acid was then added rapidly and the resulting reaction mixture stirred at room temperature for several
hours. The ether insoluble aniline hydrobromide was removed by filtration and the filtrate concentrated on the steam bath. The red, oily residue was digested for several minutes on the steam bath with dilute, aqueous alkali, then chilled and the resulting solid collected on a Buchner funnel. Any 5-phenylaminotetrazole, if formed, would be in the alkaline filtrate, because of its acidic character. That no appreciable amount of this compound was formed was evident since neutralization of the filtrate precipitated no solid material.

A rather large amount of oily contaminant was removed from the crude, alkali-insoluble material by extraction with ether. The ether-insoluble solid was recrystallized from water from which it separated as faintly pink plates weighing 26 g., which showed the following behavior on heating: melted at 163-163.5° C., solidified at about 165° C., and then remelted with decomposition at 205-206° C. The significance of this behavior on heating is discussed in Part IV.

A small amount of material that was not soluble in boiling water was recrystallized from 50% aqueous ethanol to give 1 g. of colorless, microcrystals which were soluble in dilute aqueous acid and insoluble in dilute aqueous alkali, m.p. 163.5-164.5° C.
The melamine formed from phenylcyanamide is reported to melt at 162-163° C. (29).

The oily material, obtained by evaporating the solvent from the ether extract, was extracted with hot aqueous ethanol. On cooling the ethanolic solution 12.6 g. of fine, colorless plates were obtained, m.p. 146-147° C. (uncorr.), soluble in dilute aqueous acid, insoluble in dilute aqueous alkali. s-Diphenylguanidine is reported to melt at 147° C. (30).

The reaction of hydrazoic acid with p-nitrophencylanamide.
A solution containing 6.0 g. of p-nitrophencylanamide, 50 ml. of absolute ethanol, and 100 ml. of xylene containing 16 g. of hydrazoic acid was heated under reflux for two hours. On cooling, fine, tan-colored needles separated which weighed 3.6 g. The crude product was recrystallized from a 1:1 mixture of acetonitrile and dioxane from which it separated as pale yellow plates, yield 3.5 g. On heating in a capillary tube the product began to darken at about 170° C., shrank suddenly at about 176° C., and melted with frothing and decomposition at 221°-223° C. The compound was identical with the nitration product of 1-phenyl-5-aminotetrazole (see below). The significance of the changes observed on heating this compound is discussed in Part IV.
Analysis. Calc'd for C\textsubscript{7}H\textsubscript{6}N\textsubscript{6}O\textsubscript{2}: C, 40.8; H, 2.93; N, 40.8. Found: C, 40.7; H, 2.97; N, 40.6.

From the xylene-alcohol mother liquor in which the reaction was carried out, 2.8 g. of p-nitrophenylcyanamide was recovered by evaporation of the solvent in a stream of air.

The Reduction of 1-p-Nitrophenyl-5-aminotetrazole

A solution of 4.1 g. of 1-p-nitrophenyl-5-aminotetrazole, obtained from p-nitrophenylcyanamide and hydrazoic acid, in 200 ml. of absolute ethanol was shaken with 5% palladium on charcoal catalyst under three atmospheres of hydrogen until the calculated amount of hydrogen had been absorbed. The catalyst was removed by filtration and the residue remaining after evaporation of the solvent crystallized from acetonitrile as transparent, flat, diamond-shaped plates, m.p. 200-201° C. The product was readily soluble in dilute, aqueous acids, insoluble in dilute aqueous alkalies and gave a typical coupling product with β-naphthol after treatment with nitrous acid.

Analysis. Calc'd for C\textsubscript{7}H\textsubscript{8}N\textsubscript{6}: C, 47.7; H, 4.58; N, 47.7. Found: C, 47.8, 48.0; H, 4.73, 4.65; N, 47.8, 47.8.
The Nitration of 1-Phenyl-5-aminotetrazole

Twelve grams of 1-phenyl-5-aminotetrazole were dissolved in 50 ml. of concentrated sulfuric acid and, while mechanically stirred and cooled in an ice-water bath, 50 ml. of concentrated nitric acid were added over a period of two hours. The reaction mixture was poured onto ice and the nearly colorless, granular solid which precipitated was collected on a Buchner funnel, washed repeatedly with water, and then air dried. The dry product weighed 15 g. and had the following behavior when heated slowly in a capillary: began to darken at about 170° C., shrank suddenly at about 176°, and melted with frothing and decomposition at 221-223° C. This material was soluble in dilute, warm, aqueous hydrochloric acid, insoluble in cold dilute aqueous hydrochloric acid and dilute alkali, and crystallized as pale yellow plates from a 1:1 mixture of acetonitrile and dioxane. The product was identical in all respects with the material obtained by interaction of p-nitrophenylcyanamide with hydrazoic acid.

Analysis. Calc'd for $\text{C}_7\text{H}_6\text{N}_6\text{O}_2$: C, 40.8; H, 2.93; N, 40.8. Found: C, 41.1, 41.1; H, 3.00, 3.00; N, 41.4, 41.4.
The Reduction of 1-p-Nitrophenyl-5-aminotetrazole

A solution of 3.1 g. of 1-p-nitrophenyl-5-aminotetrazole, obtained by nitration of 1-phenyl-5-aminotetrazole, in 200 ml. of absolute ethanol was shaken with 5% palladium on charcoal catalyst under three atmospheres of hydrogen until the calculated amount of hydrogen had been absorbed. The catalyst was removed by filtration and the residue remaining after evaporation of the solvent crystallized from acetonitrile as transparent, flat, diamond-shaped plates, m.p. 200-201° C. The product was readily soluble in dilute aqueous acids, insoluble in dilute, aqueous alkalies and gave a typical coupling product with β-naphthol after treatment with nitrous acid. The product was identical in all respects with the 1-p-aminophenyl-5-aminotetrazole obtained by reduction of 1-p-nitrophenyl-5-aminotetrazole from p-nitrophenylcyanamide.

Analysis. Calc'd for C\textsubscript{7}H\textsubscript{8}N\textsubscript{6}: C, 47.7; H, 4.58; N, 47.7. Found: C, 48.0, 47.7; H, 4.68, 4.63; N, 47.8, 48.0.

The Action of Nitrous Acid on N-Methyl-N'-aminoguanidine

A solution of 1.5 g. (0.01 mole) of N-methyl-N'-aminoguanidine nitrate (27) in 10 ml. of water was treated in the cold
with a solution of 1.4 g. (0.02 mole) of sodium nitrite in 10 ml. of water. The cloudy mixture was then warmed gently on the steam bath for fifteen minutes during which time a red gummy material separated. The red material was rapidly transformed into a white crystalline solid which was collected and recrystallized from a small amount of water. The colorless needles thus obtained melted at 228-229° C. and were identical in all respects with a sample of 1-methyl-5-aminotetrazole prepared according to the method of von Braun and Keller (12).
### TABLE V

THE CONVERSION OF MONOALKYLICYANAMIDES INTO THE CORRESPONDING MONOALKYLUREAS

\[ \text{RNHCN} \rightarrow \text{RNCONH}_2 \]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield of Urea</th>
<th>M.P. °C.</th>
<th>Formula</th>
<th>Analysis, % N</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
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<td>Calc'd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
<td></td>
</tr>
<tr>
<td>Isobutyl-</td>
<td>77</td>
<td>141.5-142</td>
<td>C_5H_{12}N_2O</td>
<td>24.1</td>
<td>31</td>
</tr>
<tr>
<td>n-Amyl-</td>
<td>52</td>
<td>99-100</td>
<td>C_6H_{14}N_2O</td>
<td>21.5</td>
<td>32</td>
</tr>
<tr>
<td>n-Hexyl-</td>
<td>81</td>
<td>108.5-109</td>
<td>C_7H_{16}N_2O</td>
<td>19.4</td>
<td>32</td>
</tr>
<tr>
<td>n-Heptyl-</td>
<td>91</td>
<td>111.5-112.5</td>
<td>C_8H_{18}N_2O</td>
<td>17.7</td>
<td>32</td>
</tr>
<tr>
<td>n-Octyl-</td>
<td>33</td>
<td>101-102</td>
<td>C_9H_{20}N_2O</td>
<td>16.3</td>
<td>32</td>
</tr>
<tr>
<td>Benzyl-</td>
<td>68</td>
<td>150-150.5</td>
<td>C_8H_{10}N_2O</td>
<td>18.7</td>
<td>33</td>
</tr>
</tbody>
</table>

1 The yield was based on the amount of primary amine used.
## TABLE VI

1-SUBSTITUTED-5-AMINOTETRAZOLES FROM MONOALKYLCYANAMIDES

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Yield of Trazole</th>
<th>M.P. °C.</th>
<th>Formula</th>
<th>Analysis, % N</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
<td>Calc'd</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Found</td>
<td></td>
</tr>
<tr>
<td>Methyl-</td>
<td>49</td>
<td>228-229</td>
<td>C₂H₅N₅</td>
<td>70.7</td>
<td>12</td>
</tr>
<tr>
<td>Ethyl-</td>
<td>53</td>
<td>147.5-148.5</td>
<td>C₃H₇N₅</td>
<td>61.9</td>
<td>12</td>
</tr>
<tr>
<td>Isobutyl-</td>
<td>50</td>
<td>212-212.5</td>
<td>C₅H₁₁N₅</td>
<td>49.6</td>
<td>12</td>
</tr>
<tr>
<td>n-Amyl-</td>
<td>52</td>
<td>165-166</td>
<td>C₆H₁₃N₅</td>
<td>45.1</td>
<td>12</td>
</tr>
<tr>
<td>n-Hexyl-</td>
<td>54</td>
<td>165.5-166.5</td>
<td>C₇H₁₅N₅</td>
<td>41.4</td>
<td>11</td>
</tr>
<tr>
<td>n-Heptyl-</td>
<td>74</td>
<td>165.5-166.5</td>
<td>C₈H₁₇N₅</td>
<td>38.2</td>
<td>12</td>
</tr>
<tr>
<td>n-Octyl-</td>
<td>82</td>
<td>163.5-164.5</td>
<td>C₉H₁₉N₅</td>
<td>35.5</td>
<td>28</td>
</tr>
<tr>
<td>Benzyl-</td>
<td>69</td>
<td>191-192</td>
<td>C₈H₉N₅</td>
<td>40.0</td>
<td>11</td>
</tr>
<tr>
<td>Phenyl-</td>
<td>32</td>
<td>163-163.5</td>
<td>C₇H₇N₅</td>
<td>43.5</td>
<td>11</td>
</tr>
<tr>
<td>p-Nitrophenyl-</td>
<td>75</td>
<td>221-223</td>
<td>C₇H₆N₅O₂</td>
<td>40.8</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Yields were based on the amount of amine used except in the case of p-Nitrophenylcyanamide.
PART III

THE SYNTHESIS OF 5-MONOALKYLAMINOTETRAZoles

Discussion

When the action of hydrazoic acid on monoalkylcyanamides failed to yield 5-alkylaminotetrazoles, it became necessary to consider other, less direct, synthetic schemes for the preparation of compounds of this type.

The immediately obvious possibility of substituting the monoalkylcyanamides with an easily removable blocking group through acylation suggested itself. Acylation, however, proved to be largely fruitless. Generally, only acylated urea derivatives could be isolated from the reaction mixture in poor yield. The possibility of acetylating the monoalkylcyanamides with ketene in a nonhydrolyzing medium could be of promise, but this technique was not investigated. Only in the case of benzylcyanamide was a partial success obtained. Carbethoxylation gave a mixture, which was not completely separated, containing the acylated cyanamide and benzylurethane. This mixture, when treated with hydrazoic acid in benzene under pressure at 100° C, formed an
acids produce which gave the correct elementary analysis for
5-benzylcarbethoxyaminotetrazole. The acidic nature of the prod-
uct and the ease with which it could be converted into 5-benzyl-
aminotetrazole by hydrolysis were in conformity with the struc-
ture assumed on the basis of elementary analysis.

\[ \text{C}_6\text{H}_5\text{-CH}_2\text{-NHCN} \rightarrow \text{C}_6\text{H}_5\text{-CH}_2\text{-N-CN}^{2-} \]

The 5-benzylaminotetrazole formed by hydrolysis of the
carbethoxy derivative is soluble in dilute acid and dilute alkali
and forms an insoluble silver salt. It was characterized by
analysis and comparison with the amphoteric product which re-
sults on benzylation of 5-aminotetrazole (2) with which it was
identical in all respects.

The possibility that an N-benzyl-N'-carbethoxycarbodiimide
structure could be formed during acylation of the benzylcyanamide
was considered. The reaction of such an intermediate with
hydrazoic acid could result in the formation of either 1-benzyl-
5-carbethoxyaminotetrazole or 1-carbethoxy-5-benzylaminotetrazole.
Compounds of the former type are acidic in character while compounds of the latter type are neutral (34).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{CH}_2\text{NHCN} & \xrightarrow{\text{C}_2\text{H}_5\text{OOC\text{Cl}}} \text{C}_6\text{H}_5\text{N}=\text{C}=\text{N}-\text{COOC}_2\text{H}_5 \\
\end{align*}
\]

This course of the reaction was rather unlikely since the formation of 1-carbethoxy-5-benzylaminotetrazole could be excluded by the acidic character of the product isolated. On the other hand, if the acidic 1-benzyl-5-carbethoxyaminotetrazole had been formed, hydrolysis would be expected to lead to 1-benzyl-5-aminotetrazole, a well-known compound that possesses only weakly basic character and no acidic properties. The amphoteric nature of the product formed by this sequence of reactions as well as the marked depression of its melting point when mixed with 1-benzyl-5-aminotetrazole excluded the possibility of identity. This observation supported the conclusion that 5-benzylcarbethoxyaminotetrazole had been formed as the intermediate.
Another, possibly promising, method of obtaining the mono-
alkylaminotetrazoles was an adaptation of the von Braun degra-
dative scheme using cyanogen bromide with the 5-dialkylamino-
tetrazoles (35).

\[
\begin{align*}
R^1 \text{CN} & \rightarrow R^1 \text{CN} + R^1 \text{Br} \\
\end{align*}
\]

This method was not attempted for at this time the 5-benzyl-
methylamino-, 5-benzylethylamino-, and 5-dibenzylaminotetrazoles
were available and the selective, catalytic debenzylation (36)
seemed more readily achievable.

The 5-benzylalkylaminotetrazoles were found to undergo
debenzylation when shaken in a heated bottle with 5% palladium
on charcoal under three atmospheres of hydrogen pressure.

\[
\begin{align*}
\end{align*}
\]

\( R=CH_3, \ CH_3CH_2-, C_6H_5-CH_2- \).
In the case of 5-dibenzylaminotetrazole stepwise debenzyllation was feasible with the formation first of 5-benzylaminotetrazole and then 5-aminotetrazole. The 5-benzylaminotetrazole obtained in this way was identical with the product obtained upon hydrolysis of 5-benzylcarbethoxyaminotetrazole.

\[
\text{C}_6\text{H}_5\text{-CH}_2\hspace{1cm}N\hspace{-0.5em}\mathbf{C}\hspace{-0.5em}N\hspace{-0.5em}H \rightarrow \text{C}_6\text{H}_5\text{-CH}_2\hspace{0.5em}\mathbf{NH-C}\hspace{-0.5em}N\hspace{-0.5em}H \rightarrow \text{H}_2\text{N-C}\hspace{-0.5em}N\hspace{-0.5em}H
\]

The 5-monoalkylaminotetrazoles were characterized, as more completely described in Part I, through analysis, equivalent weight determination, silver salt formation, and determination of the apparent acid dissociation constant. They are very similar to the disubstituted compounds in all respects.

**Experimental**

**The Acylation of Monoalkylcyanamides**

Several attempts to acylate monoalkylcyanamides resulted in a preponderance of side reactions, yielding urea derivatives and unidentified, gummy materials. A typical example is the preparation and acetylation of ethylcyanamide. Ethylamine (22.5
g., 0.5 mole) was dissolved in 200 ml. of cold ether. Eighty-four grams (1.0 mole) of sodium bicarbonate was added and the mixture was then vigorously stirred, while cooling in an ice-water bath. A solution of 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of ether was added dropwise over a period of one and one-half hours. The thick, white sludge was then treated dropwise with 39.4 g. (0.5 mole) of acetyl chloride. The stirring was continued at room temperature for two hours. The solids were separated by filtration, extracted with ethyl acetate and the extract combined with the filtrate and evaporated. The yellow residue, on cooling, crystallized partially as colorless blades which were collected, washed with ether to remove a yellow oil, and dried. The crude product weighed 7.8 g. and melted at 120-122° C. Recrystallization from boiling ethyl acetate raised the melting point to 126-127° C.

This crystalline product has the same melting point as the material obtained by acetylation of ethyl urea and a mixture of the two gave no depression of the melting point.

Analysis. Calc'd for C\textsubscript{5}H\textsubscript{10}O\textsubscript{2}N\textsubscript{2}: N, 21.5. Found: N, 21.0.
The Preparation and Carbethoxylation of Benzylcyanamide

A mixture containing 48 g. (0.45 mole) of benzylamine, 126 g. (1.5 moles) of sodium bicarbonate and 200 ml. water was chilled in an ice-water bath and vigorously stirred. The mixture was treated dropwise first with 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of ethanol and then with 54 g. (0.5 mole) of ethyl chloroformate. Stirring was continued at room temperature until the gas evolution had ceased. The heavy organic layer was extracted with ether and dried over anhydrous magnesium sulfate. After removal of solvent, the residue was distilled through a 24-inch Vigreaux column under reduced pressure. The product was obtained as a colorless oil, boiling at 131-135° C. at 2.0 mm.

This product, while not a pure substance, was used without further purification in the next experiment. The main contaminant, which precipitates on chilling and seeding, is benzyl urethane, m.p. 48-49° C., showing no depression of the melting point on admixture with an authentic specimen (37).
The Action of Hydrazoic Acid on Benzylcarbethoxycyanamide

A solution of 13.8 g. of impure benzylcarbethoxycyanamide and 32 ml. of benzene containing 0.1 mole of hydrazoic acid was sealed in a heavy walled glass combustion tube and heated at 95° C. for 54 hours. After cooling, the tube contents were removed and the solvent evaporated. The brown oily residue was taken up in ether and extracted with dilute aqueous sodium hydroxide. On neutralization of the alkaline extract, a solid separated as fine, nearly colorless needles, weighing 6.8 g. and melting at 80-83° C. Crystallization from cyclohexane gave fine colorless needles, melting at 81-81.5° C. This solid was soluble in dilute aqueous alkali and insoluble in dilute aqueous acid. The product was assigned the structure of 5-benzylcarbethoxyaminotetrazole on the basis of elementary analysis and its acidic character.

Analysis. Calc'd for C_{11}H_{13}N_{5}O_{2}:  C, 53.4; H, 5.3; N, 28.3. Found:  C, 53.48, 53.65; H, 5.40, 5.38; N, 28.24, 28.22.

The Hydrolysis of 5-Benzylcarbethoxyaminotetrazole

One gram of 5-benzylcarbethoxyaminotetrazole was dissolved in 25 ml. of 0.1 N aqueous potassium hydroxide and the
solution boiled for twenty minutes. After cooling, neutralization precipitated a white solid which weighed 0.8 g. and melted at 181-181.5° C. when heated very slowly in a capillary tube. When heated more rapidly, melting points as high as 193° C. were observed. This product, while sparingly soluble in cold water, is readily soluble in either aqueous acid or aqueous alkali. The product was identical in all respects with 5-benzylaminotetrazole prepared according to Thiele and Ingle (2).

Analysis. Calc'd for C₈H₉N₅: N, 40.0. Found: N, 40.3.

The Debenzylation of 5-Benzylmethylaminotetrazole

A mixture composed of 18.9 g. (0.1 mole) of 5-benzylmethylaminotetrazole (see Part I), 150 ml. of absolute ethanol and 3.0 g. of 5% palladium on charcoal was placed in a Parr hydrogenation bottle. The hydrogenolysis was carried out by shaking under three atmospheres hydrogen pressure at about 65° C. over a period of twenty-four hours. Removal of the catalyst by filtration and evaporation of the solvent gave 9.5 g. of colorless solid melting at 171-177° C. Recrystallization from absolute ethanol gave 7.6 g. of colorless plates, melting initially at 180-182° C., resolidifying and then remelting at 225-226° C. A
further recrystallization from the minimum amount of water raised the melting point to 184-184.5° C., followed by resolidification and remelting at 225-226° C. The behavior of this compound on melting is discussed in Part IV.

The product was identified as 5-methylaminotetrazole on the basis of elementary analysis and silver salt formation (Table VII), and its equivalent weight and apparent acidic dissociation constant as determined by potentiometric titration (Table VIII).

The Debenzylation of 5-Benzylethylaminotetrazole

A mixture composed of 13.7 g. of 5-benzylethylaminotetrazole (see Part I), 150 ml. of absolute ethanol, and 2.0 g. of 5% palladium on charcoal was placed in a Parr hydrogenation bottle. The hydrogenolysis was carried out by shaking under three atmospheres of hydrogen pressure at about 65° C. for eleven hours. Removal of catalyst by filtration and evaporation of solvent gave 7.6 g. of colorless, fine needles, m.p. 172-173° C. Recrystallization from the minimum amount of absolute ethanol raised the melting point to 175-175.5° C. Identification of the product as 5-ethylaminotetrazole was based on elementary analysis and silver
salt formation (Table VII), and its equivalent weight and apparent acidic dissociation constant (Table VIII).

The Debenzylation of 5-Dibenzyaminotetrazole

A mixture composed of 12.5 g. of 5-dibenzyaminotetrazole, 100 ml. of absolute ethanol, and 2.0 g. 5% palladium on charcoal was placed in a shaker bottle of a Burgess-Parr low pressure hydrogenation apparatus and shaken under three atmospheres of hydrogen pressure at about 65° C. for eleven hours. Removal of catalyst by filtration and evaporation of solvent gave 6.4 g. of colorless solid, melting at 176-179° C. Recrystallization from absolute ethanol produced colorless plates, m.p. 181-181.5° C. The product was identical in all respects with 5-benzylaminotetrazole prepared by hydrolysis of 5-benzylcarbethoxyaminotetrazole and by benzylation of 5-aminotetrazole according to the method of Thiele and Ingle. Further identification of the product as 5-benzylaminotetrazole was based on its elementary analysis and silver salt formation (Table VII), and its equivalent weight and apparent acidic dissociation constant as determined by potentiometric titration (Table VIII).
The Debenzylolation of 5-Benzylaminotetrazole

A mixture composed of 8.8 g. (0.05 mole) of 5-benzylaminotetrazole, 100 ml. absolute ethanol, and 2.0 g. 5% palladium on charcoal was placed in a shaker bottle of a Burgess-Parr low pressure hydrogenation apparatus and shaken under three atmospheres of hydrogen pressure at 65° C. for twenty hours. After removal of the catalyst by filtration and evaporation of the solvent, there was obtained 5.9 g. of white, crystalline solid, m.p. 194-197° C. Crystallization from water gave a colorless, translucent solid which, after drying, became opaque and melted at 201.5-202° C. A mixture of this product and an authentic sample of 5-aminotetrazole (3) produced no melting point depression.

The Potentiometric Titration of 5-Monoalkylaminotetrazoles

The 5-monoalkylaminotetrazoles were titrated potentiometrically to determine their equivalent weights and apparent acidic dissociation constants. The method is described in detail in Part I. The titration curves, like those for the 5-dialkylaminotetrazoles, were typical of those for weak acids. A representative
curve is illustrated in Figure 4. The titration data are collected in Appendix I.

The Preparation of the Silver Salts of the 5-Monoalkylaminotetrazoles

The 5-monoalkylaminotetrazoles form silver salts which are insoluble in water, ethanol, and cold dilute nitric acid. They do not appear to be either sensitive to light or shock. On heating, they deflagrate mildly. The silver salt preparation and silver analyses were carried out in the manner described in Part I. The silver analyses are collected in Table VII.
Figure 4. Potentiometric titration curve of 5-methylaminotetrazole in water.
TABLE VII

THE ANALYSIS OF 5-MONOALKYLAMINOTETRAZOLES
AND THEIR SILVER SALTS

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Formula</th>
<th>Analysis</th>
<th>Silver Salts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calc'd %</td>
<td>Found %</td>
</tr>
<tr>
<td>5-Methyl-</td>
<td>C₂H₅N₅</td>
<td>C,</td>
<td>24.2</td>
</tr>
<tr>
<td>amino-</td>
<td></td>
<td>H,</td>
<td>5.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N,</td>
<td>70.7</td>
</tr>
<tr>
<td>5-Ethyl-</td>
<td>C₃H₇N₅</td>
<td>C,</td>
<td>31.9</td>
</tr>
<tr>
<td>amino-</td>
<td></td>
<td>H,</td>
<td>6.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N,</td>
<td>61.9</td>
</tr>
<tr>
<td>5-Benzyl-</td>
<td>C₈H₉N₅</td>
<td>N,</td>
<td>40.0</td>
</tr>
<tr>
<td>amino-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE VIII

APPARENT ACIDIC DISSOCIATION CONSTANTS AND EQUIVALENT WEIGHTS OF SOME 5-MONOALKYLAMINOTETRAZOLES IN APPROXIMATELY 50% AQUEOUS METHANOL BY VOLUME

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Apparent $pK_a$</th>
<th>Apparent $K_a \times 10^8$</th>
<th>Equivalent Wt.</th>
<th>Calc'd</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Methylamino-$^1$</td>
<td>6.06</td>
<td>87</td>
<td></td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>5-Methylamino-</td>
<td>6.67</td>
<td>21</td>
<td></td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>5-Ethylamino-$^1$</td>
<td>6.12</td>
<td>76</td>
<td></td>
<td>113</td>
<td>114</td>
</tr>
<tr>
<td>5-Ethylamino-</td>
<td>6.66</td>
<td>22</td>
<td></td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td>5-Benzylamino-</td>
<td>6.52</td>
<td>30</td>
<td></td>
<td>175</td>
<td>176</td>
</tr>
</tbody>
</table>

$^1$ The determination was carried out in aqueous solution.
PART IV

THE REARRANGEMENT OF CERTAIN MONOSUBSTITUTED
5-AMINOTETRAZOLE DERIVATIVES

Discussion

In the course of the work with the 5-monoalkylaminotetra-
zoles, 5-methylaminotetrazole was observed to display a double
melting point, the higher one of which corresponded almost exactly
with that of 1-methyl-5-aminotetrazole (see Part III). Before this
observation could be examined further, it was corroborated in a
private communication from Dr. R. A. Henry, who had charac-
terized the high melting material as 1-methyl-5-aminotetrazole
(20).

\[
\text{CH}_3\text{NH}^-\text{C}^-\text{N}^-\text{H} \rightarrow \text{CH}_3\text{N}^-\text{C}^-\text{NH}_2
\]

Although 5-benzylaminotetrazole does not show a double melting
point, this is probably due to the close proximity of the melting
point of 1-benzyl-5-aminotetrazole. When 5-benzylaminotetrazole
is melted and kept at the melting temperature for several minutes,
complete rearrangement to 1-benzyl-5-aminotetrazole occurs.
This observation explains the dependence of the melting point of 5-benzylaminotetrazole on the rate of heating. With very slow heating melting points as low as 181° C. have been observed, while on rapid heating the melting point may be as high as 193° C.

In Part II, attention was directed to the peculiar behavior of 1-phenyl-5-aminotetrazole and 1-p-nitrophenyl-5-aminotetrazole on heating in capillary tubes. The former melted completely at 163-163.5° C., resolidified at about 165° C., and then melted again at 205-206° C. No decomposition was apparent at the lower melting point. The latter compound, on heating in a capillary, exhibited a marked change in appearance at about 170° C., and then melted with decomposition at 221-223° C. This phenomenon was first further investigated with 1-phenyl-5-aminotetrazole. A small sample was heated at 160-165° C. in an oil bath. The compound melted and resolidified at the bath temperature. The product had acquired acidic characteristics not present in the unheated material and was completely soluble in dilute aqueous sodium hydroxide. After recrystallization the material now melted at 205-206° C. without prior melting and resolidification. In a
comparable experiment a small sample of 1-p-nitrophenyl-5-aminotetrazole was heated at 170-175° C. in an oil bath for a short time. Although considerable charring was observed, a product, soluble in dilute aqueous alkali, could be separated from the mixture. This product, after recrystallization, did not show any change on heating in a capillary tube until it melted with decomposition at 221-223° C. Analysis showed that both products resulting on thermal rearrangement had the same composition as the original compounds. Subsequently it was found that the same change could be brought about with less decomposition by boiling suspensions of either compound in xylene. The rearrangements were complete since no trace of alkali insoluble materials could be found in the products. A simple explanation of the changes is expressed by the rearrangement of the 1-aryl-5-aminotetrazole to 5-arylaminotetrazole.

\[
\text{C}_6\text{H}_5\text{-N}^\text{N} = \text{C-NH}_2 \rightarrow \text{C}_6\text{H}_5\text{NH}^\text{N} = \text{C-N-H}^\text{N}
\]

During the preparation of 1-phenyl-5-aminotetrazole from phenylthiourea, Stollé had observed the formation of a very small amount of material to which he assigned the structure of
5-phenylaminotetrazole (10). This product was described as an acidic compound and melted at 206° C., properties which were in close agreement with those observed for the material formed upon thermal rearrangement of 1-phenyl-5-aminotetrazole.

It is interesting to note that the rearrangement of 5-aminotetrazole derivatives is so dependent upon the nature of substituents at the 1-position on the ring or on the amino group. It is not surprising to find that the 5-alkylaminotetrazoles rearrange to the 1-alkyl-5-aminotetrazole form because, as was pointed out in Part II, this latter form represents the exclusive cyclization product of the monoalkyl guanyl azides. Since the 1-aryl-5-aminotetrazoles are the only cyclization products of the monoaryl guanyl azides, it is rather surprising to find that they undergo rearrangement to the 5-arylaminotetrazole structure so readily.

Other structures can be written for the rearrangement products of the 1-aryl-5-aminotetrazoles. For example, a Fischer-Hepp type rearrangement could follow the formation of a 5-arylaminotetrazole. Such a change would lead to a structure in which the aryl group was attached directly at the 5-position of the tetrazole ring. The absence of the N-C-N system should make such products less prone to rearrangement.
This possibility is rather effectively ruled out by the absence in the rearrangement products of an amino group that can be diazotized and coupled. Qualitative tests with a variety of 1-aminophenyl- and 5-aminophenyltetrazole derivatives demonstrated that such compounds can be diazotized and coupled easily.

Rearrangement could also lead to a pentazine structure.

This alternative is not very attractive. All attempts to prepare pentazine derivatives have led to the formation of 5-aminotetrazole structures (38). In this connection it may also be significant that many tetrazine structures are known to rearrange rather easily to 1,2,3-triazole or 1,2,4-triazole derivatives (39). Furthermore, interpretation of the ultraviolet absorption spectra of the arylaminotetrazoles, which are considered in a subsequent section of this Part, can be made without resorting to a pentazine structure.
It will be recalled that the structure of 1-p-nitrophenyl-5-aminotetrazole was supported by its formation both from p-nitrophenylcyanamide and by nitration of 1-phenyl-5-aminotetrazole (see Part II). It was thought that the relationship between the rearrangement products of 1-p-nitrophenyl-5-aminotetrazole and 1-phenyl-5-aminotetrazole might be established in a similar manner. Unfortunately, nitration of 5-phenylaminotetrazole with mixed acid at 0° C. resulted in a dinitro derivative. Although the distribution of the nitro groups in this product has not been determined, several possible structures must be considered. Both nitro groups may have become attached to the benzene ring in the ortho and para positions or one of the nitro groups may be attached to the amino group.

A choice between these structures cannot be made at the present time. The mildness of the conditions under which the nitration was accomplished would point to the nitrophenylnitraminotetrazole as the more probable structure. It has been shown (40) that both
5-aminotetrazole and 5-methylaminotetrazole can be converted into nitramino derivatives under very mild conditions; however, these nitramino derivatives are rather strong acids, at least ten times as strong as the dinitro 5-phenylaminotetrazole. Actually, the rather strongly acidic character of the dinitro compound could be explained on the basis of either structure (see Part V).

Before the nitration product of 5-phenylaminotetrazole had been identified as a dinitro compound, the synthesis of the isomeric meta and ortho nitrophenyl derivatives was undertaken. m-Nitrophenylcyanamide on treatment with hydrazoic acid gave only a neutral product to which the structure of 1-m-nitrophenyl-5-aminotetrazole may be assigned on the basis of its elementary analysis and chemical properties. On heating in a capillary tube this compound showed the same type of behavior noted for the para isomer. On boiling a suspension of the meta compound in xylene a change in the physical appearance of the material was noted. After this treatment the compound was found to be soluble in dilute, aqueous sodium hydroxide and on heating in a capillary tube no longer showed the typical changes observed before rearrangement. These observations support the belief that rearrangement to 5-m-nitrophenylaminotetrazole had taken place.
Potentiometric titration data and ultraviolet absorption spectra also support this conclusion.

\[
\begin{align*}
\text{m-NO}_2\text{C}_6\text{H}_4\text{-NHCN} & \quad \rightarrow \quad \text{m-NO}_2\text{C}_6\text{H}_4\text{-N}^+\text{C-NH}_2^- \\
\downarrow & \\
\text{m-NO}_2\text{C}_6\text{H}_4\text{-NH-C}^\equiv\text{N-H} &
\end{align*}
\]

The same sequence of reactions was undertaken with o-nitrophenylcyanamide. In this instance the course of the reaction with hydrazoic acid could be influenced not only by the electrical nature of the substituent group but also by intramolecular hydrogen bonding involving the nitro group and the amino hydrogen of the cyanamide residue. It was conceivable that hydrogen bonding could prevent the tautomeric shift of the hydrogen in the o-nitrophenyl guanyl azide and cause the direct formation of 5-o-nitrophenylaminotetrazole upon cyclization. The steric effect of the o-nitro group could also influence the cyclization in the same direction.
In an initial experiment with o-nitrophenylcyanamide and hydrazoic acid the product appeared to be an alkali insoluble material. After recrystallization from xylene the product was soluble in aqueous alkali and appeared to be 5-o-nitrophenylaminotetrazole. It has not been possible to repeat this initial observation. Attempts to duplicate the preparation of an alkali-insoluble product were unsuccessful. At lower temperatures, 50° and 60° C., no reaction with hydrazoic acid took place; o-nitrophenylcyanamide was recovered unchanged. At 70° C. o-nitrophenylcyanamide reacted slowly with hydrazoic acid to form only 5-o-nitrophenylaminotetrazole. At 80° C. the reaction was fairly rapid and formation of 5-o-nitrophenylaminotetrazole was complete in two hours. Potentiometric titration, ultraviolet absorption
spectrum and behavior of the product on heating support the assigned structure.

Although with one exception the product formed by interaction of o-nitrophenylcyanamido and hydrazoic acid has always been 5-o-nitrophenylaminotetrazole, it is impossible to exclude 1-o-nitrophenyl-5-aminotetrazole as an intermediate in the sequence. Unfortunately the alkali-insoluble product formed on one occasion was converted into the alkali-soluble compound when its solution in xylene was heated during an attempted purification by recrystallization.

Potentiometric titrations were done with all the acidic rearrangement products. The apparent acidic dissociation constants are given in Table X. The acids in order of decreasing strength are the dinitro 5-phenylaminotetrazole, 5-o-nitrophenylamino-, 5-p-nitrophenylamino-, 5-m-nitrophenylamino-, and 5-phenylaminotetrazole. These data are discussed more extensively in Part V.

The ultraviolet absorption data tend to support the formulation of the acidic rearrangement products as 5-nitrophenylaminotetrazoles. A rough correspondence exists between the absorption of the nitrophenylaminotetrazoles and the corresponding
nitroanilines. Thus, the pentazine structure as well as other structures which do not retain the aniline configuration are rather unlikely.

In Table IX are collected the wavelengths of maximum ultraviolet absorption for these arylaminotetrazoles. Data for certain other tetrazole derivatives and the nitroanilines are also included for comparison. One can make a number of interesting observations from these data. Tetrazole, 5-aminotetrazole, and 5-dimethylaminotetrazole are transparent throughout the range studied, 220 to 450 μ. A phenyl group in the 1-position causes no absorption while a phenyl group in the 5-position, whether directly linked or linked through a 5-amino-nitrogen, causes a peak to show up at 230 to 250 μ. A nitrophenyl group in the 1-position causes a minimum to show up at 235 to 240 μ., followed closely by a maximum.

When the group in the 5-position is nitrophenylamino the peak at 230 to 250 μ. again appears. This is followed by a minimum and another maximum corresponding to those observed in the spectra of the nitroanilines.

In the case of the dinitro 5-phenylaminotetrazole, the first peak is shifted towards the red which suggests that the nitro
groups are not both on the phenyl group. When the 5-mononitro-
phenylaminotetrazoles are compared to 5-phenylaminotetrazole,
the shift is towards the shorter wavelengths. However, the min-
umum and second maximum found for the dinitro compound suggest
that the nitroaniline structure is still intact.
### TABLE IX

**THE WAVE LENGTHS (mu.) OF MAXIMUM AND MINIMUM ULTRAVIOLET ABSORPTION OF CERTAIN TETRAZOLE DERIVATIVES AND RELATED COMPOUNDS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ultraviolet Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max.</td>
</tr>
<tr>
<td>Tetrazole</td>
<td>-</td>
</tr>
<tr>
<td>5-Aminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>5-Dimethylaminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>5-Nitraminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>1-Phenyl-5-methyltetrazole</td>
<td>-</td>
</tr>
<tr>
<td>1-Methyl-5-phenyltetrazole</td>
<td>232</td>
</tr>
<tr>
<td>5-Phenyltetrazole</td>
<td>240</td>
</tr>
<tr>
<td>2-Methyl-5-phenyltetrazole</td>
<td>240</td>
</tr>
<tr>
<td>1-Phenyl-5-aminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>1-p-Nitrophenyl-5-aminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>1-m-Nitrophenyl-5-aminotetrazole</td>
<td>-</td>
</tr>
<tr>
<td>5-Phenylaminotetrazole</td>
<td>250</td>
</tr>
<tr>
<td>5-p-Nitrophenylaminotetrazole</td>
<td>230</td>
</tr>
<tr>
<td>p-Nitroaniline</td>
<td>-</td>
</tr>
<tr>
<td>5-m-Nitrophenyaminotetrazole</td>
<td>253</td>
</tr>
<tr>
<td>m-Nitroaniline</td>
<td>-</td>
</tr>
<tr>
<td>5-o-Nitrophenylaminotetrazole</td>
<td>243</td>
</tr>
<tr>
<td>o-Nitroaniline</td>
<td>-</td>
</tr>
<tr>
<td>Dinitro 5-phenylaminotetrazole</td>
<td>260</td>
</tr>
</tbody>
</table>

1 Reference 40.  
2 Reference 41.  
3 Reference 42.
TABLE X
APPARENT ACIDIC DISSOCIATION CONSTANTS AND EQUIVALENT WEIGHTS OF SOME 5-ARYLAMINOTETRAZOLES IN APPROXIMATELY 50% AQUEOUS METHANOL BY VOLUME

<table>
<thead>
<tr>
<th>Tetrazole</th>
<th>Apparent $pK_a$</th>
<th>Apparent $K_a \times 10^6$</th>
<th>Equivalent Wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Calc'd</td>
</tr>
<tr>
<td>5-Phenylamino-</td>
<td>5.49</td>
<td>3.2</td>
<td>161</td>
</tr>
<tr>
<td>5-p-Nitrophenylamino-</td>
<td>4.34</td>
<td>46</td>
<td>206</td>
</tr>
<tr>
<td>5-m-Nitrophenylamino-</td>
<td>4.85</td>
<td>14</td>
<td>206</td>
</tr>
<tr>
<td>5-o-Nitrophenylamino-</td>
<td>4.08</td>
<td>83</td>
<td>206</td>
</tr>
<tr>
<td>Dinitro 5-phenylamino-</td>
<td>3.38</td>
<td>420</td>
<td>251</td>
</tr>
</tbody>
</table>
Experimental

The Thermal Rearrangement of 5-Benzyaminotetrazole

\[
\begin{align*}
C_6H_5-CH_2-NH-C=\overset{\text{N}}{N} & \quad \rightarrow \quad C_6H_5-CH_2-N=\overset{\text{N}}{N} \\
& \quad \rightarrow \quad C_6H_5-CH_2-N=\overset{\text{N}}{N}
\end{align*}
\]

One gram of 5-benzyaminotetrazole was heated in an oil bath at 180-185° C. for five minutes. After cooling, the product was extracted with a few mls. of aqueous 0.1 N potassium hydroxide. The alkali-insoluble residue was then recrystallized from the minimum amount of 50% aqueous ethanol; yield, 0.7 g. of fine colorless needles, m.p. 190.5-191.5° C. The product was identical with 1-benzyl-5-aminotetrazole in all respects. The alkaline extract, on neutralization, yielded no solid product.

The Thermal Rearrangement of 1-Phenyl-5-aminotetrazole

\[
\begin{align*}
C_6H_5-N=\overset{\text{N}}{N} & \quad \rightarrow \quad C_6H_5-N=\overset{\text{N}}{N} \\
& \quad \rightarrow \quad C_6H_5-N=\overset{\text{N}}{N}
\end{align*}
\]

Two grams of 1-phenyl-5-aminotetrazole were suspended in 20 ml. of xylene and heated under reflux for one hour. After
chilling, the solid was collected, dissolved in dilute aqueous potassium hydroxide and filtered. The alkaline solution was almost colorless. Neutralization precipitated a colorless solid which was collected and then recrystallized from ethanol. The product, 5-phenylaminotetrazole, was obtained as colorless plates; yield, 1.8 g.; m.p., 205-206° C.

Analysis. Calc'd for C<sub>7</sub>H<sub>7</sub>N: C, 52.15; H, 4.38; N, 43.45.

Found: C, 51.94, 52.15; H, 4.58, 4.38; N, 43.70, 43.47.

The possible presence of a primary amine function on the phenyl group of the rearrangement product of 1-phenyl-5-aminotetrazole was rendered unlikely by the following experiment. The rearrangement product, 1-p-aminophenyl-5-methyltetrazole, and 1-p-aminophenyl-5-aminotetrazole were treated, in identical qualitative tests, with nitrous acid and then with β-naphthol. All gave typical red coupling products except the rearrangement product. It should be noted that the primary amine function of 5-aminotetrazoles is not readily diazotized (43).

The Thermal Rearrangement of 1-p-Nitrophenyl-5-aminotetrazole

\[
p-\text{NO}_2\cdot \text{C}_6\text{H}_4\cdot \text{N}^\text{H}^\text{N}\to p-\text{NO}_2\cdot \text{C}_6\text{H}_4\cdot \text{NH}^\text{N}\to\text{N}^\text{H}
\]
Two grams of 1-p-nitrophenyl-5-aminotetrazole obtained by the reaction of hydrazoic acid with p-nitrophenylcyanamide was suspended in 20 ml. of xylene and heated under reflux for two hours. After chilling, the yellow solid was collected and dried. Two recrystallizations of the 5-p-nitrophenylaminotetrazole from acetonitrile gave pale yellow needles which melted with decomposition at 221-223°C. This material is readily soluble in dilute aqueous potassium hydroxide, giving a deep red solution, and is insoluble in dilute aqueous hydrochloric acid.

Analysis. Calc'd for C_{7}H_{6}N_{6}O_{2}: C, 40.77; H, 2.93; N, 40.76. Found: C, 40.24, 40.21; H, 3.29, 3.27; N, 40.88, 41.03.

The product obtained by nitration of 1-phenyl-5-aminotetrazole behaved in exactly the same manner when heated in boiling xylene. The product dissolved in aqueous alkali to give a deep red solution. It crystallized from acetonitrile as pale yellow needles melting with decomposition at 221-223°C.

Analysis. Calc'd for C_{7}H_{6}N_{6}O_{2}: C, 40.77; H, 2.93; N, 40.76. Found: C, 40.61, 40.79; H, 3.02, 3.02; N, 41.10, 40.95.
The Reaction of Hydrazoic Acid with m-Nitrophenylcyanamide

\[
\begin{align*}
\text{m-NO}_2\text{C}_6\text{H}_4\text{NH-CN} & \rightarrow \text{m-NO}_2\text{C}_6\text{H}_4\text{NH-C=NH} \\
\end{align*}
\]

A solution containing 6.0 g. of m-nitrophenylcyanamide (24), 100 ml. of xylene containing 0.37 mole of hydrazoic acid, and 50 ml. of absolute ethanol was heated under reflux for fourteen hours. After allowing most of the alcohol to evaporate, cooling caused the product to separate as fine, tan needles which were collected and dried. The crude 1-m-nitrophenyl-5-amino-tetrazole weighed 7.3 g. and melted with decomposition at 221-226° C. after shrinking suddenly at about 170° C. Crystallization from acetonitrile gave fine, yellow needles, melting with decomposition at 226.5-228° C. after shrinking at about 170° C. This product is soluble in warm, dilute hydrochloric acid from which it reprecipitates on cooling, and is insoluble in dilute aqueous potassium hydroxide.
The Thermal Rearrangement of 1-m-Nitrophenyl-5-aminotetrazole

Two grams of 1-m-nitrophenyl-5-aminotetrazole was suspended in xylene and heated under reflux for one and one-half hours. After cooling, the yellow solid was collected, dissolved in dilute aqueous potassium hydroxide and filtered. The alkaline solution was yellow in color. Neutralization precipitated a pale yellow solid which was collected and dried. Crystallization from ethanol gave fine, pale yellow needles which melted with decomposition at 226° C. The 5-m-nitrophenylaminotetrazole is readily soluble in dilute aqueous potassium hydroxide and insoluble in dilute aqueous hydrochloric acid.

Analysis. Calc'd for $\text{C}_7\text{H}_6\text{N}_6\text{O}_2$: C, 40.77; H, 2.93; N, 40.76. Found: C, 41.12, 41.21; H, 3.17, 3.15; N, 41.07, 41.07.
The Reaction of Hydrazoic Acid with o-Nitrophenylcyanamide

\[ o-\text{NO}_2\text{-C}_6\text{H}_4\text{-NH-CN} \rightarrow o-\text{NO}_2\text{-C}_6\text{H}_4\text{-NH-C=NH} \]

A solution of 3.9 g. of o-nitrophenylcyanamide, 1 50 ml. xylene containing 0.18 mole of hydrazoic acid, and 50 ml. of absolute ethanol was heated under reflux for two hours. The temperature of the boiling reaction mixture was 78° C. After evaporation of most of the alcohol, the product separated as yellow needles on chilling. The crude product, weighing 3.1 g., was completely soluble in dilute aqueous potassium hydroxide. The alkaline solution was deep red in color. Neutralization of the clear solution precipitated a yellow solid which was collected and dried. Recrystallization from acetonitrile gave very fine,

---

1 o-Nitrophenylcyanamide was prepared essentially as described by Pierron (24). Better results were obtained when the reaction time was reduced from one hour to 30 to 40 minutes.
bright yellow needles which melted with decomposition at 211° C. The acidic character of the product indicated that it was 5-o-nitrophenylaminotetrazole.

Analysis. Calc'd for $C_7H_6N_6O_2$: C, 40.77; H, 2.93; N, 40.76. Found: C, 40.99, 40.88; H, 3.07, 3.06; N, 40.95, 40.87.

When the reaction was repeated at 50° and 60° C., the starting material was recovered unchanged; at 70° C., only the acidic product was obtained along with some unchanged starting material.

In a single experiment in which o-nitrophenylcyanamide was boiled under reflux in a xylene solution of hydrazoic acid for about two hours (temperature of the boiling reaction mixture was not determined), the crude product that separated on cooling was insoluble in dilute aqueous alkali. On heating in a capillary tube the crude product melted at 151-153° C., resolidified and then melted again at 201° C. This material could not be characterized more completely because on recrystallization from xylene it was converted into the alkali-soluble material described above. All attempts to repeat this experiment have been unsuccessful.
Ultraviolet Absorption Measurements

The ultraviolet absorption spectra were determined with a Beckman quartz spectrophotometer, Model DU, using 10 mm. quartz cells and 95% ethanol as the solvent. In Figures 5 to 11, the ultraviolet absorption spectra of the following compounds are represented graphically:

1-Phenyl-5-aminotetrazole
5-Phenylaminotetrazole
1-m-Nitrophenyl-5-aminotetrazole
5-m-Nitrophenylaminotetrazole
1-p-Nitrophenyl-5-aminotetrazole
5-p-Nitrophenylaminotetrazole
5-o-Nitrophenylaminotetrazole
Dinitro 5-phenylaminotetrazole
5-Phenyltetrazole (3)
1-Phenyl-5-methyltetrazole (44)

The data from which the curves were constructed are collected in Appendix II.
Potentiometric Titrations

The acidic rearrangement products were all titrated potentiometrically to determine their equivalent weights and apparent acidic, dissociation constants. The method is described in detail in Part I. A representative curve is illustrated in Figure 12. The results are summarized in Table X and the data are collected in Appendix I.
Figure 5. Ultraviolet absorption curves: A, 5-phenyl-tetrazole; B, 1-phenyl-5-methyltetrazole.
Figure 6. Ultraviolet absorption curves: A, 5-phenylaminotetrazole; B, 1-phenyl-5-aminotetrazole.
Figure 7. Ultraviolet absorption curves: A, 5-m-nitrophenylaminotetrazole; B, 1-m-nitrophenyl-5-aminotetrazole.
Figure 8. Ultraviolet absorption curves: A, 1-p-nitrophenyl-5-aminotetrazole (from p-nitrophenylcyanamide); B, 5-p-nitrophenylaminotetrazole (the rearrangement product from the 1-p-nitrophenyl-5-aminotetrazole obtained from p-nitrophenylcyanamide).
Figure 9. Ultraviolet absorption curves: A, 1-p-nitrophenyl-5-aminotetrazole (nitration product of 1-phenyl-5-aminotetrazole); B, 5-p-nitrophenyl-aminotetrazole (the rearrangement product from the 1-p-nitrophenyl-5-aminotetrazole obtained by nitration).
Figure 10. Ultraviolet absorption curve: 5-o-nitrophenylamino-tetrazole.
Figure 11. Ultraviolet absorption curve: dinitro 5-phenylaminotetrazole.
Figure 12. Potentiometric titration of 5-o-nitrophenylaminotetrazole in 50 per cent aqueous methanol.
PART V

THE EFFECT OF SUBSTITUENTS ON THE ACIDITY OF CERTAIN TETRAZOLE DERIVATIVES

Tetrazole derivatives in which the hydrogen attached to the ring nitrogens has not been replaced by other groups are acidic compounds. The degree of acidity of the compounds may be profoundly influenced by the electrical and steric nature of the substituent on the carbon atom in position 5 of the ring. An attempt to correlate these effects will be made in this Part. The apparent acidic dissociation constants of the 5-substituted tetrazoles prepared in the course of this study are collected in Table XI.

The acidity of tetrazole itself is readily explained on the basis of the resonance concept; i.e., resonance stabilization of the anion by virtue of the increased number and the symmetry of the forms contributing to the resonance hybrid as compared with the un-ionized molecule.
Mihina and Herbst (3) have determined the apparent acidic
dissociation constants of a series of 5-alkyl- and 5-aryltetra-
zoles. They pointed out that the tetrazole nucleus in such com-
pounds can be considered as comparable to the carboxyl group.
The acidity of a similarly substituted carboxylic acid was uniformly
greater than that of the tetrazole derivative by a factor of about
ten.

R-COOH

R-\overset{\text{N-H}}{\text{N-N}}

Any effect which increases the negative character of the ring
should cause a decrease in acidity of the tetrazole system. Hence,
it is not surprising that alkyl groups in the 5-position on the tet-
razole ring, through operation of the inductive effect, cause a
significant decrease in the $K_a$ value.
In the case of 5-aminotetrazole a further decrease in acid strength is observed. Furthermore, the basic function of 5-aminotetrazole is very weak. Both of these observations may be attributed to the type of resonance picture invoked for aniline (45). The free pair of electrons of the aminonitrogen may be considered to be involved in the resonance of the attached ring system. In such a resonating system the negative character of the ring would be increased. Dissociation of a proton from the ring would become more difficult causing a decrease in acidity. Since charge separation imposes ammonium ion character on the amino group, the basicity of this group should also be decreased.

\[ \text{H H H} \quad \text{H(+)} \quad \text{H} \]
\[ \text{N} \quad \text{N-H} \quad \text{<-------------------(--> | N-H}} \quad \text{N} \quad \text{N} \]
\[ \text{N=N} \quad \text{N=N} \quad \text{N=N} \quad \text{N=N} \]

The effect upon the acidity of replacing the hydrogens of the amino group with alkyl groups appears to be primarily steric in nature. The inductive effect noted when the alkyl groups were attached directly at the 5-position (3) are not transmitted by the amino-nitrogen. 5-Amino- and 5-dimethylaminotetrazole have the same apparent acidic dissociation constants. Neither steric nor
inductive effects are apparent in this instance. Other groups which may exert little steric influence have essentially no effect on the magnitude of the dissociation constant. Thus, 5-dibenzylamino-, 5-benzylmethylamino-, and 5-diallylaminotetrazole are as strongly acidic as 5-aminotetrazole and 5-dimethylaminotetrazole. On the other hand, there is a marked decrease in acid strength in going from 5-dimethylaminotetrazole to 5-diethylamino-, 5-diisopropylamino-, 5-di-n-butyraminotetrazole and other larger 5-dialkylaminotetrazoles. Since the inductive effects of most alkyl groups are comparable, their steric influence apparently predominates. A similar decrease in acid strength accompanies the change from 5-benzylmethylamino- to 5-benzyethylaminotetrazole. There is a nice correspondence in the occurrence of a steric effect in this group with that observed in certain hindered carboxylic acids and described by Newman in terms of the "six-number" (46). Those compounds having the largest "six-number" are the weakest acids.
Apparently other factors play a part in determining the acid strength of the 5-monoalkylaminotetrazoles. 5-Methylaminotetrazole is a weaker acid than the corresponding dimethylamino compound. A similar relationship is apparent between 5-benzylamino- and 5-dibenzylaminotetrazole. On the other hand in 5-ethylaminotetrazole, where the steric effect of the single ethyl group should be appreciably less than that of the two ethyl groups in 5-diethylaminotetrazole, the anticipated increase in acid strength is realized. An explanation of the large increase in acid strength observed with 5-(N-morpholiny1)-tetrazole is not immediately apparent.

The enhanced acidity of 5-phenyltetrazole arises from the increased stabilization of the anion by virtue of the conjugation of the phenyl group and the tetrazole nucleus. This makes possible several resonance forms not present in the tetrazole anion itself.
5-Phenylaminotetrazole is a weaker acid than 5-phenyltetrazole because the conjugation of the phenyl group with the tetrazole nucleus is interrupted by the amino group. The fact that 5-phenylaminotetrazole is still more acidic than 5-aminotetrazole and its alkyl derivatives, leads one to speculate that resonance forms such as the following may be responsible.

\[
\text{(-)}: \text{[diagram of resonance structures]} \quad \text{(+)}: \text{[diagram of resonance structures]}
\]

Such forms would be expected to increase the positive character of the tetrazole nucleus inductively and result in a greater tendency for the dissociation of the proton.

This speculation is given some weight by the relative acidities of the isomeric 5-nitrophenylaminotetrazoles. The inductive effect cited above should be augmented in decreasing order by ortho, meta, and para nitro groups. Superimposed on this effect is a resonance reinforcement in the case of the ortho and para isomers. This combination of effects should cause the
orthonitrophenylaminotetrazole to be the strongest acid, the para intermediate, the meta the weakest. All of them should be stronger acids than 5-phenylaminotetrazole. This is the observed order.

\[
\begin{array}{c}
\text{(-)O}_N^{(+)} \text{H} \text{N}=\text{N} \text{N} \\
\text{(-)O} \text{N} \text{N} \text{N}^{(+)}
\end{array}
\]

In the case of the dinitro 5-phenylaminotetrazole, a relatively large increase in acidity is observed. Several possible structures were considered in Part IV. Substitution of the amino group of 5-aminotetrazole with a phenyl or a nitrophenyl group causes a marked increase in acidity. Substitution of the amino group with a nitro group causes an even greater increase in acidity (40). Introduction of a second nitro group either on the benzene ring or on the amino group of a 5-nitrophenylaminotetrazole should cause a further increase in acidity. Both types of substitution would cause augmentation of the acidic character of the tetrazole nucleus by strengthening the inductive effects described above. Although the increase in acidity observed for the dinitro compound is not as great as might have been expected for the nitramino structure, the data do not permit a definite choice between the several structures.
<table>
<thead>
<tr>
<th>Substituent</th>
<th>$K_a \times 10^8$ (water)</th>
<th>$K_a \times 10^8$ (50% aqueous methanol)</th>
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<tr>
<td>Hydrogen</td>
<td>1,600</td>
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</tr>
<tr>
<td>Methyl; ethyl; propyl</td>
<td>270; 260; 250</td>
<td>-</td>
</tr>
<tr>
<td>Amino</td>
<td>120</td>
<td>36</td>
</tr>
<tr>
<td>Dimethylamino</td>
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<tr>
<td>Diethylamino</td>
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</tr>
<tr>
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</tr>
<tr>
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<tr>
<td>Diisoamylamino</td>
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<td>Benzyldihydrazine</td>
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</tr>
<tr>
<td>Ethylamino</td>
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<td>22</td>
</tr>
<tr>
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¹ Reference (3).

² Determined in 44% by weight methanol.
SUMMARY

1. The interaction of dialkylcyanamides and hydrazoic acid in both polar and nonpolar solvents has been shown to give 5-dialkylaminotetrazoles. This constitutes an excellent method for the preparation of these tetrazole derivatives.

2. A group of fourteen new 5-dialkylaminotetrazoles has been prepared and characterized. The silver salts of all the compounds have been prepared and in two instances the hydrochlorides have been described.

3. The interaction of monosubstituted cyanamides and hydrazoic acid has been shown to give 1-substituted-5-aminotetrazoles. This constitutes a new and superior method for the preparation of these tetrazole derivatives. A group of eleven 1-substituted-5-aminotetrazoles, two of which are new compounds, has been prepared.

4. It has been shown that the tetrazole ring, when attached to the phenyl group through the nitrogen in the 1-position, exerted an ortho-para orienting influence. The nitration of
1-phenyl-5-aminotetrazole caused the formation of 1-p-nitrophenyl-5-aminotetrazole.

5. Because of the difficulty in isolating them as pure compounds, a number of monoalkylcyanamides has been characterized by alkaline hydrolysis to the corresponding ureas.

6. The interaction of benzylcarbethoxycyanamide with hydrazoic acid resulted in the formation of 5-benzylcarbethoxyaminotetrazole. On alkaline hydrolysis the latter was converted into 5-benzylaminotetrazole. Due to difficulties encountered in the preparation of alkylacylcyanamides this method for the synthesis of 5-alkylaminotetrazoles has not been explored extensively.

7. A method for the preparation of 5-monoalkylaminotetrazoles by the catalytic hydrogenolysis of the corresponding 5-alkylbenzylaminotetrazoles has been described. Three 5-monoalkylaminotetrazoles and their silver salts have been prepared and characterized.

8. The rearrangements of a number of monosubstituted 5-aminotetrazoles have been described. At their melting points, 5-alkylaminotetrazoles rearrange to the corresponding 1-alkyl-
5-aminotetrazoles. However, at the temperature of boiling xylene 1-aryl-5-aminotetrazoles rearrange to the corresponding 5-aryl-aminotetrazoles. This constitutes a convenient method for the synthesis of the otherwise difficultly accessible 5-arylaminozole.

9. The ultraviolet absorption spectra of 5-aminotetrazole, 5-dimethylaminotetrazole, the 1-aryl-5-aminotetrazoles, and the 5-arylaminozoles have been described. A correlation of structure with the ultraviolet absorption spectra has been discussed.

10. The apparent acidic dissociation constants for the 5-dialkylaminotetrazoles, the 5-monoalkylaminotetrazoles, and the 5-arylaminozoles have been determined. Possible explanations of the effect of various substituents in the 5-position on the strength of the tetrazole derivatives as acids have been discussed.
## APPENDIX I

### POTENTIOMETRIC TITRATION DATA

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<th>Apparent Ka</th>
<th>Ml. of Alk. at Equiv. Point</th>
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APPENDIX II (Continued)

5-m-Nitrophenylaminotetrazole
0.0016 g./100 ml. ethanolic solution

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1-p-Nitrophenyl-5-amino-tetrazole (from nitration) 0.0020 g./100 ml. ethanolic solution

1-p-Nitrophenyl-5-amino-tetrazole (from cyanamide) 0.0017 g./100 ml. ethanolic solution
5-<wbr/>p-Nitrophenylaminotetrazole (rearranged 1-<wbr/>p-nitrophenyl-5-<wbr/>aminotetrazole obtained from p-nitrophenylcyanamide) 0.0014 g./100 ml. ethanolic solution

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5-p-Nitrophenylaminotetrazole (rearranged 1-p-nitrophenyl-5-aminotetrazole obtained by nitration of 1-phenyl-5-aminotetrazole) 0.0014 g./100 ml. ethanolic solution

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APPENDIX II (Continued)

Dinitro-5-phenylaminotetrazole (obtained by nitrations of 5-phenylaminotetrazole)
0.0021 g./100 ml. ethanolic solution

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