

PREPARATION OF 4-AMINO-3-HYDRAZINO-5-METHYL-  
s-TRIAZOLE DIHYDROCHLORIDE AND  
CONDENSATION PRODUCTS

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## CHAPTER I

### INTRODUCTION

s-Triazoles with alkyl or aryl substituents in the 4-position were first prepared by dehydrating 2-diacylhydrazines in the presence of a primary amine (4). 4-Amino-3,5-disubstituted-s-triazoles were obtained by replacing the primary amine with hydrazine hydrate to react with s-diacylhydrazines or by heating the carboxylic acid and hydrazine hydrate in an apparatus that allows the continuous removal of water (2). Triaminoguanidine hydrochloride has been refluxed with various carboxylic acids to produce the respective 4-amino-3,5-disubstituted-s-triazoles. For example, triaminoguanidine hydrochloride (I) will react with glacial acetic acid to give 4-acetamido-3-acethydrazino-5-methyl-s-triazole (Ia) (5). (Figure 1, p. 2.)

The nucleophilic character of the 3-hydrazino group would indicate the possibility of carbonyl condensation with various aldehydes and ketones. Since triazoles have been shown to possess a high degree of stability and aromatic character (4), hydrazino-substituted triazoles would be expected to possess reactivities similar to that of phenylhydrazine in the formation of hydrazones in weakly acidic media. Thus, 4-amino-3-hydrazino-5-methyl-s-triazole hydrochlorides would be expected to react with various aromatic

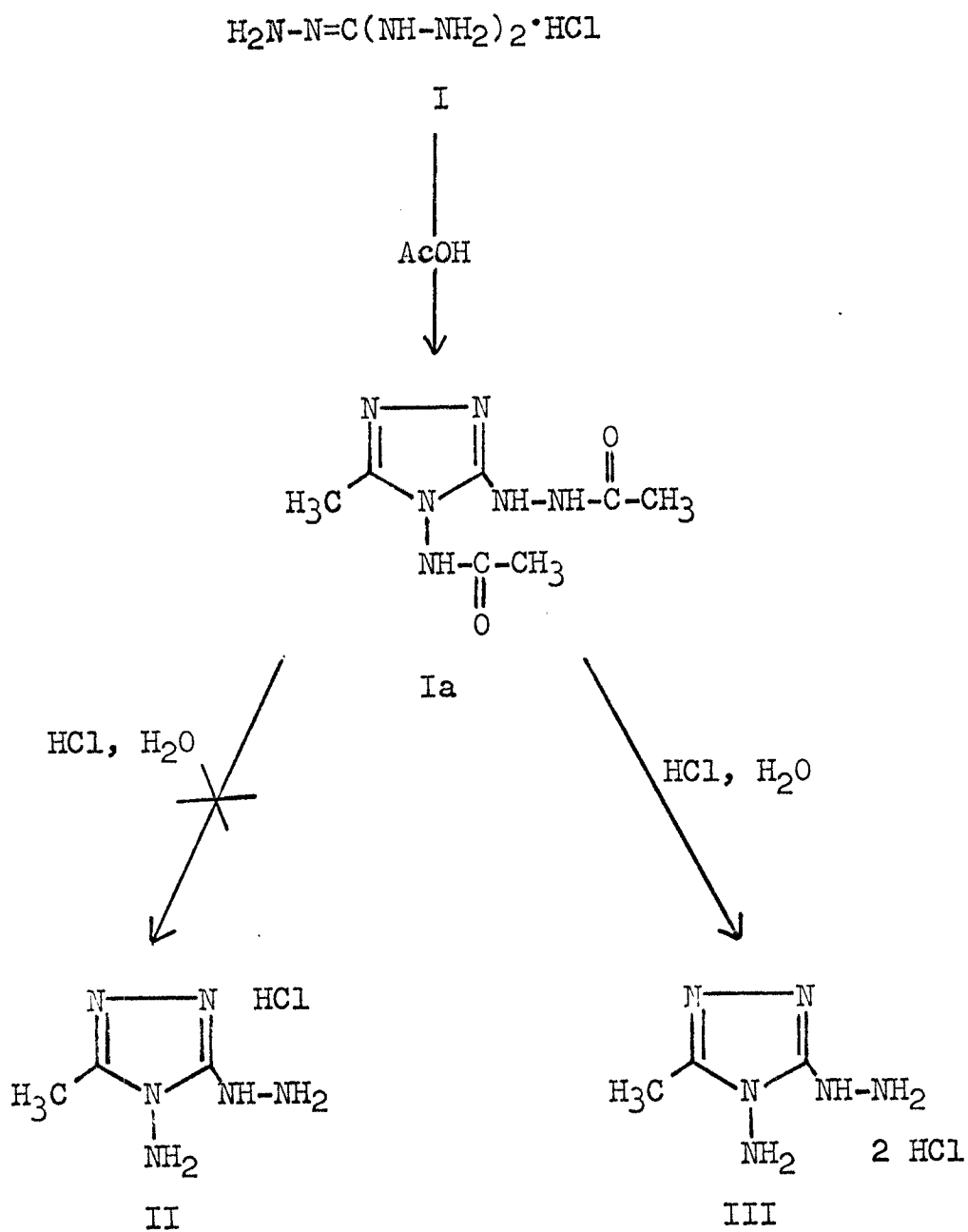


Fig. 1--Synthesis of hydrochlorides of 4-amino-3-hydrazino-5-methyl-s-triazole.

aldehydes and ketones to produce stable hydrazone derivatives. Since the benzilidene derivative of 4-amino-3-hydrazino-5-methyl-s-triazole hydrochloride has been effected in good yields from benzaldehyde (5), the condensation of substituted benzaldehydes seems feasible.

The reactivity of 4-aminotriazole with carbonyl groups indicates that the triazole readily forms Schiff's bases (4). The infrared study of aminotriazoles reveals N-H deformation characteristic of a primary amine and aromatic C-H absorptions, indicating the similarity in resonance structure between the aminotriazoles and aromatic amines (4). As would have been expected the monobenzoyl derivative of 4,5-diamino-3-phenyl-s-triazole has been isolated under mildly basic conditions and further reaction of the monobenzoyl derivative or treatment of the diamine with an excess of benzoyl chloride gave the dibenzoyl derivative (3).

Condensation of carbonyl groups with nitrogen compounds are characterized by general acid catalysis. Although it is difficult to prepare hydrazones from hydrazine because the hydrazones tend to react further, producing azines, the hydrazones of aromatic amines are generally easy to isolate; however, further polymerization and condensation have been observed for the derivatives of aromatic amines.

Catalysis by strong acids has proved to be rather ineffective because the protonation of the nucleophiles tends



to form inactive derivatives of the ammonium ion. Effective catalysis can be induced by the use of weak acids, such as acetic acid, which do not inactivate large amounts of the nucleophile (1).

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## CHAPTER II

### DISCUSSION

The procedure of Takimoto, Denault, and Hotta (3) was followed in order to prepare 4-amino-3-hydrazino-5-methyl-s-triazole hydrochloride (II) and its precursor, triamino-guanidine hydrochloride (I). (Figure 1, p. 2) The product melted thirty-eight degrees below the reported melting point for II. Nitrogen analysis and quantitative chloride analysis were in agreement with those of the compound 4-amino-3-hydrazino-5-methyl-s-triazole dihydrochloride (III). Although the procedure was repeated eight times, only the dihydrochloride (III) was obtained. An alternate procedure for the preparation of the monohydrochloride (II) (refluxing 4-acetamido-3-acethydrazino-5-methyl-s-triazole hydrochloride (3) in dilute hydrochloric acid) was employed; again only the dihydrochloride (III) was obtained.

The benzilidene derivative (V) of III was prepared for comparison with the reported (3) benzilidene derivative of II. The melting point of the yellow crystals was identical to that reported by Takimoto, Denault and Hotta (3), with a comparable per cent yield. A nitrogen analysis confirmed the isolation of 1-phenyl-3-benzilidenehydrazino-5-methyl-s-triazole hydrochloride (V).

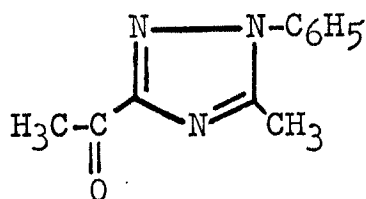
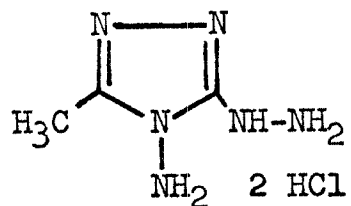
The benzilidene hydrochloride (V) was readily isolated as a 3-substitution product when a small excess of hydrochloric acid was used. The 3-methylbenzilidene hydrochloride was isolated using the same general procedure.

1-Phenyl-5-methyl-3-acetyl-s-triazole (2), prepared by the method of Regitz and Eistert (2), condensed readily with III to give 4-amino-3-[1-[3-(1-phenyl-5-methyl-s-triazoly)] ethylidene] hydrazino-5-methyl-s-triazole (IV) in aqueous solution containing an excess of sodium acetate. (Figure 2, p. 8.) Disubstitution did not occur nor was the hydrochloride of IV formed. No reaction was observed when the preparation of IV was attempted in aqueous hydrochloric acid.

The addition of sodium acetate enhanced the conversion of III to IV. The sodium acetate not only converted the ammonium ion to the free hydrazino group but also made available acetic acid which is known to be a useful catalyst in the condensation of carbonyl groups with nitrogen compounds (1).

Several mono- and disubstituted benzaldehydes were added to aqueous solutions of III and sodium acetate. In most cases precipitation occurred within the hour and within twenty-four hours in the remaining cases.

The majority of the derivatives were isolated as 3-arylidene hydrochlorides, but 3-arylidene free bases and



NaOAc

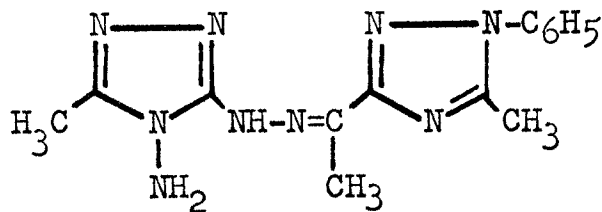


Fig. 2--Synthesis of 4-amino-3-[1-[3-(1-phenyl-5-methyl-s-triazolyl)] ethylidene] hydrazino-5-methyl-s-triazole.

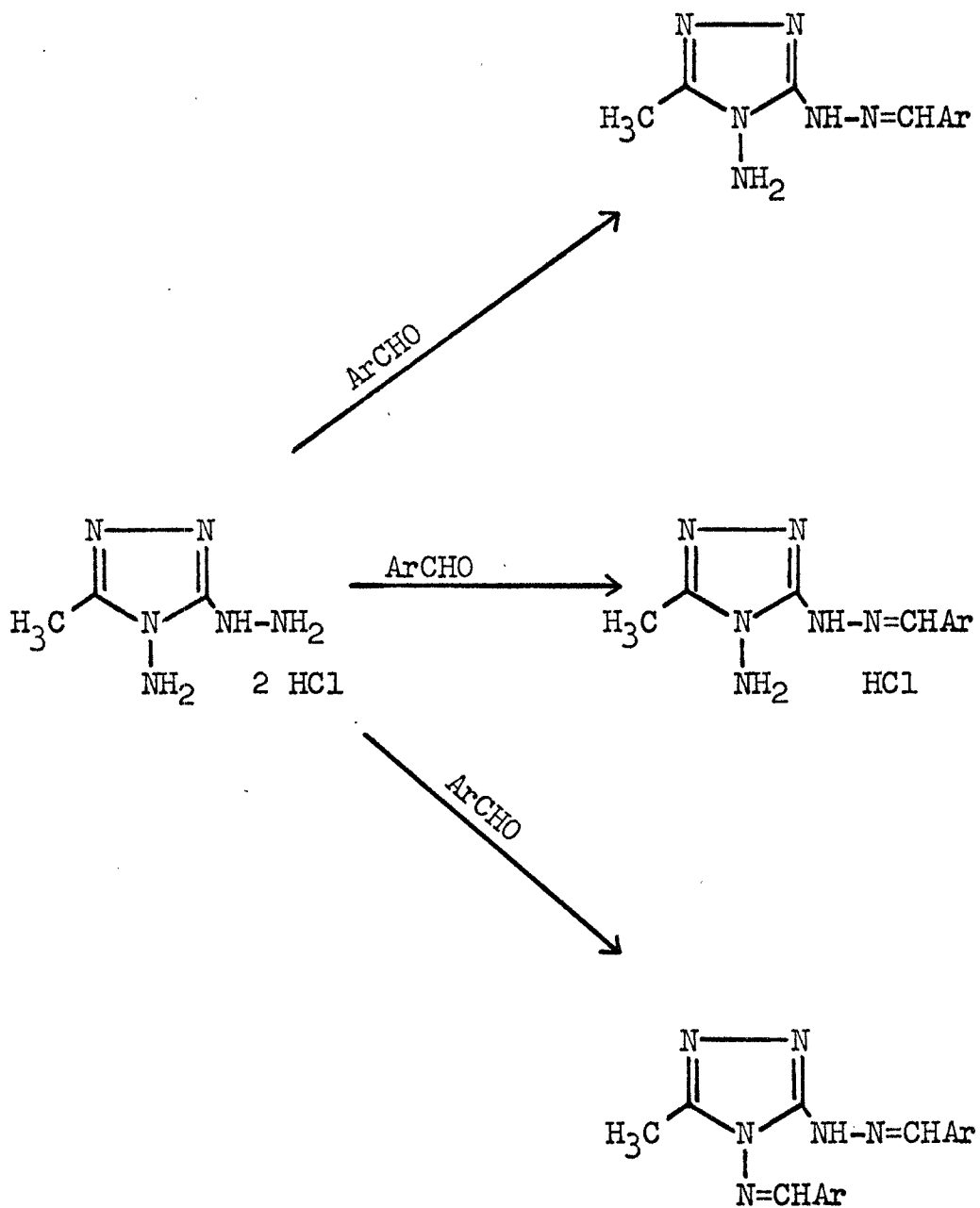


Fig. 3--Synthesis of mono- and diarylidene derivatives of 4-amino-3-hydrazino-5-methyl-s-triazole.

3,4-diarylidene derivatives were also isolated. (Figure 3, p. 9) Table I lists the particular derivatives for the corresponding arylaldehydes and the conditions accompanying the reactions.

TABLE I  
ARYLBENZILIDENE DERIVATIVES OF 4-AMINO-  
3-HYDRAZINO-5-METHYL-s-TRIAZOLE  
DIHYDROCHLORIDE (III)

Aldehyde	Isolated Compounds		
	3-Arylidene	3-Arylidene Hydrochloride	3,4-Diarylidene
Benzaldehyde		(V)	
3-Methyl-benzaldehyde		(VI)	
4-Methyl-benzaldehyde	(VII)		(XI)
4-Methoxy-benzaldehyde			(VIII)
4-Acetamido-benzaldehyde		(IX)	
2,4-Dihydroxy-benzaldehyde		(X)	
2-Hydroxy-benzaldehyde		(XII)	
4-Nitro-benzaldehyde		(XIII)	
2-Pyridine-carboxaldehyde			(XIV)
1-Phenyl-5-methyl-3-acetyl-s-triazole	(XV)		

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3. Takimoto, H. H., G. C. Denault, and S. Hotta, "Syntheses and Reactions of 5-Alkyl-4-amino-3-hydrazino- $s$ -triazoles," The Journal of Organic Chemistry, XXX (March, 1965), 711-713.



## CHAPTER III

### EXPERIMENTAL

#### 4-Amino-3-hydrazino-5-methyl-s-triazole Dihydrochloride (III)

Ten grams (0.071 moles) of I (2) were placed in 50 milliliters of glacial acetic acid and refluxed for sixteen hours, giving a light-green solution. The acetic acid was removed under partial vacuum, leaving a frothy, greenish-white residue. One hundred milliliters of 6 N hydrochloric acid were added to the residue and the resulting solution was refluxed for two hours. The hydrochloric acid was removed under partial vacuum, leaving greenish-white crystals. The residue was triturated with hot ethanol to yield 10.11 grams (70.5 per cent) which melted at 210-211° C dec.

Analysis: Calcd. for  $C_7H_{10}Cl_2N_6$ : N, 41.79; Cl, 35.32

Found: N, 41.95; Cl, 36.02

#### 4-Amino-3-[3-(1-phenyl-5-methyl-2-triazoly)] ethylidenehydrazino-5-methyl- s-triazole (IV)

One gram (0.005 moles) of III was dissolved in a minimum amount of water. One gram (0.005 moles) of 1-phenyl-5-methyl-3-acetyl-s-triazole (1) (IV) and 0.18 grams (0.0022 moles) of anhydrous sodium acetate were added, and the mixture was heated on a steam bath for thirty minutes. The white solid which formed

was suction filtered and dried in the oven overnight. Recrystallization from water, followed by several washings with acetone, gave 0.34 grams (21.9 per cent), melting at 251-252.5° C dec.

Analysis: Calcd. for  $C_{14}H_{19}N_9$ : N, 40.27

Found: N, 40.58

4-Amino-3-benzilidenehydrazino-5-methyl-  
s-triazole Hydrochloride (V)

One and sixty-five hundredths of a gram (0.0082 moles) of III were dissolved in a solution of 30 milliliters of water, two milliliters of ethanol, and one drop of concentrated hydrochloric acid. One and one-tenth grams (0.01 moles) of benzaldehyde were added dropwise. The resulting solution was gently heated on a steam bath until the yellow precipitate began to settle. After an hour the solution was filtered and the solid was dried in air. The crystals melted at 249-250° C dec., which agreed with the value reported by Takimoto, Denault, and Hotta (2). The crude product gave 2.03 grams (98 per cent).

Analysis: Calcd. for  $C_{10}H_{12}ClN_5$ : N, 27.79

Found: N, 27.63

4-Amino-3-methylbenzilidenehydrazino-5-methyl-  
s-triazole Hydrochloride (VI)

One gram (0.005 moles) of III was dissolved in a solution of 30 milliliters of water, two milliliters of

ethanol, and two drops of concentrated hydrochloric acid. Seventy-two hundredths of a gram (0.006 moles) of 3-methylbenzaldehyde were added with stirring. The solution was heated on a steam bath for 30 minutes and allowed to stand overnight. The long green crystals were recrystallized from ethanol to yield 0.87 grams (75.3 per cent) of light-yellow crystals which melted at 248-250° C dec.

Analysis: Calcd. for  $C_{11}H_{15}ClN_6$ : N, 31.50

Found: N, 31.31

4-Amino-3-(4-methylbenzilidene) hydrazino-5-methyl-s-triazole (VII)

Four hundredths of a gram (0.002 moles) of III were added to a solution containing 0.18 grams (0.0022 moles) of anhydrous sodium acetate, 15 milliliters of water, two milliliters of ethanol, and one drop of concentrated hydrochloric acid. The resulting solution was allowed to stand overnight. A small volume of dilute sodium acetate solution was added to the solution before filtration. The solid was dried in the oven overnight. Recrystallization from ethanol/water gave 0.32 grams (60.2 per cent) of light-green crystals which melted at 216-220° C dec.

Analysis: Calcd. for  $C_{11}H_{14}N_6$ : N, 36.52

Found: N, 36.11

4-(4-Methoxybenzilidene) amino-3-(4-methoxybenzil-  
idene)-hydrazino-s-methyl-s-  
triazole (VIII)

To a solution of 0.18 grams (0.0022 moles) of anhydrous sodium acetate in 15 milliliters of water and two milliliters of ethanol was added 0.4 grams (0.002 moles) of III and 0.27 grams (0.002 moles) of 4-methoxybenzaldehyde. The resulting solution was left overnight. A small volume of dilute sodium acetate solution was added before the solution was filtered. The solid was washed several times with water and then dried in the oven. Recrystallization from glacial acetic acid produced 0.09 grams (18.3 per cent) of yellow crystals which melted with decomposition at 228-233° C.

Analysis: Calcd. for  $C_{19}H_{20}N_6O_2$ : N, 23.08

Found: N, 24.12

4-Amino-3-(4-acetamidobenzilidene) hydrazino-  
4-methyl-s-triazole  
Hydrochloride (IX)

To a solution of 15 milliliters of water and two milliliters of ethanol were added 0.18 grams (0.0022 moles) of anhydrous sodium acetate, 0.4 grams (0.002 moles) of III and 0.3 grams (0.002 moles) of 4-acetamidobenzaldehyde. The solution was allowed to stand overnight. A small volume of dilute sodium acetate solution was added to the solution before it was filtered and dried in the oven. Recrystallization from glacial acetic acid gave 0.25 grams (40.4 per cent) of orange crystals which melted at 279-281° C dec.

Analysis: Calcd. for  $C_{12}H_{16}ClN_7O$ : N, 31.77; Cl, 11.5

Found: N, 30.49; Cl, 10.1

4-Amino-3-(2,4-dihydroxybenzilidene) hydrazino-5-methyl-s-triazole Hydrochloride (X)

Into a solution of ten milliliters of water and ten milliliters of ethanol were placed 0.4 grams (0.002 moles) of III and 0.2 grams (0.0024 moles) of anhydrous sodium acetate; 0.28 grams (0.002 moles) of 2,4-dihydroxybenzaldehyde was added dropwise. After the solution was left overnight, it was filtered, washed with water and acetone, and dried in an oven for several hours. The solid was recrystallized from glacial acetic acid/water and dried in the oven overnight, giving 0.06 grams (10.6 per cent). The yellow crystals melted with decomposition at  $280^{\circ}$  C.

Analysis: Calcd. for  $C_{10}H_{13}ClN_6O_2$ : N, 29.52

Found: N, 31.00

4-(4-methylbenzilidene)amino-3-(4-methylbenzilidene) hydrazino-5-methyl-s-triazole (XI)

To a solution of fifteen milliliters of water and ten milliliters of ethanol were added 0.35 grams (0.0043 moles) of anhydrous sodium acetate and 0.4 grams (0.002 moles) of III; 0.15 grams (0.00125 moles) of 4-methylbenzilidene were added dropwise. The resulting solution was heated on a steam bath for one hour and then allowed to stand for several hours. The solution was suction filtered and the

solid was washed with water before it was dried over phosphorus pentoxide overnight. The yellow crystals, which represented less than a 10 per cent yield, melted at 190.4-192.5° C with decomposition.

Analysis: Calcd. for  $C_{19}H_{20}N_6$ : N, 25.30

Found: N, 24.93

4-Amino-3-(2-hydroxybenzilidene)hydrazino-5-methyl-s-triazole Hydrochloride (XII)

To a solution of 15 milliliters of water, two milliliters of ethanol, 0.18 grams (0.0022 moles) of anhydrous sodium acetate, and 0.4 grams (0.002 moles) of III were added 0.244 grams (0.002 moles) of 2-hydroxybenzaldehyde. The solution was allowed to stand overnight. A small volume of dilute sodium acetate solution was added to the reaction mixture before filtering and drying in the oven. Recrystallization from glacial acetic acid/water gave less than 10 per cent of yellow crystals which melted at 220-223° C dec., after having turned red at 200° C.

Analysis: Calcd. for  $C_{10}H_{13}ClN_6O$ : N, 31.28

Found: N, 30.17

4-Amino-3-(4-nitrobenzilidene)hydrazino-5-methyl-s-triazole Hydrochloride (XIII)

Four-tenths of a gram (0.002 moles) of III were dissolved in 15 milliliters of water. Two milliliters of ethanol and 0.18 grams (0.0022 moles) of anhydrous sodium

acetate were added to the solution. Three-tenths of a gram (0.002 moles) of 4-nitrobenzaldehyde were then added and the solution was left overnight. A small volume of dilute sodium acetate solution was added to the solution before it was filtered and dried. The orange crystals which melted at 212-218° C represented less than 10 per cent yield.

Analysis: Calcd. for  $C_{10}H_{12}ClN_7O_2$ : N, 32.94

Found: N, 31.77

4-(2-Pyridinyl)methylideneamino-3-(2-pyridinyl)  
methylidene-hydrazino-5-methyl-  
s-triazole (XIV)

To a solution containing 0.18 grams (0.0022 moles) of anhydrous sodium acetate and 0.4 grams (0.002 moles) of III in 15 milliliters of water and two milliliters of ethanol were added 0.24 grams (0.002 moles) of 2-pyridinecarboxylic acid. The resulting solution was left overnight. The solution was filtered, washed with dilute sodium acetate solution and water, and dried in the oven. The yellowish-orange solid melted at 218-224° C dec., giving less than 10 per cent yield.

Analysis: Calcd. for  $C_{15}H_{14}N_8$ : N, 32.03

Found: N, 32.44

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## CHAPTER IV

### CONCLUSION

The 3-arylidene hydrochlorides were obtained from aqueous acidic solutions of III and the arylaldehydes. Substitution did not take place at the 4-amino position because of the formation of the ammonium ion from the 4-amino group.

The addition of sodium acetate to the reaction mixtures gave rise to varying degrees of substitution. The 2-arylidene hydrochlorides were prepared from aldehydes which contained deactivating groups. These aldehydes were not reactive enough to condense with the less nucleophilic 4-amino nitrogen. Arylaldehydes which possessed activating groups gave 3,4-diarylidenes.

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