THE ACETYLATION OF 1- (P- NITROPHENYL) 5 - AMINOTETRAZOLE AND 5 - (P- NITROPHENYLAMINO) TETRAZOLE

Thesis for the Degree of M. S.
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Jack Eldon Klingbeil
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By

Jack Eldon Klingbeil

A THESIS

Submitted to the College of Science and Arts of Michigan
State University of Agriculture and Applied Science
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

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AN ABSTRACT

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Approved Robert M. Herbst

ABSTRACT

A study of the acetylation of 1-(p-nitrophenyl)-5-aminotetrazole and 5-(p-nitrophenylamino)tetrazole was undertaken because of the possible similarity between these reactions and the acetylation of 1-phenyl-5-aminotetrazole and 5-phenylaminotetrazole (1).

During the investigation it was noted that in addition to the expected acetyl derivative, 1-(p-nitrophenyl)-5-acetylaminotetrazole, two other compounds were formed, Product A and Product B. The elemental analysis of Product A indicated that it was a compound formed by the loss of two atoms of nitrogen from 1-(p-nitrophenyl)-5-acetylaminotetrazole. The elemental analysis of Product B indicated that it could be the acetyl derivative of Product A. An identification of Product A and Product B was undertaken.

The hydrolysis of both Product A and Product B, using concentrated hydrochloric acid, yielded p-nitroaniline and hydrazine dihydrochloride. This information along with some previous work by Stollé (2) indicated that Product A could be 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole.

A synthesis of 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole was undertaken to corroborate the previous evidence by independent synthesis. Of the synthetic methods attempted the most successful was the treatment of 1-acetyl-4-phenylthiosemicarbazide with yellow mercuric

oxide in refluxing toluene. The intermediate 2-methyl-5-phenylamino-1,3,4-oxadiazole thus formed was nitrated with mixed acid to achieve the desired product.

The synthesized 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole proved to be identical with Product A and upon long treatment in refluxing acetic anhydride an acetyl derivative was formed which proved to be identical with Product B.

References Cited

1. R.M. Herbst, unpublished results.
2. R. Stollé, Ber., 62 1118 (1929).

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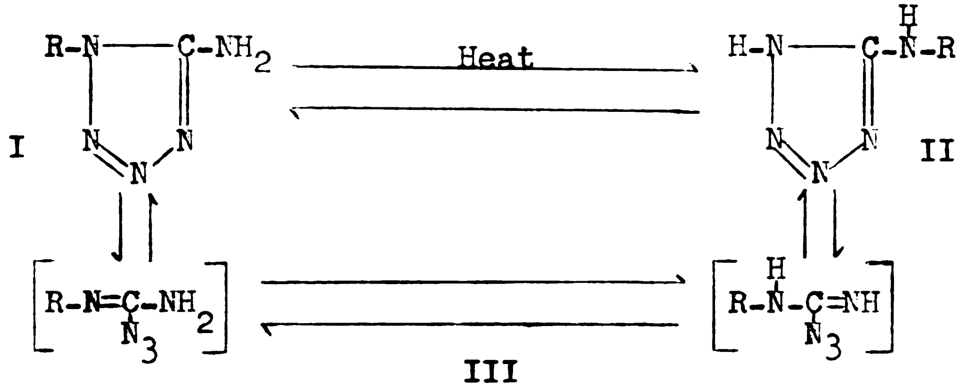
INTRODUCTION

In earlier work (1,2) it had been shown that 5-alkylaminotetrazoles and 5-phenylaminotetrazole undergo rearrangement on acetylation with the formation of 1-substituted 5-acetylaminotetrazoles. It was the purpose of this work to investigate the behavior on acetylation of 5-(p-nitrophenylamino)tetrazole and 1-(p-nitrophenyl)-5-aminotetrazole.

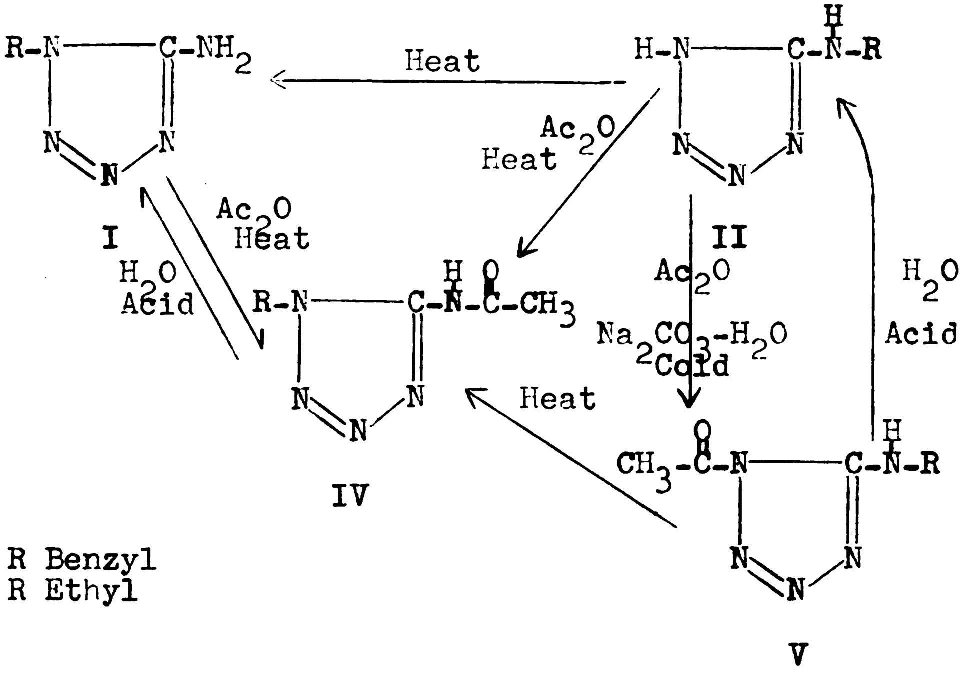
During studies investigating the acetylation of 1-(p-nitrophenyl)-5-aminotetrazole and 5-(p-nitrophenylamino)tetrazole it was noted that in addition to 1-(p-nitrophenyl)-5-acetylaminotetrazole two other compounds were formed, Product A and Product B. Elemental analysis of Product A indicated the loss of one mole of nitrogen from 1-(p-nitrophenyl)-5-acetylaminotetrazole and the elemental analysis of Product B indicated that it could be the acetyl derivative of Product A. The crux of the problem was to identify Product A and Product B and to determine their structures, if possible, by independent synthesis.

HISTORICAL

R.A. Henry (3) observed that an equilibrium existed between 5-aminotetrazole derivatives with an alkyl or aryl substituent in the 1-position (I) in the first instance and on the amino nitrogen (II) in the other.



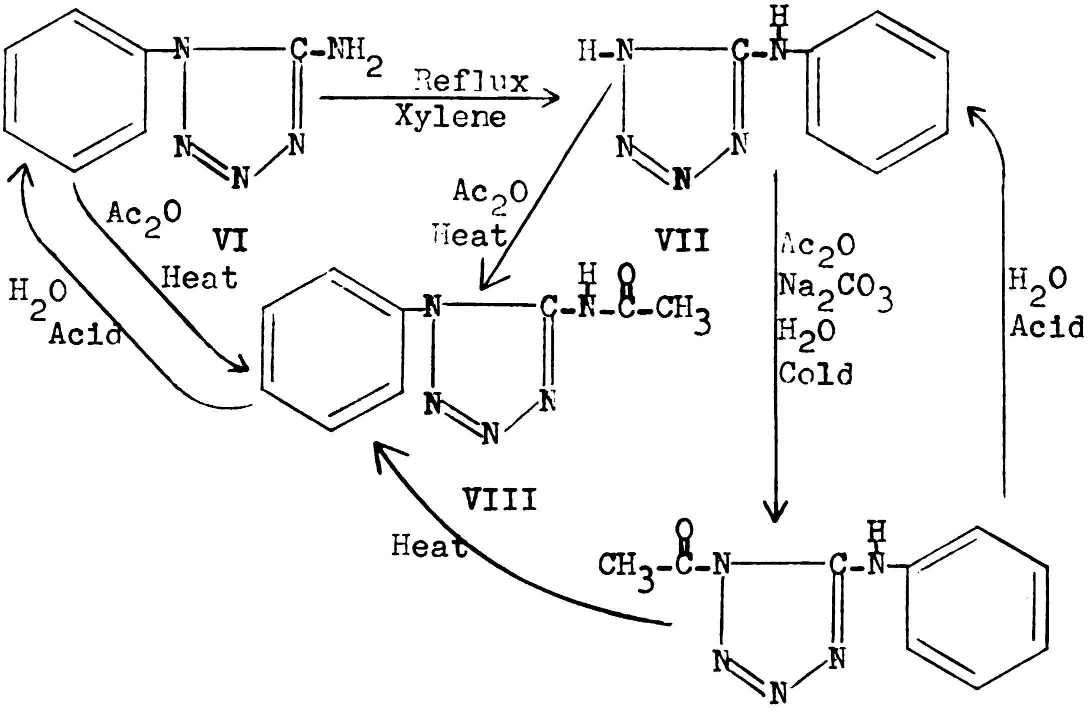
If the substituent R group was alkyl the equilibrium was shifted to the left while if the R group was aryl the equilibrium was shifted to the right. A possible mechanism to explain this equilibrium could be the formation of a guanyl azide intermediate (III) followed by recyclization. If the substituent R group was electronegative in character the 5-substituted aminotetrazole (II) was favored while if the R group was electropositive in character the 1-substituted 5-aminotetrazole (I) was favored. It was interesting to note that the isomerization of 5-alkylaminotetrazoles, 1-phenyl-5-aminotetrazole, and 1-phenyl-5-alkylaminotetrazoles go essentially to completion (4). If an equilibrium existed here it was far to one side. Studies of the acetylation of 1-alkyl-5-aminotetrazoles and 5-alkylaminotetrazoles (1) showed an interesting conversion cycle from the 5-alkylaminotetrazole to the 1-alkyl-5-aminotetrazole. Acetylation of either 1-benzyl-5-aminotetrazole (Ia) or 5-benzylaminotetrazole (IIa) with hot acetic anhydride gave only the 1-benzyl-5-acetylaminotetrazole (IVa). Acetylation of IIa in the cold with acetic anhydride in the presence of sodium carbonate gave 1-acetyl-5-benzylaminotetrazole (Va). The latter on heating isomerized to 1-benzyl-5-acetylaminotetrazole (IVa). This cycle was illustrated as follows:



It was interesting to note that although both compounds Ia and IIa were formed by benzylation of 5-aminotetrazole, it was impossible to convert compound Ia into compound IIa by this cycle of reactions.

In a similar study of the acetylation of 1-phenyl-

5-aminotetrazole and 5-phenylaminotetrazole a comparable cycle of conversions was noted. Acetylation of either 1-phenyl-5-aminotetrazole (VI) or 5-phenylaminotetrazole (VII) with hot acetic anhydride gave only 1-phenyl-5-acetylaminotetrazole (VIII). Acetylation of VII in the cold with acetic anhydride in the presence of sodium carbonate gave 1-acetyl-5-phenylaminotetrazole (IX). The latter, on heating, isomerized to 1-phenyl-5-acetylaminotetrazole (VIII). This series of reactions could be illustrated by a similar diagram (4,5,12):



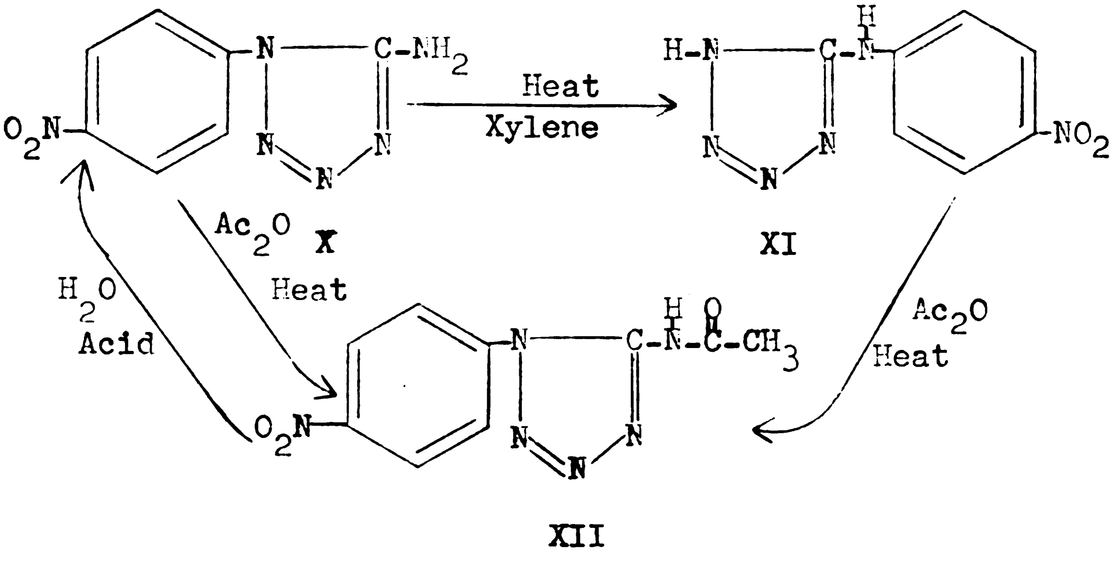
Through this series of reactions it was possible to make a complete cycle to form either compound VI or compound VII from any point in the cycle. 1-(p-Nitrophenyl)-5-

aminotetrazole was synthesized (2) to study a similar series of reactions.

DISCUSSION

In connection with studies concerning the thermal rearrangement of 1-aryl-5-aminotetrazoles it was observed that 1-(p-nitrophenyl)-5-aminotetrazole would undergo rearrangement to 5-(p-nitrophenylamino)tetrazole in boiling xylene (5).

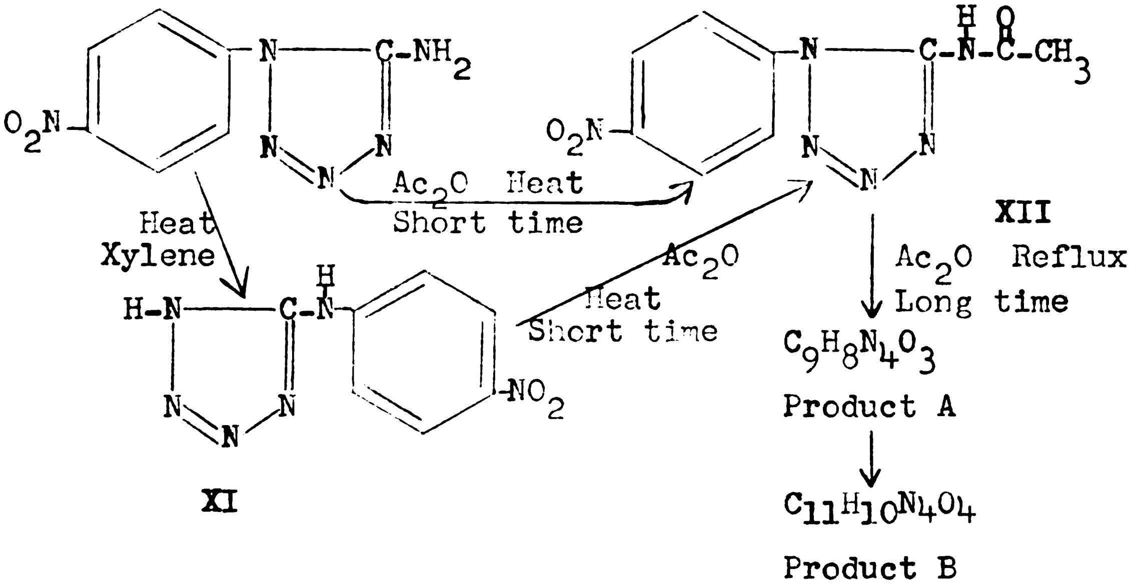
The acetylation of both 1-(p-nitrophenyl)-5-aminotetrazole and 5-(p-nitrophenylamino)tetrazole with boiling acetic anhydride was studied first. In both instances the same acetyl derivative was formed. Hydrolysis of this acetyl derivative gave only 1-(p-nitrophenyl)-5-aminotetrazole.



It is interesting to note that the same cycle of conversions takes place with the p-nitrophenyl 5-aminotetrazoles as was observed with the phenyl 5-aminotetrazoles (5). This is particularly noteworthy since the p-nitrophenyl group is usually considered to be distinctly more electronegative than the phenyl group.

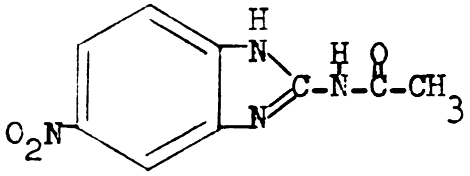
It was noted that during the acetylation of 1-(p-nitrophenyl)-5-aminotetrazole by refluxing with acetic anhydride a second compound, Product A, was formed. Elemental analysis of Product A indicated that it differed from the acetyl derivative (XII) by the loss of two nitrogen atoms. It was also noted that the amount of Product A could be increased by prolonging the reaction period with the acetic anhydride.

Since Product A was evidently formed by the partial decomposition of 1-(p-nitrophenyl)-5-acetylaminotetrazole a supply of Product A was synthesized by prolonged treatment of 1-(p-nitrophenyl)-5-aminotetrazole with an excess of acetic anhydride under reflux. The result of this experiment was a mixture of two compounds, Product A and Product B. Product B was separated from Product A by extraction with cold chloroform. The elemental analysis of Product A agreed with the empirical formula, $C_9H_8N_4O_3$. Product B gave an elemental analysis in agreement for an acetyl derivative, $C_{11}H_{10}N_4O_4$, of Product A. It was also shown that Product A was formed when 1-(p-nitrophenyl)-5-acetylaminotetrazole was heated with acetic anhydride for several hours. It is also significant that Product A was formed on prolonged heating of 5-(p-nitrophenylamino)-tetrazole (XI) with acetic anhydride. In this instance too Product A probably resulted from thermal degradation of the initially formed acetyl derivative (XII). It is interesting to note that the treatment of 1-phenyl-5-aminotetrazole with acetic anhydride, under reflux, for a period of 120 hours gave only the expected acetyl derivative as an isolable product. This indicated that the effect of the nitro group attached to the para position of the benzene ring aided the decomposition.

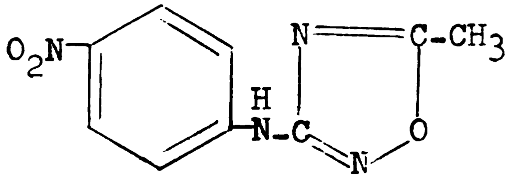


When Product A was subjected to hydrolysis with concentrated hydrochloric acid, p-nitroaniline and hydrazine dihydrochloride were isolated. The former was identified by a mixture melting point with a known sample of p-nitroaniline and the latter was identified by the formation of benzalazine with an alcoholic solution of benzaldehyde. When Product B was subjected to the same conditions the products isolated were also p-nitroaniline and hydrazine dihydrochloride.

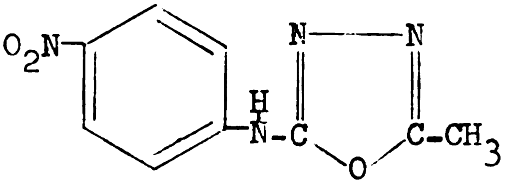
Three structures came to mind as possible formulas for Product A:



XIII



XIV

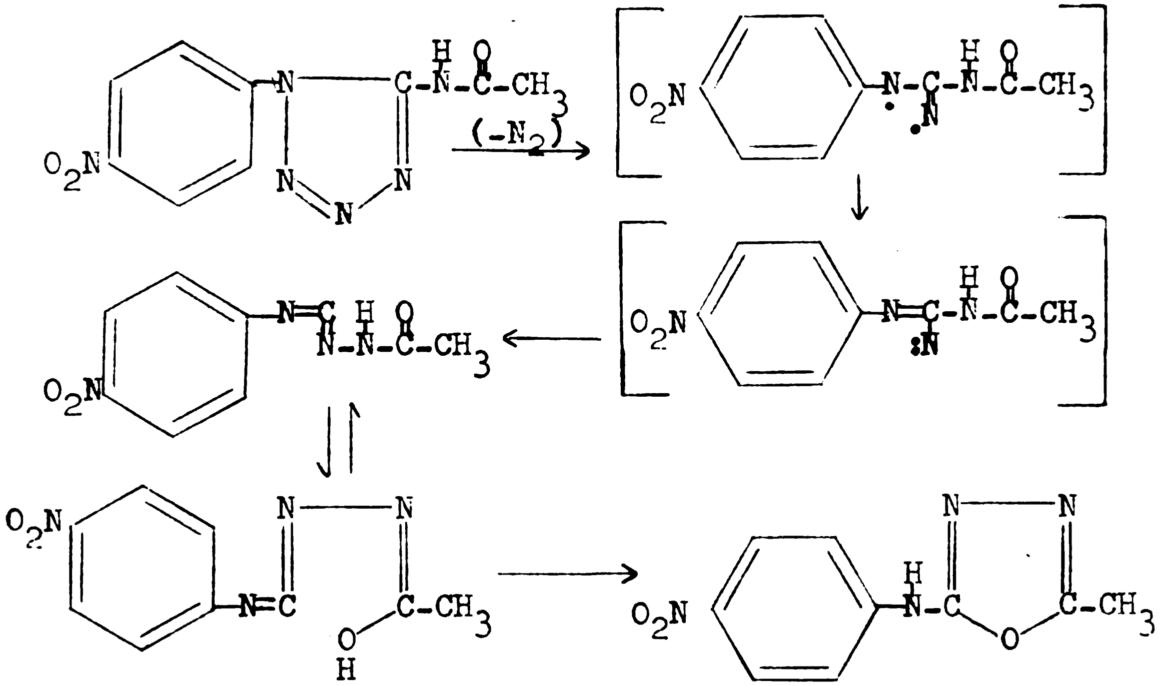


XV

The formation of XIII and XIV can be pictured by an opening of the tetrazole ring followed by a loss of a mole of nitrogen and recyclization. In formula XIII the recyclization would involve the benzene ring forming a benzimidazole while in formula XIV the cyclization would occur with the carbonyl portion of the molecule forming the 1,2,4-oxadiazole structure.

Under the conditions of hydrolysis XIII would be expected to yield 4-nitro-o-phenylenediamine and XIV would be expected to yield p-nitroaniline. Since no 4-nitro-o-phenylenediamine was recovered upon hydrolysis, XIII was discarded as a probable structure. The fact that hydrazine dihydrochloride was a product of hydrolysis in addition to the p-nitroaniline made XIV a doubtful choice.

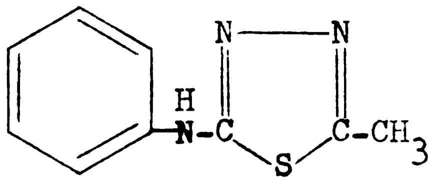
Both p-nitroaniline and hydrazine dihydrochloride could be hydrolysis products of XV. However, the formation of such a structure from 1-(p-nitrophenyl)-5-acetylaminotetrazole would entail not only an opening of the tetrazole ring followed by loss of a mole of nitrogen, but also a rearrangement in order to form a structure with two adjcent nitrogen atoms. Stollé <u>et al</u>. (6), in 1929, had noted this type of rearrangement with simpler 5-aminotetrazole molecules. Their explanation of such a rearrangement involved the formation of a carbodiimide as an intermediate:



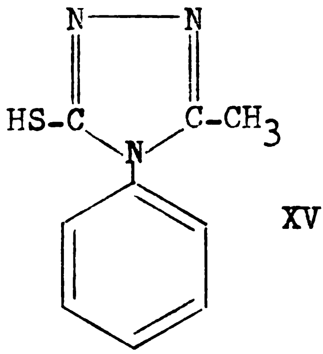
On evaluation of the information from the hydrolysis of Product A and Product B along with the evidence which Stollé <u>et al</u>. (6) had collected, the synthesis of 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole was undertaken in an attempt to identify Product A.

Stollé (7) had shown that treatment of 1,2-diacetylhydrazine with acetic anhydride led to the formation of 2,5-dimethyl-1,3,4-oxadiazole. With this in mind the synthesis of 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole by treatment of 1-acetyl-4-(p-nitrophenyl)semicarbazide with acetic anhydride was attempted without success. Two variations of this technique were tried. p-Nitrophenyl isocyanate was treated with hydrazine and the resulting 4-(p-nitrophenyl)semicarbazide was heated with acetic anhydride. In another attempt p-nitrophenyl isocyanate was treated with acetyl hydrazine and the resulting 1-acetyl-4-(p-nitrophenyl)semicarbazide was heated with acetic anhydride. In each instance a product melting at 209-210°C. was obtained. Since these products exhibited a melting point at least 20°C. below that of Product A an alternate method of synthesis was attempted. No effort was made to identify the compound melting at 209-210°C.

In 1929 Stollé and Fehrenbach had synthesized some 2-amino-1,3,4-oxadiazoles by the treatment of acyl thiosemicarbazides with lead oxide (11). In an attempt to synthesize 2-methyl-5-phenylamino-1,3,4-oxadiazole this procedure was applied to 1-acetyl-4-phenylthiosemicarbazide. Two experiments performed by this method yielded a compound melting at 217-218°C. The elemental analysis for this compound agreed well with the values calculated for $C_9H_9N_3S$. Since a compound melting at 193-194°C. had been assigned the structure of 2-methyl-5-phenylamino-1,3,4-thiadiazole (XVI) (8), a possible structure for the compound, m.p. 217-218°C., would be that of 3-mercapto-5-methyl-4-phenyl-1,2,4-triazole (XVII). The assignment of this structure was supported by the fact that this compound was soluble in dilute base and insoluble in dilute acid. Other experiments performed under slightly different conditions yielded, variously, a product melting at 160-165°C. (1-acetyl-4-phenylsemicarbazide melts at 169°C.) and another product which melted with decomposition at 309-311°C. No further attempt at identification of these products was made.



XVI

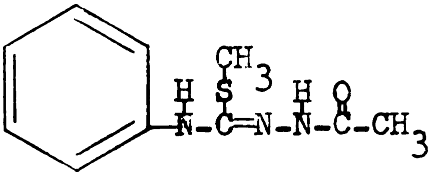


XVII

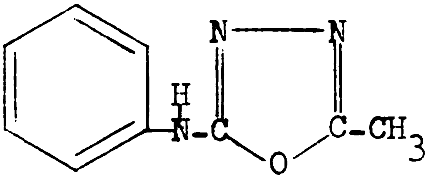
Hoggarth (9) recently showed that certain S-methyl-1-acyl-thiosemicarbazides would cyclize on heating to give 2-amino-5-aryl-1,3,4-oxadiazoles along with small amounts of isomeric 1,2,4-triazoles. Following this procedure S-methyl-1-acetyl-4-phenylthiosemicarbazide (XVIII) was prepared. By warming this intermediate a small amount of 2-methyl-5-phenylamino-1,3,4-oxadiazole (XIX) could be separated from the reaction mixture.

However, the major product was a sulfur-containing material which may have been 3-methyl-5-methylmercapto-4-phenyl-1,2,4-triazole (XX). This latter product was insoluble in dilute base but soluble in dilute aqueous acid. The yields of oxadiazole obtained by this method were low and often not reproducible.

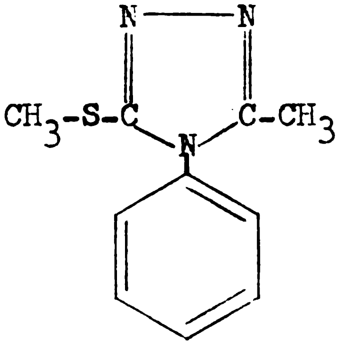
Because of the usefulness of mercuric oxide in the formation of carbodiimides (10) it was thought that a similar method using 1-acetyl-4-phenylthiosemicarbazide could prove useful for the synthesis of 2-methyl-5-phenylamino-1,3,4-oxadiazole. After treatment of 1-acetyl-4-phenylthiosemicarbazide with yellow mercuric oxide in boiling toluene, 2-methyl-5-phenylamino-1,3,4-oxadiazole could be isolated consistently in yields of 54-64%.



XVIII

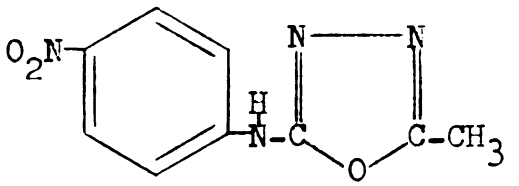


XIX



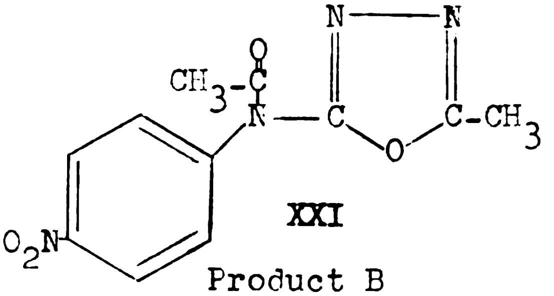
XX

Several attempts to nitrate the 2-methyl-5-phenylamino-1,3,4-oxadiazole by dissolving the powdered oxadiazole in either cold concentrated sulfuric acid or cold acetic anhydride followed by the dropwise addition of concentrated nitric acid, while swirling the flask in an ice bath, proved unsuccessful. After quenching the nitration mixture with ice only a viscous red oil or gum could be isolated. Because of this difficulty the nitration was attempted by adding powdered 2-methyl-5-phenylamino-1,3,4-oxadiazole in small portions to an ice cold solution of mixed acid. The heat generated by each addition was dissipated by constant swirling of the flask in an ice bath. When the resulting nitration mixture was poured over ice a flocculent yellow precipitate formed. This precipitate could be separated into two fractions by extraction with cold chloroform. The chloroform insoluble material, after recrystallization from isopropyl alcohol, proved to be identical with Product A, thus supporting the assumption that Product A is 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole (XV). Acetylation of the chloroform insoluble material with acetic anhydride gave Product B, an observation in conformity with the suggestion that Product B (XXI) was the acetyl derivative of Product A. (Other isomeric structures for XXI could be drawn with the acetyl group attached to the ring. No attempt was made to locate the actual position of the acetyl group.)



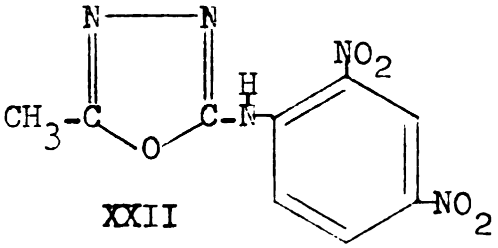
XV

Product A



XXI

Product B



XXII

The chloroform soluble portion of the nitration mixture could be separated into a product whose elemental analysis suggested that it was 2-(2,4-dinitrophenylamino)-5-methyl-1,3,4-oxadiazole (XXII) and a small amount of nitroanilines. The structure of the oxadiazole was based upon its hydrolysis to 2,4-dinitroaniline and hydrazine dihydrochloride.

The structure of Product A was thus established through the identification of its hydrolysis products and by independent synthesis as 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole (XV). Product B was similarly identified as the acetyl derivative (XXI) of 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole.

EXPERIMENTAL[1,2]

Preparation of 1-Phenyl-5-aminotetrazole

In a space in the hood area a 3 l. three-necked flask was placed in an ice bath and was equipped with an alcohol thermometer, a reflux condenser, a mechanical stirrer, and an exhaust vent. The flask was charged with 600 ml. of 95% ethyl alcohol and 93 g. (91 ml., 1 mole) of aniline. All reagents used in subsequent steps were added with continuous stirring while the temperature of the reaction mixture was kept below 10°C. After the alcohol and aniline solution had cooled to the desired temperature, 106 g. (1 mole) of cyanogen bromide, dissolved in 400 ml. of 50% ethyl alcohol, was added slowly through a dropping funnel. This addition was completed in approximately one hour. A solution of 40 g. (1 mole) of sodium hydroxide dissolved in 100 ml. of water was then added in the same manner. This addition took about 30 minutes. The reaction mixture was then stirred without further addition for 90 minutes. A solution of 81 g. (1.25 moles) of sodium azide dissolved in 250 ml. of water was then added. This addi-

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[1] Microanalyses by Micro-Tech Laboratories, Skokie, Illinois

[2] Melting points were taken in open capillary tubes and were uncorrected.

tion could be made quite rapidly. A solution of 101 ml. of concentrated hydrochloric acid and 100 ml. of water was then added through a dropping funnel, taking special precaution to keep any fumes from escaping from the hood. (Hydrazoic acid was liberated at this stage of the process.) The reaction flask was then removed from the ice bath, placed on a steam bath, the temperature raised to the boiling point, and the solution maintained at reflux temperature for six hours. Following the reflux period the reaction mixture was cooled in an ice bath. The solid product was collected by suction filtration. The crude product was recrystallized from 50% isopropyl alcohol. The yields in two preparations were 80 g. (50%) and 95 g. (59%). The higher yield was obtained by evaporation of some of the alcohol from the filtrate and allowing this solution to stand for a period of time followed by filtration of the crystalline material. The recrystallized product melted at 158-160°C., resolidified, and remelted at 201-203°C. A melting point of 163-163.5°C., resolidification, and remelting at 205-206°C. was reported for a purified product (2).

Nitration of 1-Phenyl-5-aminotetrazole (2)

Two hundred milliliters of concentrated sulfuric acid was placed in a 1 l. three-necked flask equipped with an alcohol thermometer and a mechanical stirrer.

The flask was placed in an ice bath and the acid cooled, with stirring, to 5°C. Stirring and cooling were continued throughout the subsequent operations. While keeping the temperature of the reaction mixture below 10°C., 48 g. (0.41 moles) of powdered 1-phenyl-5-aminotetrazole was added in small portions. Following the addition of the 1-phenyl-5-aminotetrazole no further operations were performed until all of the solid material had been dissolved. At this time 200 ml. of concentrated nitric acid was added dropwise. Because of the exothermic effect this addition took 90 to 120 minutes. Following the addition of the nitric acid the reaction mixture was left in the ice bath for 20 minutes. The stirrer was then disconnected and the nitration mixture was poured over approximately 1000 g. of ice, allowed to stand for several hours (until the ice had melted), and the precipitate collected by filtration. The crude product was recrystallized from a 5:3 glacial acetic acid: water mixture. The yield was 35 g. (58%) of product that melted at 179-181°C., resolidified, and remelted with effervescence at 219-221°C. Garbrecht and Herbst (2) reported melting at 176°C., resolidification, and remelting at 221-223°C. Other runs under the same conditions gave yields of 57%, 46%, and 53%.

Acetylation of 1-(p-Nitrophenyl)-5-aminotetrazole

In a 50 ml. round-bottomed flask were placed 2 g. of recrystallized 1-(p-nitrophenyl)-5-aminotetrazole and 20 ml. of acetic anhydride. The reaction mixture was boiled under reflux for 30 minutes after which the mixture was transfered to a beaker. Ten milliliters of isopropyl alcohol and 5 ml. of water were added and the solution was then eveporated to dryness on a steam bath. The residue was recrystallized from 99% isopropyl alcohol. The yield of 1-(p-nitrophenyl)-5-acetylaminotetrazole was 1.7 g. (74%). The crystals formed were pale yellow needles melting at 191°C. with gas evolution, resolidifing, and remelting at 224-225°C.

Analysis. Calculated for $C_9H_8N_6O_3$: C, 43.55; H, 3.25; N, 33.86. Found: C, 43.51; H, 3.31; N, 34.13.

A second reaction was run with the same amounts of reactants and the same conditions with the exception that the time of reflux was extended to 45 minutes. The yield of this run was 1.7 g. (74%) melting at 192°C. with gas evolution, resolidifing, and remelting at 225-226°C.

A third run with the same amounts and conditions was made with the reflux time extended to one hour. From this reaction the yield of 1-(p-nitrophenyl)-5-acetylaminotetrazole was only 1.0 g. (44%), melting at 190°C.

with gas evolution, resolidifing, and remelting at 223-224°C.

Following the same procedure with a reflux time of three hours, a fourth run showed a different texture of residue after the evaporation to dryness. This residue was dissolved in 99% isopropyl alcohol and allowed to stand for several hours. During this period a few crystals of 1-(p-nitrophenyl)-5-acetylaminotetrazole had formed. This material was collected by filtration and showed the same melting point characteristics as the previous three samples. The filtrate was evaporated to dryness and recrystallized from 99% isopropyl alcohol, yielding a yellow powder (Product A) melting at 233-234°C. A very small amount of this substance gave a brilliant red color in dilute base, while purified 1-(p-nitrophenyl)-5-acetylaminotetrazole gave no color when added to dilute base.

Decomposition of 1-(p-Nitrophenyl)-5-aminotetrazole by Treatment with Acetic Anhydride

Twenty grams of 1-(p-nitrophenyl)-5-aminotetrazole was placed in a round-bottomed flask containing 200 ml. of acetic anhydride. The reaction mixture was boiled under reflux for eleven and one half hours. Following the reflux period, 125 ml. of acetic anhydride was distilled from the reaction vessel and the remaining solution was added to 50 ml. of 99% isopropyl alcohol. This solution was evaporated nearly to dryness on a steam bath, and redissolved in approximately 300 ml. of 99% isopropyl alcohol. Approximately 5 ml. of this solution was removed and placed in a small flask. The remainder of the solution was poured into 500 ml. of distilled water and ice, the precipitate collected by filtration and dried in a vacuum desiccator. The yield of crude product was 24 g. The 5 ml. portion of solution mentioned above was diluted with approximately 20 ml. of water and treated with enough solid potassium bicarbonate to neutralize the acetic acid. A light yellow powder was separated. The beaker was set aside and allowed to stand over night. The next day the powder was collected by filtration, washed with dilute hydrochloric acid, and then with distilled water. Upon recrystallization from 99% isopropyl alcohol this material formed pale amber prisms which melted at 158°C. (Product B).

The bulk of the reaction product was recrystallized from 99% isopropyl alcohol. Initial inspection of the crystals formed indicated the presence of two different crystal structures, fine yellow needles and light yellow transparent prisms. The mixture of crystalline material was collected by filtration and dried. A small portion of this crystalline material was subjected to physical separation. The yellow needles melted at 227-228°C.

(Product A) and the pale yellow transparent prisms melted at 158°C. (Product B). It was found that Product B could be separated from Product A by extraction with cold chloroform. The crude recrystallized product was extracted with several portions of cold chloroform. The residue was recrystallized from 99% isopropyl alcohol and gave Product A, yellow needles, m.p. 232-233°C.

Analysis. Calculated for $C_9H_8N_4O_3$: C, 49.09; H, 3.66; N, 25.45. Found: C, 49.38; H, 3.90; N, 25.31.

The chloroform filtrates were collected, evaporated to dryness, and the solid recrystallized from 99% isopropyl alcohol to give Product B, pale yellow transparent prisms, m.p. 158°C.

Analysis. Calculated for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.51, 50.72; H, 4.04, 3.90; N, 22.21, 22.00.

Decomposition of 1-(p-Nitrophenyl)-5-acetylaminotetrazole

A 50 ml. round-bottomed flask was charged with 3 g. of 1-(p-nitrophenyl)-5-acetylaminotetrazole and 20 ml. of acetic anhydride. This mixture was boiled under reflux for four and one half hours. Following the reflux period the hot solution was placed in a beaker with 10 ml. of glacial acetic acid, 5 ml. of water, and the solution was evaporated to dryness on a steam bath. The residue was placed in 100 ml. of a saturated potassium bicarbonate solution and let stand for 36 hours. The solid material was collected by filtration, washed with dilute hydrochloric acid, and rinsed several times with distilled water. After the product was dried in the air it was recrystallized from 50% isopropyl alcohol. The crystals, which were formed, were collected by filtration and exhibited a melting point of 230-231°C. A mixture melting point with a previously prepared sample of Product A showed no depression.

Hydrolysis of Product A

In a 50 ml. round-bottomed flask was placed 1 g. of Product A and 20 ml. of concentrated hydrochloric acid. The solid material dissolved upon heating as the solution was boiled under reflux for two hours. The clear amber colored solution was allowed to stand overnight. The next morning amber prismatic crystals had formed in the flask. These crystals were recovered by filtration and the filtrate evaporated to dryness on a steam bath. The crude crystals melted at 192-194°C. An aqueous solution of several crystals gave an immediate white flocculent precipitate with silver nitrate solution. Another portion of an aqueous solution of the crystalline material gave a pale yellow flocculent precipitate when it was shaken with several drops of an alcoholic solution of benzaldehyde. This precipitate, when dried, melted at 90-91°C. A mixture melting point of this precipitate with a known sample of benzalazine showed no depression. These facts were evidences for the assignment of hydrazine dihydrochloride (m.p. 198°C.) as the structure for the crystalline material.

The residue from the filtrate which had been evaporated to dryness was recrystallized from hot water. Yellow needles were formed which melted at 146°C. A mixture melting point with a known sample of p-nitroaniline (m.p. 147°C.) showed no depression. Thus p-nitroaniline was assigned as the structure for the filtrate residue.

Hydrolysis of Product B

The hydrolysis of Product B was carried on under the same conditions as those used for the hydrolysis of Product A. Hydrazine dihydrochloride and p-nitroaniline were also the identified products of this hydrolysis. These facts along with the elemental analysis of Product B indicated that Product B was the acetyl derivative of Product A. This was corroborated by synthesis at a later point in the work.

Thermal Rearrangement of 1-(p-Nitrophenyl)-5-aminotetrazole to 5-(p-Nitrophenylamino)tetrazole (5)

Two grams of 1-(p-nitrophenyl)-5-aminotetrazole was placed with 20 ml. of xylene in a 50 ml. round-bottomed flask and the solution was boiled under reflux for two and one half hours. The solution was cooled and the needle shaped crystals which formed were collected by filtration. The yield was 1.9 g. (95%) of 5-(p-nitrophenylamino)tetrazole melting sharply at 224°C. with no indication of yellowing or shrinking at 190°C. A mixture melting point of this material with 1-(p-nitrophenyl)-5-aminotetrazole yellowed and shrank to approximately one half its volume at 190°C. and melted sharply at 223°C. When a small amount of 5-(p-nitrophenylamino)tetrazole was placed in dilute base it dissolved to give an intensly red solution, while 1-(p-nitrophenyl)-5-aminotetrazole did not produce a color with dilute base.

Acetylation of 5-(p-Nitrophenylamino)tetrazole

One and one half grams of 5-(p-nitrophenylamino)-tetrazole and 20 ml. of acetic anhydride were placed in a 50 ml. round-bottomed flask and boiled under reflux for 45 minutes. The resulting solution was diluted with 20 ml. of isopyonyl alcohol and evaporated to dryness on a steam bath. The residue was recrystallized from 99%

isopropyl alcohol yielding 0.9 g. of acetyl derivative which melted at 185°C. with gas evolution, resolidified, and remelted at 221°C. A mixture melting point with 1-(p-nitrophenyl)-5-acetylaminotetrazole exhibited no depression.

Analysis. Calculated for $C_9H_8N_6O_3$: C, 43.55; H, 3.25; N, 33.86. Found: C, 43.31; H, 3.45; N, 34.05.

Hydrolysis of 1-(p-Nitrophenyl)-5-acetylaminotetrazole

One gram of 1-(p-nitrophenyl)-5-acetylaminotetrazole was placed with 40 ml. of 20% hydrochloric acid in a 100 ml. beaker and the mixture was evaporated to dryness on a steam bath. The residue was dissolved in hot water and made just acidic to Congo Red paper with hydrochloric acid. The solution was cooled and the crystals collected by filtration. After recrystallization from 50% isopropyl alcohol this product melted at 175°C., resolidified, and remelted at 220-221°C. A mixture melting point with 1-(p-nitrophenyl)-5-aminotetrazole showed no depression.

Acetylation of 1-Phenyl-5-aminotetrazole

Four grams of 1-phenyl-5-aminotetrazole was placed in a 50 ml. round-bottomed flask which contained 30 ml. of acetic anhydride. The mixture was boiled under reflux for 120 hours. The solution was set aside to cool and the precipitate which formed was collected by filtration.

This precipitate was recrystallized from 95% ethyl alcohol using Norite. The purified crystals melted at 216°C. The filtrate, which had blackened during the reaction under long reflux, was evaporated to dryness and the residue was recrystallized from 95% ethyl alcohol using Norite. The crystalline material formed also melted at 216°C. A mixture melting point with approximately equal portions of each of these two samples and a known sample (13) of 1-phenyl-5-acetylaminotetrazole showed no depression. This indicated that the 1-phenyl-5-aminotetrazole would not undergo the same type of decomposition as did the 1-(p-nitrophenyl)-5-aminotetrazole.

Preparation of 1-Acetyl-4-phenylthiosemicarbazide

Finely powdered 4-phenylthiosemicarbazide (10 g.) was added to 40 ml. of ice cold acetic anhydride and the reaction mixture was swirled in an ice bath. Within a few minutes a fine white powder precipitated. This powder was collected by filtration and dried in the air. The yield of crude product (m.p. 166-170°C.) was 11 g. (85%). This crude product was recrystallized from absolute methyl alcohol and gave a melting point of 172°C.; the melting point has been reported as 173°C. (14). A number of preparations of this compound were completed with yields of crude product varying from 75-88%.

Attempted Synthesis of 2-Methyl-5-phenylamino-1,3,4-oxadiazole Using Lead Oxide (11)

A 300 ml. round-bottomed flask, equipped with a reflux condenser and mechanical stirrer, was charged with 3.3 g. (0.016 moles) of 1-acetyl-4-phenylthiosemicarbazide, 3.5 g. (0.016 moles) of lead oxide, and 150 ml. of 95% ethyl alcohol. The mixture was heated under reflux, with stirring, for 26 hours. The reaction mixture was filtered while hot and the filtrate evaporated to approximately 30 ml., using a steam bath. This solution gave crystals, 2 g., melting at 214-217°C., which were recrystallized from 95% ethyl alcohol, m.p. 217-218°C. Another experiment, using similar conditions with the exception that the reflux period was shortened to 14 hours, also gave 2 g. of crude product which exhibited similar melting point characteristics. A mixture melting point of the crystals from each of these experiments showed no depression.

A small sample of this material was fused with sodium followed by a qualitative test for sulfur, which proved positive.

Analysis. Calculated for $C_9H_9N_3S$: C, 56.62; H, 4.74; N, 21.97. Found: C, 56.17, 56.01; H, 4.79, 4.68; N, 22.59, 22.83.

Since a melting point of 193-194°C. has been assigned to 2-methyl-5-phenylaminothiadiazole (8), a possible structure for this compound would be 3-mercapto-4-phenyl-5-methyl-1,2,4-triazole. The fact that this compound was soluble in dilute base added support for the assignment of the triazole structure.

A third experiment was completed following the same procedure with the exception that the reflux period was six hours and the quantity of lead oxide was lowered by 6%. This process gave a crude material, m.p. 140-150°C., which was recrystallized from 95% ethyl alcohol yielding a compound which melted at 160-165°C. This material may have been 1-acetyl-4-phenylsemicarbazide, m.p. 169°C., but no further attempt at identification was made.

A fourth experiment using a reflux period of 12 hours and a 40% excess of lead oxide yielded 1 g. of crude product melting at 309-311°C., with decomposition. No attempt was made to identify this material.

In all of these experiments using lead oxide the weight of precipitate formed in the reaction flask was in excess of the theoretical weight of lead sulfide which could have been formed. This precipitate, in each case, was dark gray instead of the black color of lead sulfide. An attempt to extract the gray precipitate with hot 95% ethyl alcohol was unsuccessful.

Attempted Synthesis of 2-Methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole from p-Nitrophenyl Isocyanate

Equal molar portions of p-nitrophenyl isocyanate and acetylhydrazine were placed in a small beaker and the mixture melted and resolidified almost instantly yielding a crude product which decomposed at 300-301°C. This crude material was placed in a 100 ml. round-bottomed flask and was heated under reflux with 40 ml. of acetic anhydride for 16 hours. All the solid material had dissolved after approximately five hours of the reflux period had elapsed. The reaction mixture was added to 50 ml. of isopropyl alcohol, evaporated to dryness on a steam bath, and recrystallized, using norite, from 99% isopropyl alcohol yielding a granular material which shrank at 205°C. and melted at 209-210°C. No attempt was made to identify this material.

Attempted Synthesis of 2-Methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole from 4-(p-Nitrophenyl)semicarbazide

A 50 ml. round-bottomed flask was charged with 2 g. of 4-(p-nitrophenyl)semicarbazide and 30 ml. of acetic anhydride. A flocculent white precipitate was formed almost immediately. A small portion of this precipitate was collected, dried, and recrystallized from 99% isopropyl alcohol, exhibiting a melting point of 242°C. The remainder of the precipitate was heated under reflux for 20 hours, during which time the precipitate dissolved. The reaction mixture was added to 50 ml. of isopropyl alcohol, evaporated to dryness, and recrystallized from 99% isopropyl alcohol yielding a granular material which melted at 209-210°C. A mixture melting point with the product formed from the previous attempt to synthesize 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole from p-nitrophenyl isocyanate showed no depression. No further attempt was made to identify the compound.

Synthesis of 2-Methyl-5-phenylamino-1,3,4-oxadiazole from S-Methyl-1-acetyl-4-phenylthiosemicarbazide

The following experiment was based on a technique developed by Hoggarth for the synthesis of 1,3,4-oxadiazoles (9). Fifty milliliters of 1 N sodium hydroxide solution was mixed with 10 g. (0.048 moles) of powdered 1-acetyl-4-phenylthiosemicarbazide and the flask was swirled to dissolve the powdered material. To this solution was added 7.6 g. (0.054 moles, 3.4 ml.) of methyl iodide diluted with 10 ml. of 99% isopropyl alcohol. The flask was stoppered and shaken. A slight pressure which developed was released and the shaking was continued. After a period of five minutes the precipitate which had formed was filtered by suction. The filtrate was replaced in the flask but further shaking for a period of ten minutes failed to produce any additional precipitate. In another experiment the precipitate which formed redissolved upon continued shaking and could not be recovered, hence the filtration of the precipitate after the five minute shaking period. The precipitate was dried under reduced pressure at room temperature. The crude product weighed 4.2 g. (39%) and melted at 121-124°C. with a disagreeable odor.

Three grams of the crude precipitate was dissolved in 60 ml. of 99% isopropyl alcohol and this solution was boiled under reflux for 20 hours. During the first several hours the odor of methyl mercaptan was evident at the top of the reflux condenser. Following the reflux period the alcoholic solution was evaporated to dryness under reduced pressure at room temperature. The yield was 2.4 g. of crude product melting at 90-100°C. This crude material was recrystallized from 99% isopropyl alcohol. The pyrimidal shaped crystals which resulted melted at 171-173°C. A mixture melting point with 1-acetyl-4-phenylthiosemicarbazide (m.p. 173°C.) was depressed to 145-155°C. A small portion of the compound was fused with sodium. A qualitative test for sulfur with lead acetate proved to be negative. The remaining crystals were recrystallized from 99% isopropyl alcohol, m.p. 174-175°C.

Analysis. Calculated for $C_9H_9N_3O$: C, 61.72; H, 5.15; N, 23.99. Found: C, 61.59; H, 5.16; N, 23.90.

Although the desired product was achieved with this synthesis, the yield was very low. Several succeeding attempts failed to give the same product. In all cases the major product of the reaction was a transparent crystalline compound, m.p. 119-120°C., which was soluble in dilute acid and insoluble in dilute base. A qualitative test for sulfur was positive and the compound showed no change after refluxing for 26 hours in isopropyl alcohol. A possible structure for this compound would be 3-methyl-4-phenyl-5-methylmercapto-1,2,4-triazole (XX).

Analysis for $C_{10}H_{11}N_3S$: C, 58.50; H, 5.40; N, 20.47; S, 15.62. Found: C, 58.20, 58.44; H, 5.55, 5.78; N, 20.86, 20.60; S, 15.28, 15.24.

No further attempt was made at identification.

Synthesis of 2-Methyl-5-phenylamino-1,3,4-oxadiazole from 1-Acetyl-4-phenylthiosemicarbazide

A mixture of 15 g. (0.072 moles) of 1-acetyl-4-phenylthiosemicarbazide and 15.5 g. (0.072 moles) of yellow mercuric oxide was placed in a 1 l. three-necked flask equipped with a mechanical stirrer and a reflux condenser. The reactants were suspended in 800 ml. of toluene. The mixture was heated with stirring to the boiling point and maintained there for 20 minutes. Even before the boiling point of the mixture was reached the mercuric oxide gave indication of darkening. Within five minutes after the boiling point was reached the reaction mixture had become black. After the completion of the reflux period the hot reaction mixture was filtered with suction through a large diameter fritted glass funnel of medium porosity. The filtrate was allowed to cool and the precipitate of white needles was collected by filtration. The yield was 8 g. (64%) of crude material melting at 170-171°C. The oxadiazole was recrystallized from 99% isopropyl alcohol forming large clear prisms melting at 175°C. Other runs made under these conditions gave yields of 54% and 56%.

If the reflux period was extended beyond 20 minutes the filtrate often was amber or red in color. This color was removed by treatment with Norite. There was no significant change in the yield.

Nitration of 2-Methyl-5-phenylamino-1,3,4-oxadiazole

A solution of mixed acid (25 ml. of concentrated sulfuric acid and 25 ml. of concentrated nitric acid) was prepared and cooled in an ice bath. To this solution was added, in small portions, 16.8 g. of crude powdered 2-methyl-5-phenylamino-1,3,4-oxadiazole. The solution was stirred after each portion of powdered oxadiazole was added and the mixture was allowed to cool in the ice bath after each addition. Following the final addition a stirring rod was used to break up any undissolved

material and the flask was swirled in the ice bath until all the solid material had dissolved. The resulting solution was poured over approximately 400 g. of ice. A yellow, flocculent precipitate resulted. The crude product was collected by filtration, washed with water, and dried in a vacuum desiccator under reduced pressure. The yield was 21 g. After one recrystallization from absolute methyl alcohol the product shrank at 210°C. and melted at 212-214°C. The crude material was extracted with several portions of cold chloroform. The residue of crude 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole was recrystallized several times from absolute methanol. This material melted at 232-234°C. and a mixture melting point with Product A showed no depression.

The chloroform extracts were collected in one flask and evaporated to dryness. After evaporation most of the precipitate was bright yellow in color. This portion of the residue was manually separated from a small amount of orange residue on the sides of the flask and was recrystallized several times from absolute methyl alcohol. This material melted at 218-219°C. and was subsequently shown to be 2-(2,4-dinitrophenylamino)-5-methyl-1,3,4-oxadiazole.

Identification of the By-products of the Nitration of 2-Methyl-5-phenylamino-1,3,4-oxadiazole

One gram of the yellow crystalline by-product, melting at 218-219°C., was boiled under reflux with 30 ml. of concentrated hydrochloric acid for three hours. After approximately 30 minutes of the reflux time had passed a yellow flocculent material began to form in the flask. The amount of this material seemed to remain constant after one hour of the reflux time had elapsed. The refluxed solution was allowed to cool for approximately 15 minutes and then was filtered. The filtrate was allowed to stand overnight.

The yellow precipitate was recrystallized from aqueous acetone, m.p. 178-180°C. A mixture melting point with a known sample of 2,4-dinitroaniline (m.p. 180°C.) showed no depression.

The filtrate, which had been left overnight, contained clear prismatic crystals These crystals were collected on a filter and dried. They exhibited a melting point of 195-200°C. with evolution of a gas (Hydrazine dihydrochloride melts at 198°C.). A solution of a few of these crystals in 5 ml. of water was treated with several drops of an alcoholic solution of benzaldehyde. After a short period of agitation a flocculent yellow precipitate formed. This precipitate was collected by

filtration and dried. The melting point, 92-93°C., was similar to that of benzalazine (93°C.) and a mixture melting point with a known sample of benzalazine showed no depression.

From this evidence it was concluded that the by-product melting at 218-219°C. was 2-(2,4-dinitrophenylamino)-5-methyl-1,3,4-oxadiazole.

Analysis. Calculated for $C_9H_7N_5O_5$: C, 40.77; H, 2.65; N, 26.42. Found: C, 40.77, 40.55; H, 2.71, 2.68; N, 27.07, 26.91.

The orange material, which had been physically separated from the 2-(2,4-dinitrophenylamino)-5-methyl-1,3,4-oxadiazole, was recrystallized from hot water, giving a flocculent precipitate melting at 140-141°C. A mixture melting point with p-nitroaniline (m.p. 147°C.) melted over a range from 135-142°C. This material could have been a mixture of p-nitroaniline and 2,4-dinitroaniline formed by hydrolysis of the appropriate oxadiazoles. No further identification was attempted since the amount of this material was very small.

Acetylation of 2-Methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole

A suspension of 1.5 g. of 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole in 30 ml. of acetic anhydride was boiled under reflux for eight and one half hours. The resulting solution was poured into a 125 ml. beaker and left overnight. The next day 100 ml. of 99% isopropyl alcohol was added and the mixture evaporated to dryness on a steam bath. The residue was powdered and extracted with several portions of cold chloroform. The filtered chloroform solution was evaporated to dryness and the residue recrystallized several times from absolute methyl alcohol. The resulting colorless prisms melted at 157-159°C. A mixture melting point with Product B showed no depression.

Analysis. Calculated for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.19; H, 3.95; N, 21.57.

SUMMARY

1. The acetylation, with acetic anhydride, of both 1-(p-nitrophenyl)-5-aminotetrazole and 5-(p-nitrophenylamino)tetrazole produced 1-(p-nitrophenyl)-5-acetylaminotetrazole.

2. The long heating, with acetic anhydride, of 1-(p-nitrophenyl)-5-aminotetrazole, 5-(p-nitrophenylamino)tetrazole, or 1-(p-nitrophenyl)-5-acetylaminotetrazole produced 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole and the acetyl derivative of 2-methyl-5-(p-nitrophenyl)-1,3,4-oxadiazole.

3. The synthesis of 2-methyl-5-phenylamino-1,3,4-oxadiazole was accomplished, with fair yield, by the treatment of 1-acetyl-4-phenylthiosemicarbazide with yellow mercuric oxide in refluxing toluene.

4. The nitration of 2-methyl-5-phenylamino-1,3,4-oxadiazole, using mixed acid, yielded not only 2-methyl-5-(p-nitrophenylamino)-1,3,4-oxadiazole but also 2-methyl-5-(2,4-dinitrophenylamino)-1,3,4-oxadiazole.

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