AN IMPROVED SYNTHESIS OF 2-NITRO-6-AMINOTOLUENE

Thesis by

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In Partial Fulfillment of the Requirements

For the Degree of

Master of Science

California Institute of Technology

Pasadena, California

1948

ACKNOWLEDGEMENT

The author wishes to thank Professor Carl Niemann for his invaluable assistance and advice throughout the course of this work.

TABLE OF CONTENTS

INTRODUCTION

Aromatic fluorides have been prepared and known for a long time (1), but not much work has been done with them until comparatively recently when they have assumed considerable importance as starting materials for the preparation of fluorinated α-amino acids. A considerable number of fluorinated α-amino acids have been prepared during the past fifteen years, chiefly fluorine derivatives of phenylalanine (2), tyrosine (3,4,5,6,7), and thyronine (5,8).

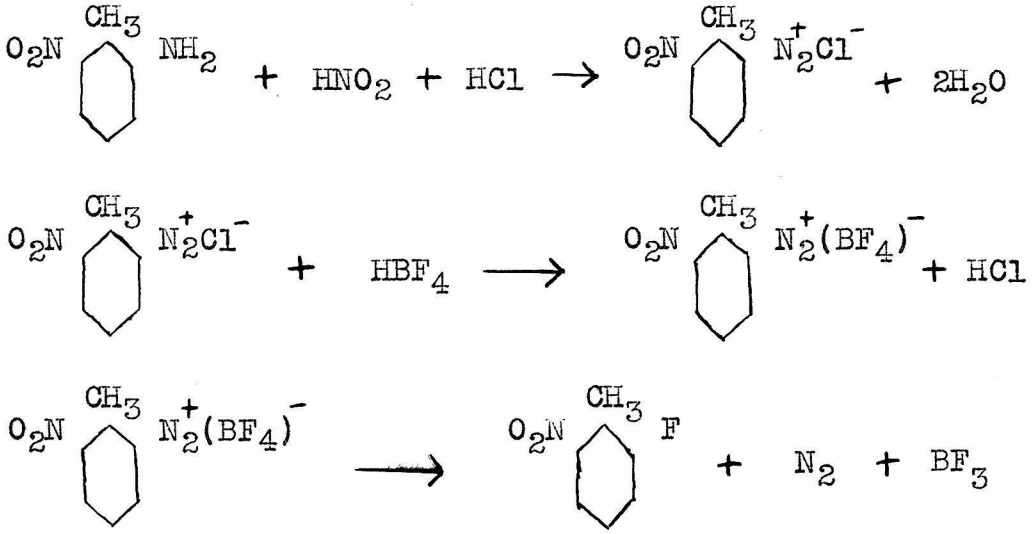
Fluorine derivatives of tryptophane have to date not been described in the literature. The compound 2-nitro-6-fluorotoluene was desired as a starting material later to be used in an attempt to synthesize a fluorine derivative of tryptophane; hence this work was undertaken in an effort to achieve an improved synthesis of the nitrofluorotoluene.

Van Loon and V. Meyer (9) first prepared 2-nitro-6-fluorotoluene by treatment of 2-nitro-6-hydroxytoluene with gaseous hydrogen fluoride, and by conversion of 2-nitro-6-aminotoluene to the diazopiperide which was subsequently heated with dry hydrogen fluoride and potassium fluoride. This synthesis is only of academic interest, however, and the authors state that even in the most favorable cases the yields were extremely poor.

The next report on the preparation of this compound appeared in the literature when Schiemann (10) announced that nitration of o-fluorotoluene gave 2-nitro-6-fluoro-

toluene and 5-nitro-6-fluorotoluene in yields of 14 and 72 per cent, respectively.

Lock (11), in 1936, reported the preparation of 2-nitro-6-fluorotoluene from 2-nitro-6-aminotoluene using the method developed by Schiemann (13) for the replacement of an amino group in an aromatic nucleus by fluorine. This method consists in the diazotization of the amine followed by treatment of the diazo salt with fluoboric acid or sodium fluoborate, which causes the insoluble diazonium fluoborate to precipitate. The dried diazonium fluoborate is then thermally decomposed liberating nitrogen and boron trifluoride; leaving the nitroaryl fluoride which may then be distilled off. The reactions may be represented as follows:



The yields obtained in these reactions are 80% of the theory of the diazonium fluoborate and a 63% yield of the aryl nitrofluoride calculated from the diazonium fluoborate, which

gives approximately a 50% over-all yield of the nitrofluorotoluene. While this yield is perhaps none too high, it is reasonably satisfactory, and apparently the best method yet devised for the preparation of the desired compound. Therefore it was chosen as the method to be used in this investigation subsequent to the preparation of 2-nitro-6-aminotoluene.

2,6-Dinitrotoluene has been prepared by several methods since it was first obtained as a nitration product of toluene by Cunerth (12), but the yields from the various syntheses were low. The method of Holleman and Boeseken (13) which consisted of selective reduction of 2,4,6-trinitrotoluene by ammonium sulfide to 2,6-dinitro-4-aminotoluene, which was then deaminated by reduction of the diazo salt of the amine by ethanol, was one of the best methods reported though their over-all yield of dinitrotoluene was low. Consequently a new method for the preparation of 2,6-dinitrotoluene was sought.

A logical approach to the problem seemed to be via the hydrolysis of 2,6-dinitro-p-toluenesulfonic acid which is readily obtained from toluene by sulfonation followed by nitration (14). To this end a quantity of 2,6-dinitro-p-toluenesulfonic acid was prepared, but all attempts to hydrolyze it to 2,6-dinitrotoluene met with failure. The usual methods for the hydrolysis of sulfonic acids of steam and superheated steam distillations, refluxing with dilute

and strong mineral acids were all applied, but resulted in the formation of negligible amounts of the desired dinitrotoluene. Consequently this method was abandoned and the known syntheses were studied in the hopes of ameliorating the yields obtained by earlier investigators.

2,6-Dinitro m- and p-Toluenesulfonic Acids

To 184 g. of concentrated sulfuric acid, 100 g. of toluene were added dropwise. The reaction mixture was allowed to cool to room temperature, and 500 g. of fuming nitric acid (sp. g. 1.50) were slowly added with frequent agitation of the reaction vessel. The reaction mixture was then refluxed for 4 hours under the hood. Excess nitric acid was distilled off, and upon cooling a mixture of isomeric dinitrotoluenesulfonic acids crystallized. This mixture consists principally of the p-isomer with a small amount of the m-isomer present (14).

Hydrolysis of the dinitrotoluenesulfonic acids was attempted by refluxing aqueous solutions for long periods of time, but no 2,6-dinitrotoluene was formed. In other experiments, hydrolysis of the sulfonic acids was attempted in sulfuric and nitric acid solutions of various concentrations, but these efforts were also unsuccessful from a preparative viewpoint. Steam and superheated steam distillations at 180° likewise gave no appreciable yields of the desired dinitrotoluene.

2,4,6-Trinitrotoluene

To a mixture of 200 g. concentrated nitric acid and 800 g. concentrated sulfuric acid contained in a 3-necked liter flask equipped with a stirrer, were added, in small portions, 100 g. of p-nitrotoluene. The reaction mixture was continuously stirred while the temperature was slowly raised to 120° over a period of five hours. The reaction mixture was allowed to cool to about 90°, and was then poured into ice water. The trinitrotoluene was filtered, washed well with water, and recrystallized from 90% ethanol. The yield obtained was 145 g. (about 82% of the theoretical value) of 2,4,6-trinitrotoluene, m.p. 81°-82°.

2,6-Dinitro-4-Aminotoluene

To 100 g. of 2,4,6-trinitrotoluene suspended in 500 ml. of ethanol are added 2.5 ml. of concentrated ammonium hydroxide. The solution is cooled in an ice bath, and hydrogen sulfide gas is passed into the reaction mixture until all of the trinitrotoluene has reacted. As the reduction proceeds, the flask is filled with a flocculent, yellowish precipitate, and the reaction is complete when all of the heavy trinitrotoluene crystals, which settle to the bottom of the flask, have disappeared. The reaction mixture is heated on the steam funnel, and then filtered. The sulfur precipitate is washed with hot ethanol until the filtrate runs through colorless. The alcoholic filtrate is poured into an excess of water, whereupon the insoluble hydroxylamine is precipitated. After allowing to stand for a few minutes, the precipitate is collected and heated with potassium iodide and concentrated hydrochloric acid. Heating is continued until the reaction mixture ceases to liberate free iodine vapors. Water is added to the crude dinitroamine; the product is filtered, and washed well with water. The residue is extracted with hot dilute hydrochloric acid until a test portion of the extract no longer gives a precipitate of the amine upon neutralization. The combined extracts are neutralized with

ammonium hydroxide, and the precipitated 2,6-dinitro-4-aminotoluene is collected. The yield is 47.5 g. (55%). The product is purified by recrystallization from 40% acetic acid, or from 60% ethanol.

2,6-Dinitrotoluene

A. Ethanol Deamination of 2,6-Dinitro-4-Aminotoluene.

1. Diazotization in H_2SO_4 with Nitrosylsulfuric Acid.

Four grams of 2,6-dinitro-4-aminotoluene are dissolved in 30 ml. concentrated H_2SO_4. The solution is cooled to 0^o in an ice bath and 2.2 g. $NaNO_2$ dissolved in 10 ml. concentrated H_2SO_4 are slowly added with continuous rapid stirring of the reaction mixture. After the diazotization is complete, the reaction mixture is poured into 200 ml. of boiling ethanol and refluxed for 15 minutes. The alcoholic solution is then poured into about 4 times its volume of water, and the residue which separates upon cooling is filtered off and steam distilled. The yield of 2,6-dinitrotoluene is 0.7 g.; about 25% of the theory. The compound is purified by recrystallization from low boiling petroleum ether. M.P. - 61^o-62^o.

2. Diazotization in HNO_3 with Sodium Metabisulfite.

To 50 ml. fuming nitric acid (sp. g. 1.49) is added in small portions, with vigorous stirring, a mixture of 9.8 g. 2,6-dinitro-4-aminotoluene and 5.9 g. sodium metabisulfite. After the last portion has been added, the reaction is allowed to continue until a test drop of the reaction mixture placed in a little water gives a clear solution. The reaction mixture is then poured into 300 ml. boiling ethanol and refluxed for

10 minutes. One liter of water is added, and the reaction mixture is cooled to 0°. Upon cooling, 2,6-dinitrotoluene crystallizes, and is filtered from the solution. It is purified by steam distillation, and recrystallization from petroleum ether. The yield is 4.4 g.; about 48% of the theoretical.

B. Hypophosphorus Acid Deamination of 2,6-Dinitro-4-Amino-Toluene.

In 50 ml. glacial acetic acid are dissolved 1.97 g. (0.01 mole) of 2,6-dinitro-4-aminotoluene. The solution is cooled to 0°, and 45 ml. of concentrated HCl are added. To this mixture 2.1 g. (0.03 mole) $NaNO_2$ are slowly added with rapid stirring, maintaining the temperature of the reaction mixture at 0°-5°. The reaction is allowed to continue for 10 minutes after all the nitrite has been added, and then 5.2 ml. of 50% H_3PO_2 (0.05 mole) are added dropwise. After all the H_3PO_2 has been added, stirring is continued for one hour, and the reaction mixture, loosely stoppered, is then stored in the refrigerator at approximately 0°. The reaction takes about 24 hours to reach completion, and the 2,6-dinitro-4-aminotoluene is recovered from the reaction product by steam distillation. It is purified by recrystallization from petroleum ether. The yield is 0.95 g. -- 52% of the theory.

The percentage yields obtained using other proportions of $NaNO_2$ and H_3PO_2 with HCl and H_2SO_4 as the solvents for

the amine are shown in Table I below.

Table I

Deamination of 2,6-Dinitro-4-Aminotoluene

Solvent	Moles of Amine	Moles of $NaNO_2$	Moles of H_3PO_2	Yield of Dinitrotoluene
H_2SO_4	0.01	0.01	0.10	27%
H_2SO_4	0.01	0.01	0.05	24%
HCl	0.01	0.01	0.05	38%
HCl	0.01	0.01	0.10	40%
HCl	0.01	0.05	0.05	39%
HCl	0.01	0.04	0.05	50%
HCl	0.01	0.03	0.05	52%
HCl	0.01	0.02	0.05	46%

2-Nitro-6-Aminotoluene

To 25 g. of 2,6-dinitrotoluene are added 100 ml. of ethanol and the mixture is brought to boiling on the steam funnel. Then 140 ml. of 15% ammonium sulfide are gradually introduced with frequent agitation of the reaction flask. The solution is refluxed for 15 minutes after all the ammonium sulfide has been added. Most of the alcohol is then removed, and the residue is repeatedly extracted with hot dilute HCl. The combined extracts are neutralized with NH_4OH, cooled, and the precipitated amine collected. The amine is purified by recrystallization from water. The yield is 16.6 g. (80% of the theory), m.p. 90°-91°.

2-Fluoro-6-Nitrotoluene

To 20 ml. concentrated HCl are added 13 g. 2-nitro-6-aminotoluene. The solution is cooled in an ice bath, and 8.55 g. $NaNO_2$ in concentrated aqueous solution are slowly added with continuous stirring. After the diazotization is complete, the solution is filtered rapidly into a cold flask, and 13.0 g. of $NaBF_4$ in concentrated aqueous solution (precooled to 0°) are added. A white, curdy precipitate of the diazonium fluoborate is formed immediately. After allowing to stand for a few minutes, the solution is filtered and the diazonium fluoborate collected. The precipitate is washed with concentrated $NaBF_4$ solution, then with methanol, and finally with cold water. The product is dried in vacuo over P_2O_5. The yield is 20 g.

Ten grams of the diazonium fluoborate are placed in a 50 ml. distilling flask to which is attached a small Liebig condenser. The receiver is connected to a series of three gas washing bottles containing dilute aqueous NaOH to absorb the boron trifluoride liberated in the decomposition. The system is evacuated to about 30 mm. pressure, and the reaction flask heated cautiously with a small free flame. As soon as the decomposition starts, the flame is removed and not reapplied until the reaction moderates. When all the diazonium fluoborate has decomposed,

the reaction flask is heated more strongly until all the 2-nitro-6-fluorotoluene has distilled over. The product is taken up with ethyl ether, and washed with dilute aqueous NaOH. The ethereal solution is dried with $CaCl_2$. The ether is distilled off, and the 2-nitro-6-fluorotoluene is redistilled. The yield is 3.5 g. (60% calculated from the diazonium fluoborate); b.p. - 205°.

Analysis:	C	H	N
Calc.	54.20	3.90	9.04
Found	54.43	3.98	9.22

Discussion

The influence upon the ease of hydrolysis of various substituents in the nucleus of aryl sulfonic acids is difficult to predict with certainty, but Armstrong and Miller (15) have shown that, in general, the presence of methyl ortho or para to the sulfonic acid group facilitates hydrolysis. Bromine appears to retard the reaction, and many di, tri, and tetrabromobenzenesulfonic acids hydrolyze only when treated with concentrated hydrochloric or hydrobromic acids at temperatures ranging from 150° to 250° (16,17,18,19). 3,5-Dinitro-4-bromobenzenesulfonic acid is unchanged by refluxing with 60% H_2SO_4 or by heating with 20% H_2SO_4 at 170° (20). If, in this molecule, the bromine is replaced by methyl, we obtain 2,6-dinitro-p-toluenesulfonic acid which compound should be more easily hydrolyzed than the bromosulfonic acid if a methyl group para to the sulfonic acid group increases the ease of hydrolysis. Nevertheless, it has been shown in this investigation that the 2,6-dinitro-p-toluenesulfonic acid is very difficult to hydrolyze. It is interesting to note that the fully substituted sulfonic acid, 3,5-dinitro-2,4,6-tribromobenzenesulfonic acid is hydrolyzed by heating in aqueous solution at 230° (19). Very little work on the hydrolysis of aromatic nitrosulfonic acids appears in the literature. Vesely and Stojanova (21) have reported on the hydrolysis of variously substituted aryl sulfonic acids by concentrated phosphoric acid.

They were unable to decompose nitrobenzenesulfonic acid by the use of phosphoric acid even at temperatures above 200°. It thus appears, from what little evidence that is available, that the nitro group exerts an inhibiting effect upon the hydrolysis of aryl sulfonic acids.

In addition to the procedure already described, toluene was nitrated to 2,4,6-trinitrotoluene using higher temperatures and shorter periods of nitration. These nitrations, however, were not nearly as effective as the other method. For example, nitration at 120°-125° for a period of 2½ hours gave only a 71% yield of trinitrotoluene. Furthermore, if the temperature of the reactants is raised too rapidly, when approximately 120° is reached, the violence of the reaction causes so much heat to be developed that external cooling must be applied to bring the temperature of the reaction mixture down within the bounds of safety.

Considerable difficulty was at first experienced in the reduction of 2,4,6-trinitrotoluene to 2,6-dinitro-4-aminotoluene in appreciable yields. The early work on the synthesis of this compound by Tiemann (21), Beilstein (22), and Holleman and Boeseken (13) consisted in the selective reduction of the trinitrotoluene to the dinitroamine by the use of ammonium sulfide. The work of Holleman and Boeseken who reported yields of the order of 20% of the theoretical value was repeated with essentially the same results as they obtained. The reaction product was

difficult to work with, and the crude amine had to be repeatedly recrystallized before attaining a sufficiently high degree of purity. Cohen and co-workers (23,24) were the first to report good success in the reduction of various polynitro aromatic compounds using hydrogen sulfide and only a trace of ammonia. The ammonia ostensibly merely catalyzes the reaction inasmuch as it may be replaced by other bases such as primary, secondary, and tertiary alifatic amines, benzylamine, or piperidine. The weak bases, aniline, pyridine, and phenylhydrazine, however, are not suitable for effecting the reduction. Such a reduction results, in the case of 2,4,6-trinitrotoluene, in a mixture of 2,6-dinitro-4-aminotoluene and 2,6-dinitro-4-hydroxylaminotoluene. Heating with concentrated hydrochloric acid and potassium iodide reduces the hydroxylamine to the amine. This method is preferable to reduction by ammonium sulfide in many cases. In addition to the large amounts of gummy polysulfides formed when much ammonia is used, which make it difficult to work up the reaction product, Cohen and McCandlish have shown that some hydroxylamines are very sensitive to the action of ammonia, forming in some cases new crystalline compounds, in others tarry products. In both cases the diminished yield of amine which is frequently experienced when much ammonia is used may be thus explained.

A considerable portion of the work of the investigation consisted in the study of the deamination of 2,6-dinitro-4-

aminotoluene. Although Holleman and Boeseken (13) reported the deamination of 2,6-dinitro-4-aminotoluene in "almost theoretical yield" to 2,6-dinitrotoluene by diazotization of the amine in sulfuric acid with sodium nitrite, followed by reduction of the diazo salt with ethanol, numerous attempts to repeat their work gave at best only a few per cent yield of the dinitrotoluene. They carried out the diazotization using equal quantities of concentrated sulfuric acid and water as the solvent for the amine, and aqueous sodium nitrite. Since this method proved ineffective, modifications of the procedure were adopted using higher concentrations of sulfuric acid and nitrosylsulfuric acid as well as aqueous sodium nitrite for the diazotization. None of these modifications, however, produced a yield of 2,6-dinitrotoluene of more than about 25% of the theoretical, which yield was obtained when concentrated sulfuric acid was used for the solvent, and nitrosylsulfuric acid was used for the diazotization. Diazotization of the amine using the method of Witt (25) gave considerably better results. The principle of this method is to use concentrated nitric acid as the solvent for the amine, and at the same time derive from it the nitrous acid necessary for diazotization by the action of a suitable reducing agent such as sodium metabisulfite. This method gave a more nearly complete diazotization than could be achieved in sulfuric acid. The amine may also be diazotized by dissolving it first in glacial acetic acid, then adding

concentrated hydrochloric acid and sodium nitrite.

Deamination of the diazotized amine with hypophosphorus acid was found to give somewhat better results than ethanol deamination. The reduction of a diazotized amine by hypophosphorus acid (27) may be represented by the following equation:

$$ArN_2^+X^- + H_3PO_2 + H_2O \longrightarrow ArH + H_3PO_3 + HX + N_2$$

According to the equation, one mole of hypophosphorus acid will be required per diazo group, but in laboratory practice an excess of five to ten, or in some cases even more, moles of hypophosphorus acid per mole of diazonium compound is usually necessary to achieve the best results. This is not invariably true, however, and in the case of 3-nitro-4-aminotoluene as little as 0.76 mole gives a 70% yield of m-nitrotoluene (26). The proper amount to be used with an individual amine must be determined by experiment. In the case of 2,6-dinitro-4-aminotoluene, 5 moles of hypophosphorus acid per mole of diazotized amine was found to be the correct proportion to use for the deamination. It was also determined that a proportion of 3 moles of sodium nitrite per mole of amine gave maximum yields.

Deamination of the diazotized amine using the stabilized diazonium salt method of Hodgson and Marsden (28) was also investigated. In this method, an aqueous solution of the diazotized amine is treated with the molar quantity of naphthalene-1,5-disulfonic acid or with

2-naphthol-1-sulfonic acid which causes the insoluble diazonium salt to precipitate. The dry salt is then reduced at room temperature in ethanol containing zinc or copper. The method was found to be unsuitable for the deamination of 2,6-dinitro-4-aminotoluene. Of the reducing agents investigated, hypophosphorus acid gave the best results.

2-Nitro-6-aminotoluene has usually been prepared by ammonium sulfide reduction of 2,6-dinitrotoluene in the cold or at room temperatures (12,29). This procedure usually results in fair yields of the product, but the reaction mixture is invariably contaminated with tarry polysulfides and is difficult to purify. It was discovered that if the reaction is carried out at the temperature of boiling ethanol, the yields are somewhat higher, and the product is more easily purified.

Summary of Thesis

1. The following compounds were synthesized: 2,6-dinitro-p-toluenesulfonic acid, 2,4,6-trinitrotoluene, 2,6-dinitro-4-aminotoluene, 2,6-dinitrotoluene, 2-nitro-6-aminotoluene, and 2-nitro-6-fluorotoluene.

2, 2,6-Dinitro-p-toluenesulfonic acid could not be hydrolyzed in yields greater than a few per cent by application of the ordinary methods for the hydrolysis of aryl sulfonic acids.

3. The optimum experimental conditions for the deamination of 2,6-dinitro-4-aminotoluene by hypophosphorus acid were determined.

4. An improved method for reducing 2,6-dinitrotoluene to 2-nitro-6-aminotoluene was devised.

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