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QUARTERLY PROGRESS REPORT NO. 1

THE INTERACTION OF THE AZIDO GROUP IN ORGANIC COMPOUNDS WITH ADJACENT FUNCTIONAL GROUPS

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By

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OBJECTIVES

The objectives of this research are the preparation and study of tertiary alkyl azides and of aryl azides in which the azido group is adjacent to formal unsaturation.

SUMMARY

There are three lines of investigation under way:

1. Preparation of aryl azides with carbon-carbon and carbon-nitrogen unsaturation in an adjacent position. β-(o-azidophenyl)ethyl alcohol has been prepared as part of a synthesis of o-azidostyrene. 6-Nitro-3,4-dimethoxycinnamic acid has been prepared as part of a synthesis of 6-azido-3,4-dimethoxycinnamic acid. o-Nitrobenzyl azide and cyanide have been prepared as part of the synthesis of cyano azides which might cyclize.

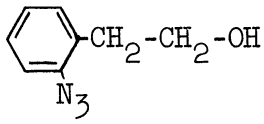
2. Preparation of aryl azides with other aromatic rings (such as benzenoid) in an ortho position. Attempts to prepare 1-(o-nitrophenyl)-tetrazole have so far failed. 2-Nitro-2',5'-dihydroxybiphenyl and its methyl ether have been prepared from diazotized o-nitroaniline and hydroquinone.

3. Development of a preparative method suitable for the synthesis of tertiary alkyl azides. Three N-aminourethanes have been prepared and treated with nitrous acid to give nitroso compounds.

INTRODUCTION

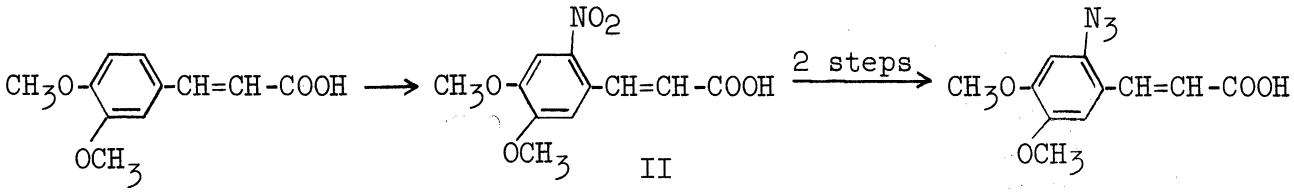
Synthetic approaches to several types of compounds having an azido group adjacent to reactive centers have been undertaken, and a new reaction which may eventually be adaptable to the synthesis of tertiary alkyl azides is being studied.

β-(o-Azidophenyl)ethanol (I), m.p. 48°C, has been prepared from the corresponding diazotized amine and characterized as the phenylurethane, m.p. 89°C. Thermal decomposition of the azido alcohol in decalin solution gave an amorphous, unidentified product. The intention is to convert the alcohol into o-azidostyrene for study of interaction of the azido and vinyl groups.



I

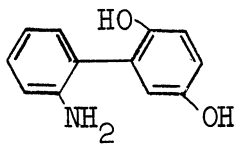
Preliminary investigations indicate that nitration of 3,4-dimethoxycinnamic acid produces 6-nitro-3,4-dimethoxycinnamic acid (II), m.p. 285-90°C, in fair yield. The following syntheses are projected to provide another compound with an ethylenic double bond adjacent to the azido group:



II

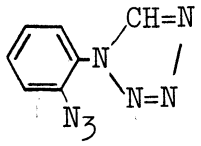
o-Nitrobenzyl azide has been prepared from o-nitrobenzyl bromide and sodium azide. This compound is a yellowish, crystalline solid at dry-ice temperatures, but is a red oil at room temperature, and has not yet been purified. The intention is to investigate its possible conversion into a homofuroxan.

For further study of the interaction of the azido group with aromatic rings, 2-nitro-2',5'-dihydroxybiphenyl[1] has been prepared and converted to 2-nitro-2',5'-dimethoxybiphenyl and the 2-amino compound (III), from which it is planned to prepare the azide.



III

For a similar purpose, it was desired to prepare 1-(o-azidophenyl)-tetrazole (IV) for possible conversion to tetrazoloindole. To this end two approaches to 1-(o-nitrophenyl)tetrazole have been tried, but so far without success.

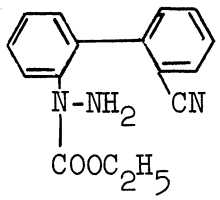


IV

For the investigation of a possible reaction[2]

$$R\text{-}\underset{\underset{COOEt}{|}}{N}\text{-}NH_2 + HNO_2 \longrightarrow R\text{-}N_3 + CO_2 + EtOH + H_2O ,$$

N-amino-2-carbethoxyamino-2'-cyanobiphenyl (V), N-amino-N-p-tolylurethane, and N-amino-N-ethylurethane have been prepared by reduction of the corresponding nitroso compounds. The results of their analyses are expected shortly. An initial attempt to convert the p-tolyl compound to the azide has not yet given conclusive results, but the product obtained appears to be the nitroso derivative of the aminourethane.



V

EXPERIMENTAL WORK*

β-(o-Azidophenyl)ethanol

A commercial grade of β-(o-aminophenyl)ethanol was purified by freezing, suction filtration, and distillation at reduced pressure and was stored in the refrigerator.

To an ice-cold solution of 6.85 gm (0.050 mole) of the amine (b.p. 173-76°C) in 20 ml of water was added 12.75 ml (0.15 mole) of ice-cold concentrated HCl (which yielded a clear, colorless solution), followed by a

*Analyses are by Microtech Laboratory, Skokie, Illinois.

solution of 3.60 gm (0.050 mole) sodium nitrite in 5 ml of water. To the orange diazonium solution was added immediately 5.00 gm (0.075 mole) sodium azide in 15 ml of ice-cold water. The slightly frothing solution was kept cold for 3 hours; the tarry, yellow, solid product was then removed by rapid filtration and triturated with dilute sodium bicarbonate solution. The resulting yellow oil solidified during storage at -10°C and the crude, moist product (8.65 gm) was recrystallized from 20 ml of 50% methanol. Seeding at -10°C yielded 2.5 gm of tan crystals, m.p. 39-48°C. Additional crops of lower purity were obtained by dilution of the filtrate. Three recrystallizations from 50% methanol gave colorless needles, m.p. 47.0-48.5°C.

Anal. Calculated for $C_8H_{11}NO$: C, 58.89; H, 5.56. Found: C, 59.14; H, 5.58.

β-(o-Azidophenyl)ethyl-N-phenylurethane

To 1.4 gm of the azido alcohol was added 1.0 ml phenyl isocyanate; the mixture was warmed 5 minutes on the steam bath, cooled to -10°C, and washed with carbon tetrachloride. After two recrystallizations from carbon tetrachloride, two from toluene, and one more from carbon tetrachloride, the pale-yellow crystals of the urethane melted at 87.5-89.0°C.

Anal. Calculated for $C_{15}H_{14}N_4O_2$: C, 63.81; H, 5.00. Found: C, 63.58, 63.53; H, 5.24, 5.00.

Both the azido alcohol and its phenylurethane decompose with a puff when a small portion is dropped into concentrated sulfuric acid at room temperature. The former darkens on exposure to air and light.

Thermal Decomposition of β-(o-Azidophenyl)ethanol

A mixture of 1.00 gm (0.61 mole) of the azide and 100 ml of distilled decalin was heated under reflux. The azide dissolved at 80°C; decomposition began at 155°C, was vigorous at 170°C, slow after 1/2 hour at 185°C, and complete after 2 additional hours at 185 ± 4°C. The hot orange solution was filtered (no residue) and cooled to -10°C, yielding a trace of amorphous tan material which turned to tar when washed with ether. Evaporation of the decalin filtrate under an air stream on the steam bath yielded more tar. Recrystallization from methanol gave a tan solid which turned to tar on standing. Digestion of the tar with 20% HCl on the steam bath for 1 hour gave, after filtration, washing, and drying, 0.15 gm of a brown power which decomposed slightly without melting between 300 and 360°C. This product is insoluble in aqueous sodium bicarbonate.

o-Nitrobenzyl Azide

A solution of 1.08 gm (0.005 mole) of o-nitrobenzyl bromide[3] and 0.65 gm (0.01 mole) of sodium azide in 28 ml of 82% alcohol stood at room temperature for 2 weeks and yielded, after dilution with water, extraction with ether, and evaporation of the dried extracts, a small amount of a red oil. A solution of the oil in absolute ethanol and petroleum ether was cooled on dry ice and the excess solvent decanted from the solid which precipitated. Two such partial purifications gave a product which is a red oil at -10°C and gives a sudden puff with concentrated sulfuric acid and a negative Beilstein test.

Attempted Preparation of 1-(o-Nitrophenyl)tetrazole by the Dimroth[4] Procedure

A solution of 1.44 gm (0.02 mole) of sodium nitrite in 5 ml of water was added very slowly to a mixture of 0.02 mole of o-nitroaniline in 14 ml of 7N HCl. The reaction mixture was kept at 0°C or below; then 5 gm of sodium acetate and 10 ml of 5N NaOH were added in small portions. This diazonium salt solution was then added in small portions to a solution of 0.02 mole of diformylhydrazide in 60 ml of 1.5N Na_2CO_3 at 0°C or below.

As this addition was made, the reaction mixture turned gradually brown, and finally a dark-brown solution resulted with small amounts of a brown tarry material dispersed throughout the solution. The tar was filtered off on a cotton plug, which was then extracted three times with 15-ml portions of ligroin. The tar was treated with acetone, but not a trace of a crystalline substance could be recovered from the extracts. A repetition of this experiment gave the same results.

Attempted Preparation of o-Nitrophenyl Isocyanide*

A mixture of 44 gm of o-nitroaniline and 37 gm of chloroform was added very cautiously to a suspension of 40 gm of KOH in 100 cc of benzene. This mixture was added through a dropping funnel into a three-necked round-bottomed flask. The middle neck was fitted with a reflux condenser and the flask placed on a steam bath until ebullition began. The KOH could be held in suspension only with frequent shaking of the mixture.

The reaction which occurred was very exothermic and was completely self-sustaining for 1-1/2 hours. After the reaction had stopped, the solution was heated for 15 minutes more on the steam bath. The benzene was then

*By the general method of Malatesta, Gazz. chim. ital. 77, 238 (1947).

distilled off until the temperature reached 88°C. The reaction mixture was cooled and treated with petroleum ether. A light-yellow solid crystallized immediately and was filtered and washed with petroleum ether. The dry solid had a melting point of 70-71°C, undepressed when mixed with the starting material, o-nitroaniline. The reaction observed was apparently only the alkaline hydrolysis of chloroform.

2-Nitro-2',5'-dihydroxybiphenyl[1]

In a 300-ml three-necked flask fitted with a stirrer was placed 13.8 gm (0.1 mole) of o-nitroaniline with 25 ml of concentrated sulfuric acid and 60 ml of water. After a clear red solution was obtained, the flask was placed in an ice-salt bath and cooled to between 0 and 5°C. To the stirred solution was added 3.8 gm (0.11 mole) of sodium nitrite in 40 ml of water, the temperature being kept below 10°C. After the addition was complete, stirring was continued for 15 minutes and urea was then added. After the evolution of bubbles ceased, the diazonium salt solution was filtered.

In a 3-liter flask, 22 gm (0.2 mole) of hydroquinone was dissolved in 1100 ml of water, and with continued stirring the above solution was added dropwise, keeping the temperature at about 20°C. When the addition was complete, it was stirred for several hours and then filtered. The filtrate was extracted with ether. The ethereal solution was then extracted with a 10% sodium hydroxide solution to which sodium bisulfite had been added. The alkaline solution was neutralized with hydrochloric acid and allowed to cool. The orange-colored needles that formed were filtered off and the aqueous solution extracted with ether, which was evaporated to give a small amount of solid which was largely hydroquinone. The yield of orange-colored needles, m.p. 163-167°C, varied between 11.5 and 13.5% in four trials.

Reaction of N-Amino-N-p-tolylurethane with Nitrous Acid

To a stirred solution of 2.80 gm (0.0144 mole) of ethyl N-amino-N-p-tolylcarbamate in 20 ml of 50% sulfuric acid in a 100-ml flask at about 0°C was added 1.04 gm (0.015 mole) of sodium nitrite in 10 ml water, in small portions. After the addition was complete, the solution was stirred for 1/2 hour, at which time the solid which had formed was filtered off; it was a white crystalline solid of m.p. 51-54°C and weighed 2.24 gm, which is more than the theoretical yield of p-tolylazide. It is perhaps an N-nitroso compound, and attempts are being made to convert it to p-tolylazide.

N-Ethyl-N-nitrosourethane

To a stirred solution of 13.6 gm (0.116 mole) of N-ethylurethane, 300 ml of glacial acetic acid, 150 ml of acetic anhydride, 24 gm of potassium acetate, and 2 gm of phosphorus pentoxide in a 1-liter flask fitted with a thermometer was added dropwise, at about 8°C, 7.86 gm (0.12 mole) of nitrosyl chloride (81 ml of an acetic acid solution). The mixture was stirred 1/2 hour after the addition and then poured onto ice. The cold solution was treated with sodium hydroxide until an oil formed (it was not neutralized). The solution was then extracted with ether, dried over magnesium sulfate, and distilled. A forerun distilled at 25-85°C/25 mm; the product, which is a slightly pinkish liquid, was collected at 85-6°C/25 mm. The yield was 6.28 gm (37.5%), and the product gives a positive Liebermann test. Subsequent experiments have suggested that it may be prepared more conveniently with aqueous nitrous acid.

N-Amino-N-ethylurethane

To a stirred suspension of 5 gm of zinc dust in 20 ml of 50% acetic acid was added dropwise 6.28 gm of N-ethyl-N-nitrosourethane in 20 ml of 50% acetic acid. The temperature was kept at less than 20°C during the addition, and then was raised to 50-60°C for about 1 hour. The solution turned clear. At this time, the hot solution was filted and the filtrate was made alkaline and extracted with ether. The ethereal solution was dried and distilled. The product was a colorless liquid boiling at 75-80°C/ 25 mm, weighing 2.58 gm (45.5%).

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