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QUARTERLY PROGRESS REPORT NO. 2

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

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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

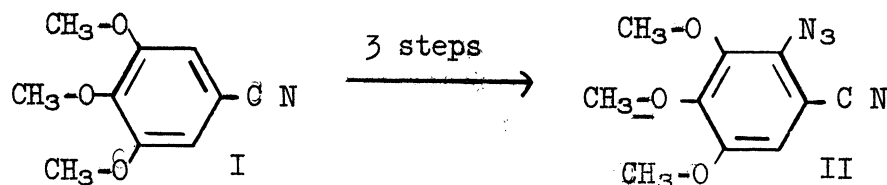
1. One *o*-azidobenzonitrile has been prepared, and the synthesis of another has been begun.
2. The "diazosulfide" from diazotized *o*-mercapto-aniline would not react with hydrogen azide.
3. Some hydroxy- and methoxy-carbazoles have been prepared by the thermal cyclization of some new *o*-azidobiphenyls.
4. *N*-amino-*N*-ethylurea has been prepared and characterized.

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The experimental details of the nitration of 3,4-dimethoxycinnamic acid mentioned in the previous report, are given herewith. The product, 2-nitro-4,5-dimethoxycinnamic acid, has not yet been successfully reduced to the amine, which is required for conversion to the azide.

For the investigation of the interaction of the azide group with the cyano group, *o*-nitrobenzyl cyanide has been prepared from the corresponding bromide. It is expected to reduce the nitro group to an amine and convert it to an azide shortly. Another azido nitrile has been completely synthesized, however. Nitration of 3,4,5-trimethoxybenzonitrile (I), has given 2-nitro-3,4,5-trimethoxybenzonitrile, albeit in poor yield (12 percent). Reduction of the nitro group alone was accomplished in 63 percent yield with tin and hydrochloric acid, and the resulting amine was converted to 2-azido-3,4,5-trimethoxybenzonitrile (II) in 70 percent yield.



An attempt to prepare *o*-mercaptophenyl azide from diazotized *o*-mercaptoaniline was unsuccessful.

The 2-nitro-2',5'-dihydroxybiphenyl (III) reported in the previous report was successfully reduced to the amine, but conversion to the azide has been hindered by the excessive sensitivity of the amine to oxidizing agents such as nitrous acid and air. To avoid this difficulty, the nitro compound has been methylated, and the resulting dimethyl ether has been successfully reduced to the amine and converted to the azide (IV). Thermal decomposition of the azide gives 1,4-dimethoxycarbazole (V). This is the first time that

remained between 5 and 10°C. When all the solid had been added, the thermometer, stirrer, and sides of the flask were rinsed with 10 ml conc. nitric acid, and the cloudy red solution was stirred for 45 minutes at 9±1°. The reaction mixture was poured onto crushed ice, the yellow product washed until colorless, triturated with dilute NH₄OH, washed, and dried at 50°; yield: 1.45g (12 percent) of colorless powder mp 130.5-132.5°C. Four recrystallizations from 95 percent ethanol afforded colorless needles, mp 137.0-138.0°C. Anal.: Calc'd for C₁₀H₁₀N₂O₅: C, 50.41; H, 4.23. Found: C, 50.61; H, 4.37.

2-Amino-3,4,5-trimethoxybenzotrile

One gram of the above nitro compound was suspended in 12 ml of conc. hydrochloric acid and reduced with three 0.85g portions of granulated tin added during the course of two hours heating at 80° on the steam bath. Working up in the usual manner and recrystallization of the moist amine from ether gave 0.55g (63 percent) of 2-amino-3,4,5-trimethoxybenzotrile, pink cubes, in 78-81° with previous softening at 59°. Rectystallization from carbon tetrachloride and then 50 percent methanol (with charcoal) gave pink crystals, in 80.0-81.5°C. Anal.: Calc'd. for C₁₀H₁₂N₂O₃: C, 57.68; H, 5.81. Found: C, 57.57; H, 5.71.

2-Azido-3,4,5-trimethoxybenzotrile

A solution of 0.95 (0.0046 mole) of the above amine in 36 ml of 20 percent hydrochloric acid was cooled in an ice bath. The hydrochloride precipitated to some extent, and the suspension was diazotized with sodium nitrite solution and a three-fold excess of cold aqueous sodium azide was added. Copious white foam was evolved from the yellow solution; after one-half hour in the ice bath, all the yellow color had disappeared. The mixture was allowed to warm to room temperature, the solid product was removed by filtration, triturated with dilute sodium bicarbonate solution, washed, and dried overnight at room temperature; yield: 0.75g (70 percent) of colorless powder, mp 110-115°C (dec.). Three recrystallizations from aqueous methanol gave pink needles of 2-azido-3,4,5-trimethoxybenzotrile, melting with decomposition at about 122° (preheated bath). Anal.: Calc'd for C₁₀H₁₀N₄O₃: C, 51.28; H, 4.30. Found: C, 52.18; H, 4.35.

2-Azido-3,4,5-trimethoxybenzotrile decomposes readily after about five minutes heating at five degrees below its melting point. It gives a puff of gas and a deep purple color when dropped into concentrated sulfuric acid. Its solutions in carbontetrachloride and methanol give tarry decomposition products after several hours exposure to bright sunlight. Its thermal decomposition has not yet been further investigated.

Attempts to add hydrogen azide to 3,4,5-trimethoxybenzotrile to give the 5-aryl tetrazole have so far been unsuccessful.

6-Nitro-3,4-dimethoxycinnamic acid

To a solution of 4.16g (0.020 mole) of 3,4-dimethoxycinnamic acid in 50 ml of glacial acetic acid at 50° was added with stirring 1.50 ml (0.024 mole) of conc. nitric acid (d. 1.42). The mixture was kept at 50° for one-half hour and then cooled to room temperature; the yellow product was removed by filtration, washed with water, and dried. There was obtained 3.10g (60 percent) of 6-nitro-3,4-dimethoxycinnamic acid, mp 280-285°C (dec.), essentially free from other nitro isomers (reported* mp 282° dec.).

o-Nitrobenzylcyanide

This has been prepared by a modification of the method of Bamberger** One-tenth of a mole of potassium cyanide was refluxed in 100 ml of methanol for two hours, the hot, pink solution filtered (2.5g KCN recovered), and 11.4g (0.050 mole) of o-nitrobenzylbromide and 80 ml of methanol added to the filtrate. A violet color appeared immediately and changed to a dark brown after 14 hours of refluxing. The solution and a water-soluble residue were poured onto 300g of crushed ice; the 5.3g of dark brown tarry material which was thus obtained together with 1.7g of tar obtained by acidification (HCl) of the filtrate yielded yellow crystals of o-nitrobenzylcyanide, mp 78-79°C (with previous softening at 73°) (82.5°C**) and several lower melting crops, upon recrystallization (with charcoal) from 50 percent ethanol.

Benzo-1,2,3-thiadiazole, mp 35°C (dec.), has been prepared from o-aminobenzenethiol and has so far resisted conversion to o-azidobenzenethiol by treatment with sodium azide.

The thermal (in 1 percent decalin solution) decomposition products of the phenylurethane of β -[o-azidophenyl]-ethyl alcohol have not yet been identified.

2-Hydroxycarbazole

One gram (0.0047 mole) of 2-azido-4'-hydroxybiphenyl was dissolved in 100 ml of kerosene in a 150 ml beaker and heated on a hot plate to 190°C for one hour.

After the solution had cooled to room temperature, the solid crystals which formed were filtered off, and the filtrate was evaporated to dryness with an air jet on the hot plate. The residue was taken up in about 10 ml of

* Arch. Pharm. 272, 770 (1934).

** E. Bamberger, Ber. 19, 2635 (1886).

solvent, filtered, and the entire solid material washed with 40-60° petroleum ether.

The yield of 2-hydroxycarbazole was 0.76g (87.5 percent), mp 255-260°C. After two recrystallizations from acetone-water, 0.05g, mp 266.5-269.5°C, of light tan platelets was obtained. Anal.: Calc'd. for $C_{12}H_9ON$: C, 78.67; H, 4.95. Found: C, 78.78; H, 4.90. (Clark Microanalytical Laboratory, Urbana, Illinois).

2-Azido-4'-methoxybiphenyl and 2-Methoxycarbazole

In a 200-ml three-neck flask fitted with a stirrer, 3.56g (0.0151 mole) of 2-amino-4'-methoxybiphenyl hydrochloride was dissolved in a mixture of 50 ml of water and 5 ml of conc. sulfuric acid. The flask was immersed in an ice-salt bath, and the reaction mixture cooled to 0°C with stirring.

To the cold, stirred solution, a solution of 1.1g (0.016 mole) of sodium nitrite in 30 ml of water was added dropwise, keeping the temperature below 5°C. The solution was stirred one-half hour, then a small portion of urea was added to destroy the excess nitrous acid. The resulting solution was filtered.

To the diazonium solution was added 1.04g (0.016 mole) of sodium azide in 30 ml of water dropwise. The resulting solution was stirred several hours, and the oily material (2-azido-4'-methoxybiphenyl) which was formed was extracted into ether.

The ethereal solution was dried over magnesium sulfate, filtered, and the ether blown off. The residue was taken up in 50 ml of kerosene and heated slowly in a 100 ml beaker to 180°C on a hot plate and kept there for 15 minutes. It was then allowed to cool overnight.

The resulting precipitate was filtered off and washed with 40-60° petroleum ether. The yield of 2-methoxycarbazole was 2.13g (71.8 percent) mp 227-234°C. It was recrystallized from acetone-water twice to obtain 0.76g, mp 234-235.5°C of light tan plates. Anal.: Calculated for $C_{13}H_{11}ON$: C, 79.16; H, 5.62. Found: C, 79.47; H, 5.73.

2-Nitro-2',5'-dimethoxybiphenyl

In a 300-ml, three-necked flask fitted with a stirrer was placed 13.8g (0.1 mole) of o-nitroaniline with 25 ml of conc. sulfuric acid and 25 ml water. After a clear solution was obtained, the flask was placed in an ice-salt bath, stirred rapidly, and 50 ml more water was added to give a cloudy suspension. The flask was cooled to between 0 and 50C and 3.8g (0.11 mole) of sodium nitrite in 40 ml of water was added, the temperature being

kept below 10°C. After the addition was complete, stirring was continued for 15 minutes and urea was then added to destroy the excess nitrous acid. After the evolution of bubbles had ceased, the diazonium solution was filtered.

In a 3-liter flask, 22g (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 distilled to remove the ether, and the residue taken up in about 50 ml of water.

In a 2-liter flask, 40g of sodium hydroxide was dissolved in a liter of water, and the water solution obtained above was added. To the solution, which was stirred and heated to 60-70°C, was added dropwise 50.4g (0.4 mole) of dimethyl sulfate. To the same solution was added another water solution of the residues and 50.4g more of dimethyl sulfate. The dimethoxybenzene which is formed from the unreacted hydroquinone sublimes at the temperature of the reaction and thus does not contaminate the product. The solution is heated overnight, allowed to cool, and then filtered. The yield of crude, brown 2-nitro-2',5'-dimethoxybiphenyl was 5.43g, 10.5 percent, mp 100-105°C.

It was taken up in ether, washed with a normal sodium hydroxide solution until the washings were colorless, and then with water several times to remove the base. The ethereal solution, pale yellow in color, was dried over magnesium sulfate, filtered and evaporated to a small volume. From 4.54g of crude material, 3.18g, mp 100-102°C, and 0.45g, mp 96-101°C, of light yellow crystals was obtained. Anal.: Calc'd for $C_{14}H_{13}O_4N$: C, 64.86; H, 5.05. Found: C, 65.17; H, 4.91.

2-Amino-2',5'-dimethoxybiphenyl

In a Parr bottle was placed 3.33g (0.0128 mole) of 2-nitro-2',5'-dimethoxybiphenyl with about 200 ml of methanol and a small amount of platinum dioxide. It was shaken with hydrogen until the pressure reading on the gage was constant (about 16 hours).

The solution was filtered, the methanol evaporated, the residues taken up in acetone, and water added. The crude brownish product weighed 1.60g (56.5 percent) mp 65-68°C. It was recrystallized once from acetone-water, and once from methanol-water, to obtain 0.08g of fine white needles, mp 68-69°C. Anal.: Calc'd for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.59. Found: C, 73.16; H, 6.54.

2-Azido-2',5'-dimethoxybiphenyl

In a 100-ml, three-necked flask was placed 2g (0.00875 mole) of 2-amino-2',5'-dimethoxybiphenyl with 25 ml water and 5 ml conc. sulfuric acid. The mixture was heated on a steam bath until the amine went into solution. It was then cooled in an ice-salt bath with stirring to between 0 and 5°C.

To the stirred solution was added dropwise 0.63g (0.009 mole) of sodium nitrite in 5 ml of water. After the addition, stirring was continued for 20 minutes and then urea was added. After the evolution of bubbles had ceased, the solution was filtered. Sodium azide (0.58g, 0.009 mole) in 5 ml water was then added dropwise, and the solution stirred for two hours. The solution was filtered, yielding 1.36 (61 percent) of crude product.

From 0.36g recrystallized from methanol-water was obtained 0.30g of light tan needles which darkened on standing, mp 81.5-83.5°C. Anal.: Calc'd. for $C_{14}H_{13}O_2N_3$: C, 65.87; H, 5.13. Found: C, 66.07; H, 5.24.

1,4-Dimethoxycarbazole

One gram of 2-azido-2',5'-dimethoxybiphenyl was dissolved in 50 ml of kerosene in a 100-ml beaker and heated to 180°C slowly. After nearly all evolution of bubbles had ceased, it was maintained at that temperature for an additional 20 minutes. It was allowed to cool overnight.

The kerosene solution was filtered, evaporated with an air jet on a hot plate, and cooled. Crystals formed slowly. The crystals were filtered off and washed with 30-40° petroleum ether. The residue of tars, which remained in the beaker was dissolved in ether, 30-40°, petroleum ether was added, and the solution was evaporated to a small volume. The crystals were filtered and washed with more petroleum ether. The first batch weighed 0.13g, mp 109-112°C, and the second batch weighed 0.50g, mp 107-111°C, to give a total yield of 71 percent. The first crop was recrystallized from methanol-water to give fine white crystals, 0.04g, mp 111.5-112.8°C, and 0.03g, mp 110.5-112.5°C. Anal.: Calc'd for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77. Found: C, 74.03; H, 5.85.

N-Nitrosoethylurea (Ref.: F. Arndt, Angew. Chem., 43, 445 (1930))

In a 3-liter, three-necked flask was placed 40g (0.89 mole) of ethyl-amine, 265 ml of water, 85 ml of conc. hydrochloric acid, and 90g of potassium cyanate. The flask was heated slowly with a water bath, which was slowly brought to boiling, and boiled 15 minutes. The solution was filtered and allowed to cool.

The flask was placed in an ice-salt bath and cooled to between 0 and 5°C, and 75g of sodium nitrite was added. A dropping funnel with an extension leading to the bottom of the flask was used to add 150g of conc. nitric acid which had been diluted with 150g of ice. After all the nitric acid had been added, the product was filtered off and washed with water to remove the acid. The yield of N-nitrosoethylurea was 73.8g (71 percent), mp 99.5-102.5°C with decomposition.

N-Amino-N-ethylurea

To stirred suspension of 20g of zinc dust in 70 ml of 50 percent acetic acid in a 500-ml three-necked flask was added dropwise a solution of 10g (0.085 mole) of N-nitrosoethylurea in 50 ml of glacial acetic acid and 25 ml water. The temperature of the reaction was kept at about 20°C during the addition, and then raised to 50-60°C for one hour. The zinc dust was filtered from the hot solution, and the filtrate was made basic (dissolving all the zinc hydroxide) and extracted continuously with ether. After several days, the ether extract yielded 0.57g of a substance which melted at 97-103°C. From 0.47g recrystallized from dimethoxyethane, 0.15g, mp 105.5-107.5°C, and a second crop weighing 0.05g, was obtained.

By continuing the ether extraction, a total of 2.73g, 31 percent, was obtained. Anal.: Calc'd. for $C_3H_9ON_3$: C, 34.94; H, 8.80. Found: C, 35.02; H, 8.70.

N-ethyl-N-(p-chlorobenzylideneamino) urea

In a 25 ml Erlenmeyer flask was placed 0.1g (0.0085 mole) of N-amino-N-ethylurea and 0.14g (0.001 mole) of p-chlorobenzaldehyde with 10 ml absolute alcohol. The mixture refluxed for 10 minutes, the solution was allowed to cool, and water was slowly added until white needles formed.

The yield of crude product, mp 153-154°C, was 0.12g (63 percent). It was recrystallized once from the same solvents to give a mp of 153.5-154°C. Anal.: Calc'd for $C_{10}H_{12}ON_3Cl$: C, 53.20; H, 5.758. Found: C, 53.19; H, 5.48.

N-ethyl-N-benzylideneaminourea

Ten grams of N-nitrosoethylurea was reduced in the same manner as described above. Instead of extracting the basic solution with ether, 10g of benzaldehyde was added and the flask was shaken on a mechanical shaker overnight.

The solid which formed was filtered off and washed with water and a very small portion of ether to remove the benzaldehyde which clings to the product. The yield of crude product was 7.14 (44 percent), mp 135-139°C. It

was recrystallized from alcohol-water once to yield fine white needles, mp 137.5-139°C. Anal.: Calc'd for $C_{10}H_{13}ON_3$: C, 62.80; H, 6.85. Found: C, 63.35; H, 6.95.

