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

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THE INTERACTION OF THE AZIDO GROUP

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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. Tert-butyl azide has been obtained in a state close to analytical purity, and its acid-catalyzed decomposition has been studied.
2. The polymer obtained from an attempted preparation of propargyl azide has an analysis consistent with the retention of all the azide nitrogens. Monomeric propargyl is violently explosive.
3. Isobutyl azide and hexahydrobenzyl azide have been prepared by a four-step route from the amines, constituting a new synthetic route to aliphatic azides.
4. o-Azidobenzenearsonic acid and O-Azidobenzenearsenoxide have now been obtained in analytical purity.
5. o-Azidobenzenearsenoxide could not be made to couple with benzenediazonium ion.
6. o-Azidodiphenylsulfoxide has been characterized and prepared in quantity. Thermal decomposition has given an intractable tar.

7. 8-Azido-2-naphthol for use as an intermediate has been prepared and characterized.

8. The supposed o-aminophenylhydroquinone diacetate reported in Progress Report No. 3 apparently has no primary amino group.

### INTRODUCTION

Research assistants whose work is described in this report are William L. Berry, John M. Clegg, Joseph J. Lagowski, and Richard K. Putney.

1. Tert-butyl azide was prepared by the direct reaction of tert-butyl chloride with sodium azide in aqueous solution buffered near pH = 7. Since this is a solvolysis reaction, it is not surprising that the product consists of tert-butyl alcohol as well as the azide. The boiling points are close and there is reason to suspect azeotrope formation; fractional distillation was therefore unsuccessful in purifying tert-butyl azide.

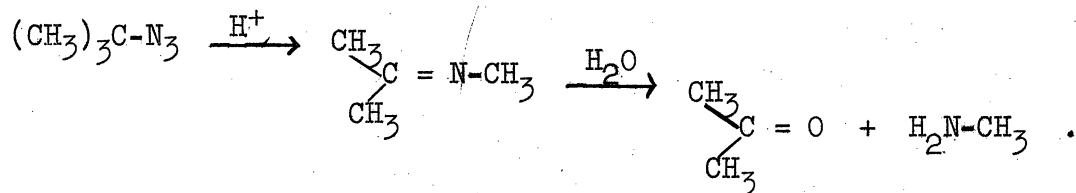
Several attempts to remove tert-butyl alcohol by washing with calcium chloride solution gave a product which in all cases showed strong absorption in the infrared spectrum in the O-H stretching region as well as at  $4.75\mu$  (characteristic of azides). Analysis showed only about half the required nitrogen content.

Esterification of the tert-butyl alcohol with benzoyl chloride and pyridine accomplished only partial purification of the azide. An attempt to remove tert-butyl alcohol by azeotropic distillation with carbon disulfide was also unsuccessful.

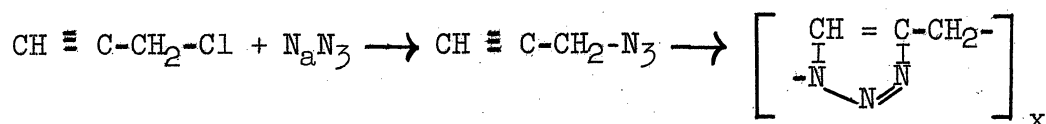
A nearly pure sample of azide was finally obtained by treatment of the mixture with acetyl chloride, which converted the alcohol impurity into tert-butyl chloride. The small amount of impurity was perhaps introduced by hydrolysis of some of the tert-butyl chloride during the washing operation prior to fractionation, and it should be possible to avoid this in future preparations.

The acid-catalyzed decomposition was investigated with a sample of azide containing about 30% tert-butyl alcohol. It evolved nitrogen readily at room temperature when treated with sulfuric acid in glacial acetic acid. Acetone was identified among the products as its 2,4-dinitrophenylhydrazone,

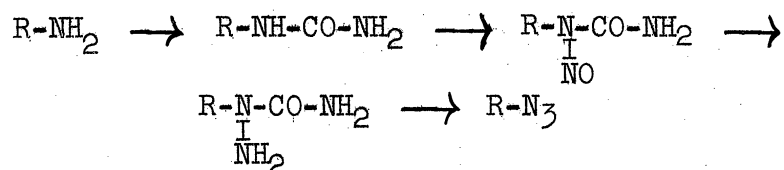
and methylamine was identified in the form of its benzoyl derivative. The decomposition therefore appears to proceed according to the equation



2. Propargyl chloride was found to react with aqueous sodium azide to produce a solid insoluble in all common solvents and possessed of no definite melting point. It is soluble only in concentrated acids, from which it reprecipitates on dilution. The behavior and analysis are consistent with a polymethylenetriazole structure. When the preparation was carried out over a shorter time, no solid was produced. The principal product was a steam-volatile oil which when dried boiled in the neighborhood of  $75^\circ$ . As it exploded with shattering violence during attempted distillation it was not further characterized, but it is presumed to be monomeric propargyl azide.



3. A possible route to the preparation of alkyl azides from amines has culminated in the synthesis of isobutyl and hexahydrobenzyl azides. The corresponding amines were converted to ureas by reaction with cyanic acid, and the ureas were nitrosated. Reduction of the N-nitroso-N-alkylureas gave 2-alkylsemicarbazides, which on treatment with nitrous acid gave the alkyl azides.



It is hoped to extend this method to the preparation of tert-alkyl azides, but tert-alkylureas have so far failed to give nitroso derivatives.

4. o-Azidobenzenearsonic acid and o-azidobenzenearsenoxide, the preparation of which was reported in Progress Report No. 3, have now been characterized by elementary analysis. The arsenoxide is decomposed by strong acids with the liberation of nitrogen, but the products have not yet been characterized.

5. Attempts to prepare o-azido-diphenylarsenious acid by arylating o-azidobenzenearsenoxide with diazonium salts have failed.

6. The o-azidodiphenylsulfoxide whose preparation was reported in Progress Report No. 3 has been characterized by analysis and infrared spectrum. It appears to have an intact azide group. It does not lose nitrogen until heated to about 160°. The product is a black tar, from which no identifiable product has been separated by various types of treatment. Cyclization of the azido group to the adjacent ring, to produce phenothiazine-S-oxide, is unaccountably more difficult than is the case with either the sulfide or sulfone analog. This perhaps indicates intermolecular reaction between the sulfoxide and azide groups, resulting in a polymeric product.

7. The 8-azido-2-naphthol, whose preparation was reported in Progress Report No. 3, has been characterized by analysis. This azide is unusually sensitive to light.

8. The substance supposed in Progress Report No. 3 to be o-amino-phenylhydroquinone diacetate has resisted all attempts at diazotization and appears to possess very little basicity. It has also resisted attempts to oxidize it to a quinone. Until it can be purified for analysis, its structure will not be subjected to further speculation.

### EXPERIMENTAL

#### Ter-Butyl Azide

The sample of product boiling at 73 to 75° obtained from the reaction of sodium azide with tert-butyl chloride in aqueous solution was buffered near pH7 with phosphate buffer, as described in Progress Report No. 3. Analysis: C, 51.15%; H, 9.78%; N, 21.95%. Calculated: C, 48.4%; H, 9.17%; N, 42.4%. The nitrogen content indicates approximately 50% tert-butyl azide.

Eight ml of this product was treated with 6 ml of benzoyl chloride in 20 ml of pyridine for 48 hours at reflux temperature. The pyridine was removed from the product by extensive washing with 10% aqueous citric acid and with water, and the dried product was fractionated. The product which boiled at 80.0° was analyzed. Found: C, 54.07%; H, 10.17%; N, 28.74%. The stillpot contained a higher boiling liquid with the characteristic odor of tert-butyl benzoate.

Eight ml of the crude azide was allowed to stand overnight with 4 ml of acetyl chloride. The mixture was then washed rapidly with 10% aqueous sodium bicarbonate and with water, dried over sodium sulfate, and fractionated. The major portion boiled at 83 to 85°. Analysis: C, 49.57%; H, 9.45%; N, 40.25%.

To a solution of 10 ml of the crude (ca 50%) azide in 20 ml of glacial acetic acid was added 10 ml of concentrated sulfuric acid in 30 ml of glacial acetic acid with stirring and cooling. When nitrogen evolution had ceased, the mixture was steam distilled, and the distillate was treated with 2, 4-dinitrophenylhydrazine. There was formed a precipitate of acetone 2, 4-dinitrophenylhydrazone, mp 124 to 125° alone, and 125 to 126° when mixed with an authentic sample.

The residue in the stillpot was made strongly alkaline and distilled into a container of dilute hydrochloric acid. Evaporation of the distillate left a residue of methylamine hydrochloride, identified by conversion to N-methylbenzamide, mp 80.5 to 81° alone, and 81 to 82° when mixed with an authentic sample.

#### Propargyl Azide

The mixing of a solution of 50 g of sodium azide in 150 ml of water with one of 50 g of freshly distilled propargyl chloride (General Aniline and Film Company) in 100 ml of methanol occurred without detectable effect other than the formation of two layers. After 1 hour of refluxing, the mixture had become yellow and after 18 hours, orange. About 100 ml was distilled to remove most of the methanol. Sodium carbonate solution was added to the distillate until salt separation occurred and a milky suspension was formed. Extraction with methylene chloride and evaporation of the solvent from the extracts left a small, sticky, pale yellow residue. The bulk of the product had remained in the stillpot where it formed a large, puttylike lump. The ambient solution was decanted and the lump was washed with water. It was insoluble in chloroform, ethanol, ethyl acetate, or pyridine. It was soluble with slight warmth in concentrated hydrochloric acid, without gas evolution, and was partially reprecipitated by dilution, completely by neutralization with ammonium hydroxide. It was also soluble in glacial acetic acid, but apparently not crystallizable from it, and slowly soluble in concentrated sulfuric acid to form a straw-colored solution from which fine gas bubbles were evolved.

The material was dissolved in concentrated hydrochloric acid, filtered, reprecipitated, and washed well with water, and the resulting mud-like cake was dried at length in vacuo. It was thus obtained in crisp, tan

chunks which softened gradually over a long range of temperature between 30 and 100°. The analysis appears to be consistent with a polymer of propargyl azide when account is taken of the difficulty of obtaining a pure sample. Calculated for  $C_3H_3N_3$ : C, 44.44; H, 3.73. Found: C, 42.89; H, 4.10. These results suggest incomplete drying.

In another run, begun as above, the refluxing was stopped after 2 hours instead of 19. The distillate consisted of two layers which were separated and the organic layer was washed with sodium carbonate solution, water, and strong calcium chloride solution. After drying over calcium chloride it was cautiously distilled.

The first drop came over at 53°, and the distilland became cloudy and turned blood-red as the temperature rose. At 60° schlieren were noticed in the distillate, and the receiver was changed at 68°. A fraction was coming over slightly cloudy at 68 to 73° when the material detonated. The stillpot, condenser, and receiver were reduced to small granules, which suggests that the distillate detonated as well as the distilland; the first fraction (53 to 68°), standing one foot away, was knocked over but did not explode. Much soot was produced.

The aqueous solution remaining from the original distillation slowly deposited a small amount of yellowish solid which appeared to be the polymer obtained in the first run.

### Isobutylurea

In a 1-l. round-bottomed flask were placed 73 g (1 mole) of isobutylamine, 105 g (1.3 mole) of potassium cyanate, 450 ml of water, and 50 ml of concentrated hydrochloric acid. The resulting solution was heated on the steam bath for 1 hour. The mixture was allowed to cool and the white crystals were filtered and washed with ice-cold water. The yield of isobutylurea, mp 133 to 136°, was 56 g (48.4%).

### Nitrosoisobutylurea

A mixture of 73 g (1 mole) of isobutylamine, 105 g (1.3 mole) of potassium cyanate, 450 ml of water, and 50 ml of concentrated hydrochloric acid was placed in a 1-l. round-bottomed flask and heated on a steam bath for 1 hour. The hot solution was poured into a 5-l. three-necked flask and 1500 ml of water was added. The suspension was stirred mechanically and the flask cooled in an ice-salt bath to 0°. A solution of 88 g (1.28 mole) of sodium nitrite in 200 ml of water was added, followed by 320 ml of 25%



sulfuric acid which was added dropwise.

Following the addition of the sulfuric acid, the solution was stirred for 1-1/2 hours and then filtered and washed with ice-cold water. The yield of pale yellow nitrosoisobutylurea was 59 g (40.7%), mp 102 to 104° with decomposition.

### 2-Isobutylsemicarbazide

In a 1-l. three-necked flask was placed 60 g of zinc dust, together with 75 ml of glacial acetic acid and 150 ml of water. The stirred suspension was cooled to about 10 to 15° and 28 g (0.193 mole) of nitrosoisobutylurea in 125 ml of glacial acetic acid was added dropwise. After the addition was completed, the solution was heated to 40° and stirred for an additional hour. The excess zinc was then filtered off and the filtrate made strongly basic and extracted with chloroform. Evaporation of the chloroform left 13.5 g (53.5%) of 2-isobutylsemicarbazide, mp 89 to 91°.

### Isobutyl Azide

In a 300-ml, three-necked flask, 26.2 g (0.2 mole) of 2-isobutylsemicarbazide was dissolved in 50 ml of concentrated hydrochloric acid and 50 ml of water and cooled to 0°. A solution of 19.3 g (0.28 mole) of sodium nitrite in 35 ml of water was added dropwise and the solution became bright green. It was stirred an additional hour and then urea was added to destroy the excess nitrous acid. The green color disappeared and the solution was made basic, causing the separation of a second layer.

The mixture was then distilled, the product being codistilled with the water. The distillate was extracted with ether and the extracts were dried over calcium chloride. The solution was distilled at 752.5 mm and the following fractions obtained.

A	(ether)	below 40°
B	7.59 g	40 to 53°
C	3.40 g	53 to 93°
D	5.53 g	93 to 95°
E	3.08 g	above 95°

Fraction D was taken up in 30 to 37° reagent petroleum ether and washed with 5% hydrochloric acid twice, once with water, dried and redistilled at 751.5 mm, giving:

1.50 g, bp 45 to 53°

2.90 g, bp 93 to 94°

0.62 g, bp > 94°

The middle fraction reacted vigorously with concentrated sulfuric acid, and flashed in a flame; it was submitted for analysis as isobutyl azide. Calculated for  $C_4H_9N_3$ : C, 48.46; H, 9.15. Found: C, 49.18; H, 9.06.

#### 1-Isobutyl-1,2,3-triazole-4,5-dicarboxylic Acid

The middle fraction of the isobutyl azide preparation was taken up in reagent petroleum ether (bp 30 to 60°), washed with two portions of 10% hydrochloric acid, once with water, dried over magnesium sulfate, and placed in a 50-ml, round-bottomed flask with 20 ml of dry ether. To this was added 4.55 g (0.034 mole) of acetylenedicarboxylic acid hydrate and the solution refluxed 1 hour, cooled, and petroleum ether added until a white solid precipitated. The yield of crude product was 5.94 g (74.7%), mp 50 to 95°.

It was recrystallized from ether-petroleum ether mixture to yield white needles which lost water at 121° and melted at 136 to 137° with decomposition. The neutral equivalent was found to be 109.3 (theoretical 106.5). The sample was allowed to stand open to the air until the weight was constant. The neutral equivalent was then found to be 118 (theoretical for the monohydrate 115.5). This sample was analyzed. Calculated for  $C_8H_{11}O_4N_3 \cdot H_2O$ : C, 41.56; H, 5.67. Found: C, 41.92; H, 5.62.

#### Hexahydrobenzylurea

In a 1-l. round-bottomed flask were placed 113 g (1 mole) of hexahydrobenzylamine, 105 g (1.3 mole) of potassium cyanate, 450 ml of water, and 50 ml of hydrochloric acid, and heated on a steam bath for 1 hour. The yield of white hexahydrobenzylurea was 108.1 g (69.5%), mp 169 to 172°.

#### Nitrosohexahydrobenzylurea

In a 2-l. three-necked flask were placed 78 g (0.5 mole) of hexahydrobenzylurea, 150 ml of ether, 50 g of ice, and 160 g (2.25 mole) of sodium

nitrite in 250 ml water. To this was added dropwise 150 g of concentrated nitric acid and 150 g of ice. Ice was added as needed, to keep the temperature below 5°. The product was filtered off and washed with cold water and the mother liquors were extracted with ether. The ethereal solution was dried and evaporated. The total yield was 47.1 g (51%), mp 118 to 121° with decomposition. The product was recrystallized from ethanol-water mixture to give an analytical sample decomposing at 120 to 123°. Calculated for  $C_8H_{15}O_2N_3$  : C, 51.87; H, 8.16. Found: C, 52.00; H, 8.14.

#### 2-Hexahydrobenzylsemicarbazide

In a 500-ml, three-necked flask were placed 30 g of zinc dust and 100 ml of 50% acetic acid. To this was added dropwise 18.5 g (0.1 mole) of nitrosohexahydrobenzylurea dissolved in 100 ml of glacial acetic acid and 50 ml of water, while the temperature was kept below 20°. After the addition was completed, the mixture was allowed to warm to room temperature and was then filtered. The filtrate was made basic and the product was filtered and washed. The filtrate was extracted with ether, which was then dried and evaporated. The combined yield of the semicarbazide was 11 g (64.5%), mp 154 to 162°. It was recrystallized twice from absolute alcohol to obtain an analytical sample, mp 160.5 to 163°. Calculated for  $C_8H_{17}ON_3$  : C, 56.11; H, 10.01. Found: C, 56.28; H, 10.04.

Hexahydrobenzyl azide was prepared from the semicarbazide in the same manner as was isobutyl azide, but the product has not yet been analyzed.

#### o-Azidobenzenearsonic Acid

This substance, whose preparation was described in Progress Report No. 3, gave the following analysis. Calculated for  $C_6H_6O_3N_3As$  : C, 29.65; H, 2.49; N, 17.28. Found: C, 29.87; H, 2.46; N, 17.45.

#### o-Azidobenzenearsenoxide

This substance, whose preparation was described in Progress Report No. 3, gave the following analysis. Calculated for  $C_6H_4ON_3As_2O$  : C, 34.48; H, 1.93; N, 20.10. Found: C, 34.83; H, 2.08; N, 20.16.

When 0.1 g of this substance was added to a mixture of 2 ml of glacial acetic acid and 4.2 ml of concentrated sulfuric acid, a steady, gentle gas evolution commenced, with the gradual development of a dull bluish-green color which eventually became quite dark. When the resulting mixture was poured on ice a clear, pale, brownish-lilac solution was formed, which

changed overnight to pale, dull green. A dark blue color was formed when the solution was made alkaline (Na OH). An attempt to isolate o-aminobenzenearsonic acid by benzylation followed by acidification gave nothing.

A second preparation of o-azidobenzenearsenoxide was made much as described before, except that the reduction mixture was allowed to stand four days before being worked up. From 1.05 g of o-azidobenzeneearsonic acid there was obtained 0.81 g (90%) of the arsenoxide, mp 167 to 168° dec., with preliminary softening and darkening above 160°.

o-Azidobenzenearsenoxide reacts slowly with concentrated hydrochloric acid at room temperature without visible gas evolution, to produce a light brown oil which is miscible with methylene chloride. The oil effervesced when added to concentrated sulfuric acid and gave a brownish-green color. It is presumed to be o-azidophenyldichloroarsine.

A diazonium solution prepared from 0.18 g of aniline, 0.6 ml of concentrated HCl, and 0.15 g of sodium nitrite in ice-water was added to a part suspension, part solution of 0.418 g of o-azidobenzenearsenoxide in an aqueous solution of 0.13 g of sodium hydroxide and 0.5 g of sodium acetate. Gas evolution began soon after mixing. A yellow-brown solid which was present after the mixture had stood overnight in a refrigerator was filtered off and washed well with methanol. There remained 0.28 g of recovered arsenoxide, mp 167 to 168° dec. Evaporation of the methanol washings left a dark, red-brown gum which was only very slightly soluble in a sodium hydroxide solution, even on warming. No crystalline material could be obtained from either the residue or from the acidified alkali extract. Acidification of the original filtrate caused no precipitation.

#### o-Azidodiphenylsulfoxide

This substance, whose preparation was described in Progress Report No. 3, has now been analyzed. Calculated for  $C_{12}H_9ON_3S$ : C, 59.24; H, 3.73. Found: C, 59.22; H, 3.80.

A solution of 0.7 g of the sulfoxide in 70 g of resorcinol dimethyl ether was heated for 11 hours at 190 to 200°. Gas evolution, which first became noticeable at 160°, had stopped at the end of this time. Evaporation of the mixture left a viscous, black tar. Attempts to separate any basic component as a picrate failed. Boiling (60 to 70°) petroleum ether extracted only a few milligrams of a low-melting, light yellow, acid-soluble substance.

8-Azido-2-naphthol

This substance, whose preparation from the amine was reported in Progress Report No. 3, has given the following analysis. Calculated for  $C_{10}H_7ON_3$ : C, 64.86; H, 3.81. Found: C, 65.05; H, 4.00.

2-amino-2', 5'-diacetoxybiphenyl

The substance of this supposed structure was prepared from o-nitrophenylhydroquinone as described in Progress Report No. 3. It is insoluble in aqueous acid, but 6.5 ml of glacial acetic acid dissolved most of 0.475 g. A mixture of 0.5 ml of concentrated hydrochloric acid, 0.29 g of manganous sulfate monohydrate, and some ice was added, followed by an aqueous solution of 0.13 g of sodium nitrite. The resulting golden solution was filtered from a large amount of precipitated starting material, treated with sulfamic acid to remove excess nitrous acid, and then with 0.13 g of sodium azide. Some gas was evolved and a trace of tan powder, mp 168° was precipitated but no substance other than starting material could be isolated in significant quantity. Several attempts gave similar results; the diazotized solutions did not give a clear-cut, positive coupling test for a diazonium compound.

o-Nitrobenzyl Azide

A solution of 20.65 g of o-nitrobenzyl bromide and 13 g of sodium azide in 400 ml of 95% alcohol and 60 ml of water was allowed to stand in the dark for four months. The orange mixture was then diluted with 900 ml of water, and the organic material was extracted with 600 ml of ether in four portions and dried over several successive portions of calcium chloride. Concentration gave 18 g of oil, which separated into two layers upon cooling to 0°. The lower layer was distilled twice at 1.4 mm to give 8 g (47%) of straw-colored liquid, bp 107 to 111° [reported 121 to 122°/2 mm by Y. Yushchenko, C. A., 31, 3467 (1937); Mem Inst Chem Ukrain Acad Sci, 2, 195-205 (1935)].

The azide reacted vigorously with concentrated sulfuric acid. When a mixture of 1.4 g of the azide and 140 ml of decalin was heated, solution became complete at 60° and the solution slowly turned to an almost opaque red when it was kept near the boiling point for 8-1/2 hours to complete the evolution of nitrogen. The solution was filtered hot and then deposited 0.65 g of brown powder, mp 108 to 122°, on cooling. Investigation is not yet complete.

Decomposition of 2-Azido-3,4,5-trimethoxybenzotrile

A solution of 0.2 g of 2-azido-3,4,5-trimethoxybenzotrile in 20 ml of decalin was refluxed for 1-1/2 hours. During the initial heating, gas evolution began at 160°. The hot decalin solution was filtered and cooled. The amorphous precipitate which separated, together with the residue from the evaporation of the decalin filtrate, gave only tarry material on attempted recrystallization.

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