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

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Project 2202

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ABSTRACT

1. Part of the work so far accomplished on this project has been organized for presentation at the National Meeting of the American Chemical Society in September, 1956.

2. For the development of a method for preparing azides from aliphatic hydrazine derivatives, isopropyl, cyclohexyl, and n-butylhydrazine have been sought by conventional reactions. The first has been converted to 2-isopropylsemicarbazide, and the preparation of other acyl derivatives has begun.

3. For the investigation of the interaction of the azide group with a diazo group, 8-azido-2-naphthol has been coupled with benzenediazonium chloride to give 1-phenylazo-8-azido-2-naphthol.

4. α -Styryl, β -styryl, and cyclohexenyl azides are in the process of preparation by way of the appropriate chlorohydrins or oxiranes, in order to provide information on the vinyl azide—triazole isomerization.

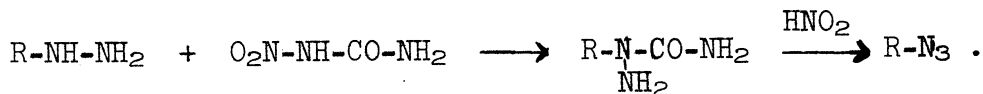
OBJECTIVES

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

INTRODUCTION

Research assistants whose work is described in this report are Francis Brady, Morton Hoffman, Barbara May, and Roger Westland.

For a preparation of alkyl azides by a method that might become a useful alternate to the alkyl halide—sodium azide process, a method involving the reaction of 2-alkylsemicarbazides was developed, and described in previous Progress Reports. In the examples given, the semicarbazides were prepared from the corresponding amines via the nitroso ureas. To demonstrate that other starting materials are possible, and to extend the number of examples of the method, the preparation of some 2-alkylsemicarbazides and related 1-alkyl-1-acylhydrazines from alkylhydrazines has been undertaken.

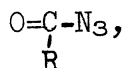


Of several examples, the isopropyl series has been carried the farthest, and the initial preparation of 2-isopropylsemicarbazide is being augmented prior to attempting the conversion to azide.

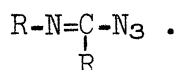
The preparation of 8-azido-2-naphthol has been described in earlier Progress Reports. It was intended to make use of the activating influence of the 2-hydroxyl on the 1-position to introduce other functional groups peri to the azido group, where they would be held in a favorable position for cyclic interaction. An azo group has now been introduced by coupling with benzene-diazonium ion, and the resulting red dye, which appears to be 1-phenylazo-2-hydroxy-8-azidonaphthalene, is being characterized and investigated. Nitration of 8-azido-2-naphthol is currently being attempted, and the selective reduction to provide 8-azido-2-hydroxy-1-naphthylamine is planned.



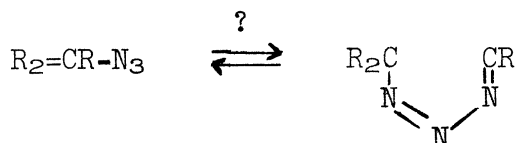
The interaction of an azido group with an α - β double bond varies from inertness in the case of acyl azides,



to rapid spontaneous cyclization in the case of carbamyl azides,



The related case of vinyl azides, $\text{R}_2\text{C=CR-N}_3$, which might be expected to cyclize to triazoles, is ambiguous on the basis of the scanty information presently available. To resolve this situation, the synthesis of several vinyl azides, notably α - and β -styryl and cyclohexenyl, is underway. It is hoped to be able to establish the structures of the products as cyclic or noncyclic by spectrographic means and to study the conditions under which the azides might be induced to form triazoles.



In this connection, the synthesis of thioacyl azides, R-CS-N_3 , is also being attempted. However, although this is closely connected with the project and is in fact an outgrowth of it, it is not at present being supported by it since the student involved is already employed in teaching for the maximum allowable time.

EXPERIMENTAL

ATTEMPTED LARGE-SCALE PREPARATION OF ISOPROPYLHYDRAZINE

(Hydroxylamine-O-Sulfonic Acid Method).—

Cf., G. Gever and K. Hayes, J. Org. Chem., 14, 813 (1949).

The synthesis described in the above reference was carried out on tenfold the authors' quantities. An attempt to isolate the alkylhydrazine as the free base from the salt cake rather than by means of the oxalate salt resulted in highly unfavorable work-up conditions caused by large quantities of inorganic salts, and no product was obtained.

ISOPROPYLHYDRAZINE

A. Lithium Aluminum Hydride Reduction of Acetone Hydrazone.—To a stirred solution of 14.4g (0.3 mole) of LiAlH_4 in 150 ml of refluxing tetrahydrofuran was slowly added (2 hr) 14.4g (0.2 mole) of acetone hydrazone. Refluxing was continued for about 15 hr, at which time the reaction mixture appeared milky white. Successive 15-ml portions of water, 15% sodium hydroxide solution, and water were cautiously added. Ether was added and the ether-tetrahydrofuran solution was filtered from the inorganic salts. The filtrate

was dried twice over KOH pellets and distilled. The product distilled at 106° - 110° , wt 2.7 g (18%).

B. Catalytic Reduction of Acetone Hydrazone.—A solution of 5 g (0.07 mole) of acetone hydrazone, 5.8 ml of conc'd. hydrochloric acid, and 25 ml of water was hydrogenated over reduced platinum oxide catalyst in a Parr shaker. After 3.5-4 hours the theoretical amount of hydrogen had been absorbed (5.5 lb). The mixture was filtered and concentrated in vacuo after the addition of benzene. The resulting salt cake was triturated with ether and filtered, giving white crystals, wt 7.0 g (approx. theoretical for hydrochloride). One gram was recrystallized from ether-alcohol mixture, giving a first crop of 0.6 g of glistening platelets, mp 105° - 115° (reported mp 112°). The crystalline form of the product distinguished it from hydrazone monohydrochloride, which forms needles. To the remaining 6.0 g of hydrochloride was added a solution of 4.0 g of sodium hydroxide in 10 ml of water and the resulting mixture was distilled at atmospheric pressure. The liberated free base was dried twice over potassium hydroxide pellets, using dry ether for transfer washes. The ether solution was distilled to give the following fractions (weights after removing ether): (1) 0.2 g, bp $< 100^{\circ}$; (2) 3.5 g (80% yield using 0.06 moles as theory), bp 100° - 106° . The dibenzoyl derivative prepared from fraction (1) had mp 160° - 161° (reported mp 161.5°). The above constants are inconsistent with either hydrazine or acetone azine compounds.

On a somewhat larger scale, 30 g (0.417 mole) of acetone hydrazone was hydrogenated at three atmospheres of hydrogen, using 35 ml of conc'd. hydrochloric acid and 100 ml of water. The initial hydrogen uptake rate was comparable to the smaller scale reaction in that after 3 hr, 30% of the theoretical volume of hydrogen had been absorbed. Complete hydrogen uptake occurred only after about 30 hr of shaking with the addition of fresh catalyst after about 20 hr. Initial distillation at atmospheric pressure afforded a very small quantity of low-boiling liquid which was identified (by its 2,4-dinitrophenylhydrazone) as acetone. No isopropyl alcohol could be detected. Benzene was added and the remaining mixture was concentrated under reduced pressure to a salt cake which was triturated with benzene, filtered, and dried in a vacuum desiccator; wt 42.6 g (92% crude salt). One-half gram of the salt was treated with 1.5 g of benzoyl chloride to give 1.1 g of dry derivative, mp 130° .

Free base: The above salt was treated with 17 g of sodium hydroxide and 20 ml of water and the liberated base was distilled. The wet distillate was dried over solid potassium hydroxide and distilled. Fraction 1 weighed 13.4 g, bp 99° - 104° ; fraction 2 weighed 13 g, bp 104° - 105° ; total yield 26.4 g (87%).

REACTIONS OF ISOPROPYLHYDRAZINE

Reaction of Ethyl Chlorocarbonate with Isopropylhydrazine.—To a solution of 1.5 g (0.02 mole) of isopropylhydrazine in a few ml of 10%

potassium carbonate was added 2.5 g of ethyl chlorocarbonate. The reaction mixture was shaken intermittently for 15-20 minutes. The separated oil, which had no acid chloride odor, was taken up in ether. The ether extract was dried over anhydrous sodium sulfate, decanted, and distilled. The product was distilled in vacuo (water aspirator) giving two fractions: (1) 0.5 g, bp 80°; (2) 0.5 g, bp 150°-155°. The products have not yet been characterized further.

Reaction of Isopropylhydrazine with Cyanic Acid.—To a stirred solution of 3.5 g (0.049 mole) of isopropylhydrazine and 4.0 g (0.05 mole) of potassium cyanate in 25 ml of water was slowly added a solution containing 3.0 g of glacial acetic acid in 30 ml of water during a 6-hr period. The reaction was stirred overnight and then allowed to stand at room temperature until a total reaction time of 24 hr had elapsed. The reaction mixture was concentrated very cautiously in vacuo, using benzene to help remove the water at a lower temperature. The residual salt cake was dried overnight at high vacuum and subsequently dissolved in 20 ml of hot ethanol. Three crystalline crops were obtained, all of which contained potassium acetate. The final mother liquor provided additional crystals in addition to an oil; neither has been characterized at this time, since the method obviously was not suitable for synthesis of 2-isopropylsemicarbazide.

Reaction of Isopropylhydrazine with Nitrourea.—A mixture of 3.0 g (0.041 mole) of isopropylhydrazine, 4.5 g (0.0425 mole) of nitrourea, and 25 ml of water, which afforded a single phase within minutes, was allowed to stand at room temperature for 36 hr. There was a steady evolution of gas (presumably N₂O) during at least the first 24 hr, with apparent cessation after 36 hr. The solution was filtered and concentrated in vacuo (with benzene addition) to dryness. The solid was triturated with benzene and filtered to give sticky, colorless crystals; wt 4.0 g, mp 93°-100° (dec.). The solid was recrystallized from ethanol-water mixture giving 1.0 g of powdery crystals, mp 214°-215° (clear melt, softens at 208°). Two additional crops (very small in quantity) of the above solid, which was difficultly soluble in absolute ethanol, were filtered from the mother liquors. The final mother liquor then afforded a mass of larger, softer crystals, wt 1.0 g, mp 128°-130°. The final mother liquor taken to dryness gave 1.5 g of crude, off-white crystals; recrystallization from benzene gave 1.1 g, mp 121°-125°. The 128°-130° crop was recrystallized from ethanol, and then had mp 131°-133° (clear melt); mixed mp with nitrourea, 88° (dec.). This crop and the residue from evaporating its mother liquor were combined and recrystallized from benzene, affording 0.8 g. This substance is presumed to be 2-isopropylsemicarbazide, pending analysis.

Reaction of 2-Isopropylsemicarbazide with Benzaldehyde.—Mixing 100 mg of the low-melting product from the foregoing reaction, which was presumed to be 2-isopropylsemicarbazide, with 100 mg of benzaldehyde resulted in near homogeneity followed by heat evolution and solidification. Ether was added and the mixture was filtered, giving 130 mg of solid, mp 138°-140°. It was recrystallized from 50% ethanol, and then formed needles, mp 140°-144°. Analysis is pending.

CYCLOHEXANONE HYDRAZONE

To 250 g of stirred 64% aqueous hydrazine was slowly added 196 g (2.0 moles) of cyclohexanone. The mixture was refluxed for about 5 hr and the water was then removed azeotropically with benzene. The distillation was continued to remove the benzene and hydrazine (bp 120°), which were followed by cyclohexanone hydrazone at 130°/5 mm; yield 160 g (74%).

REACTION OF ISOPROPYLHYDRAZINE WITH ETHYL ACETATE

A solution of 3 g (0.041 mole) of isopropylhydrazine and 3.6 g (0.041 mole) of ethyl acetate in 30 ml of dry ether was allowed to stand at room temperature for about 20 hr and then refluxed for another 15 hr. Distillation of the ether was followed by a significant quantity of ethyl acetate. The conditions were apparently not vigorous enough to cause reaction, and it is planned to try stronger methods.

PREPARATION OF BUTYL HYDRAZINE

The ultimate product of this series of experiments is to be n-butyl azide, prepared from the corresponding hydrazine. In all cases, the general preparation of methyl hydrazine sulfate, as given by Blatt, Org. Syn, Coll. Vol. II, Page 395, was modified. Benzalazine was reacted with n-butyl bromide, butyl benzenesulfonate, and butyl sulfate.

Reaction of n-Butyl Bromide with Benzalazine.—Benzalazine (20 g, 0.096 mole), 45 ml of benzene, and 0.21 mole (28.77 g, 21.5 ml) of n-butyl bromide were mixed and refluxed over a steam bath for 4 days. A large quantity of yellow solid separated on cooling; wt 17.5 g. A small amount of it was dried by pressing between filter paper, and melted over the range 77°-87°. A mixed melting point with pure benzalazine gave no depression, and the product was therefore assumed to be recovered benzalazine.

Preparation of n-Butyl Benzenesulfonate.—Following the directions of Hahn and Walter, Ber., 54, 1540, for the preparation of propyl benzenesulfonate, 1 mole (74 g, 92.5 ml) of n-butyl alcohol was mixed with 176 g (130 ml) and 1000 ml ether. Crushed KOH (120 g) was added slowly while the temperature of the mixture was kept at 3°-4°C by immersion in an ice bath. The mixture was mechanically stirred and kept at the low temperature overnight. The inorganic material was extracted with water and the ether extract washed with water and dried over anhydrous sodium sulfate. The ether solution was filtered and the ester distilled under reduced pressure; bp 134°-135°/1.5 mm, wt 151.6 g (70.8% yield).

Reaction of n-Butyl Benzenesulfonate with Benzalazine.—Benzalazine (10 g, 0.048 mole), 30 ml of benzene, and 0.10 mole of n-butyl benzenesulfonate (21.4 g, 18.2 ml) were mixed and refluxed on a steam bath for a week. The mixture turned appreciably dark and a small amount of solid material separated when the mixture was cooled. Some of the solid was isolated and dried between filter paper; it melted over the approximate range 77°-87° and gave no depression of melting point when mixed with pure benzalazine. The mixture was steam distilled until no more benzaldehyde came over in the distillate. The residual liquor was left to stand overnight with a little bit of benzaldehyde in order to remove any hydrazine remaining. This material assumed to contain n-butylhydrazine, is now being worked up.

Preparation of n-Butyl Sulfate.—n-Butyl sulfate was prepared according to the directions of Barkenbus and Owen, J.A.C.S., 56, 1204-6 (1934). n-Butyl chlorosulfonate was prepared by the action of 1 mole (74 g, 93 ml) of n-butyl alcohol added slowly and with stirring to 1 mole (135 g, 82 ml) of sulfuric chloride which had been cooled in ice water. All the HCl produced was removed by allowing the reaction to come to room temperature and bubbling air, which had been previously dried in conc'd. sulfuric acid through the mixture. n-Butyl sulfite was prepared by adding slowly and with stirring 1.1 moles of thionyl chloride (131 g, 80 ml) to 2.2 moles (163 g, 205 ml) of n-butyl alcohol. The HCl was removed in a similar fashion and the crude chlorosulfonate mixture was added slowly to the crude sulfite solution and heated to about 130°-140°C. The solution was extracted with ether, washed with sodium carbonate solution, again with water and dried over anhydrous magnesium sulfate. The ether was evaporated and the n-butyl sulfate distilled at reduced pressure; bp 91.2°-93.0°C/1 mm, wt 65.8 g (31.4% yield). Reaction of n-butyl sulfate with benzalazine is currently underway.

DIAZO COUPLING WITH 8-AZIDO-2-NAPHTHOL

8-Azido-2-naphthol was treated in sodium hydroxide solution with an equimolar quantity of aqueous benzenediazonium chloride. An immediate red precipitate formed. The filtered, washed, and dried product showed the usual characteristics of an azide—decomposition with conc'd. sulfuric acid and flashing when heated suddenly. Recrystallization from alcohol was unsatisfactory; the material turned brown on heating. Acetone-water mixture gave a satisfactory product, which, however, did not melt, but decomposed slowly at temperatures dependent on the rate of heating. It is being analyzed.

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