zene was added 0.01 mole of ethyl isocyanate. The mixture solidified. Crystallization from the appropriate solvent gave the pure compound, Table I.

CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

Azidocarbonyl Compounds. IV. Acid Catalysis of α-Azido-Carboxylic Acids and Their Esters[1]

J. H. BOYER AND J. STOCKER

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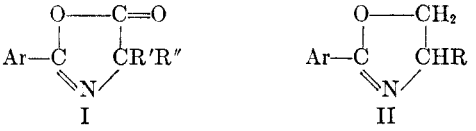
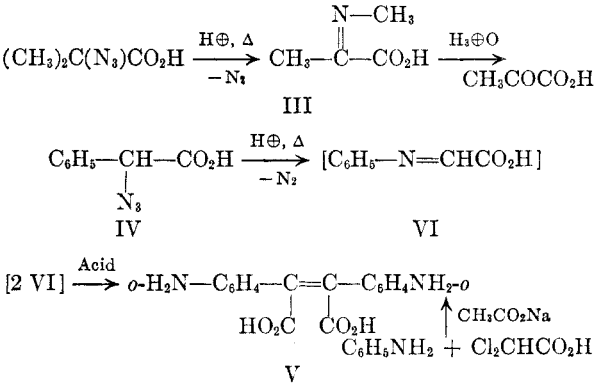
An interest in 5-ketoöxazolines (I) (azlactones) was a natural outgrowth of the discovery of the formation of oxazolines (II) from certain aromatic aldehydes and azidohydrins.[2] In order to determine the possibility of realizing an acid-catalyzed reaction between aldehydes and α-azidoacids, combinations of benzaldehyde containing sulfuric acid with α-azidoacetic, with α-azidoisobutyric, and with α-azido-α-phenylacetic acids were studied. Azlactones were not detected in the reaction products which were investigated not only for the oxazolone itself but also for its hydrolysis products as well as possible condensation products with benzaldehyde, present in excess. Apparently the presence of the aldehyde was unimportant since each azide gave the same product in acid-catalyzed reactions carried out in the absence of benzaldehyde.



I II

Acid catalysis resulted in the evolution of nitrogen with the apparent migration of methyl carbanion from carbon to nitrogen and the formation of the Schiff's base (III) from α-azidoisobutyric acid. Subsequent hydrolysis allowed the formation of pyruvic acid, isolated as its dinitrophenylhydrazone.

Competition between the migration of hydrogen and of the phenyl group apparently favored the latter in the case of α-azido-α-phenylacetic acid (IV) and its ethyl ester.[3] The product, *o,o'*-diaminostilbenedicarboxylic acid (V) (both geometric isomers assumed present) was previously obtained from the anil (VI) of glyoxylic acid upon warming in acetic acid and from treating aniline with dichloroacetic acid in a warm sodium acetate solution.[4]



III

IV VI

V

The infrared spectrum of a sample of the product (V) obtained from α-azido-α-phenylacetic acid was identical with that from a sample obtained from dichloroacetic acid and aniline.

EXPERIMENTAL[5]

Acid decomposition of α-azido-α-phenylacetic acid and its ethyl ester. α-Azido-α-phenylacetic acid[6] (1.02 g., 0.006 mole) or the ethyl ester[3] (1.021 g., 0.005 mole) was dissolved in 20 ml. of warm benzene and added dropwise to a mixture of 1.4 ml. of concentrated sulfuric acid and 15 ml. of benzene, the latter maintained at *ca.* 75° and stirred mechanically. When the reaction appeared complete, the entire mixture was poured into 20–25 g. of ice and water. The mixture was filtered by suction to remove traces of scum, and the aqueous layer was separated. Solid sodium carbonate was added in small portions, with frequent stirring, to adjust the solution to *p*H 2–3 (maximum precipitation). The yellow-brown precipitate was filtered, thoroughly water-washed, and dried in a vacuum for 24 hours. Additional material was obtained by evaporation of the filtrate, crude yield 54%. The m.p. was indeterminate, darkening of the material began about 180°, deepening to a black sintered product about 300°.[4]

The product obtained either by Heller's procedure[4] or by the present procedure was poorly soluble in water, slightly soluble in alcohol, very soluble in aqueous base (0.1 *N* or greater), including pyridine (insoluble in anhydrous pyridine). Solutions in all bases, organic or inorganic, required the addition of acid for reprecipitation. It was very soluble in dimethylformamide from which it was not easily recovered, very slightly soluble or insoluble in ethyl ether, benzene, acetone, and chloroform. Solution of the material, crude or otherwise, in 0.1 *N* sodium hydroxide and reprecipitation with dilute hydrochloric acid yielded a product with apparently unchanged properties.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 64.41; H, 4.73; N, 9.39. Calc'd for $C_{16}H_{14}N_2O_4 \cdot {}^1/_2H_2O$: C, 62.53; H, 4.92; N, 9.12. Found: C, 62.88; H, 5.51; N, 9.42. Repeat: C, 62.41; H, 4.96; N, 8.80.

The following medium to strong absorption peaks in cm.$^{-1}$ for the product (V) from either aniline and dichloroacetic

(1) A grant from the American Association of Arts and Sciences is gratefully acknowledged.

(2) J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955).

(3) Only hydrogen migration was detected from pyrolysis of ethyl α-azido-α-phenylacetate (J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, **75**, 1642 (1953)).

(4) G. Heller, *Ann.*, **332**, 268 (1904); **358**, 354 (1907); **375**, 266 (1910).

(5) Melting points are corrected. Elemental analyses by Microtech laboratories, Skokie, Illinois. Infra-red analyses by S. P. Sadtler and Son, Inc., Philadelphia, Pa. and by Mr. R. T. O'Connor, Southern Regional Research Laboratory, New Orleans, Louisiana.

(6) A. Darapsky, *J. prakt. Chem.*, 99, 179 (1919).

acid or from phenylazidoacetic acid are: 3390, 3310, 3018, 1724, 1622, 1590, 1522, 1495, 1362–1350, 1187, 833, 757. These values were obtained from potassium bromide wafers of the samples.

The material did not sublime and was insoluble in camphor. Permanaganate oxidation readily occurred; copious precipitation of manganese dioxide was observed. No organic product was isolated.

Acid decomposition of α-azidoisobutyric acid. α-Azidoisobutyric acid (4.50 g., 0.0349 ml.), a few hundred mg. at a time, was added to 10 ml. of conc'd H_2SO_4 maintained at 65–75°, with stirring. The chemical reaction was very active but easily controlled. When gas ceased to evolve, the reaction mixture was poured into 50 ml. of ice-water. The reaction mixture was placed on the steam-bath overnight, was cooled to room temperature, and filtered from a small amount (0.359 g.) of gray solid. The filtrate was extracted four times with ether. The combined ether extracts were evaporated in an air stream until all ether had been removed. The remaining liquid (1.8 g.) was treated for a ketone derivative. It was dissolved in 5 ml. of 95% EtOH, filtered of a trace of solid, added to 10 ml. of 2,4-dinitrophenylhydrazine reagent, warmed to 50°, and cooled. The DNP of pyruvic acid separated an orange-yellow solid, m.p. 214–218° (mixture m.p. gave no depression), wt. 0.628 g. (7% yield).

Attempts to prepare α-azidodiphenylacetic acid from α-bromodiphenylacetic acid as well as the diethyl acetal of azidoacetaldehyde from the diethyl acetal of bromoacetaldehyde and sodium azide were unsuccessful.

CHEMISTRY DEPARTMENT
TULANE UNIVERSITY
NEW ORLEANS 18, LOUISIANA

A New Synthesis of 1-Methyl-3-(4′-dimethylaminobutyl)-piperidine

ARTHUR P. PHILLIPS

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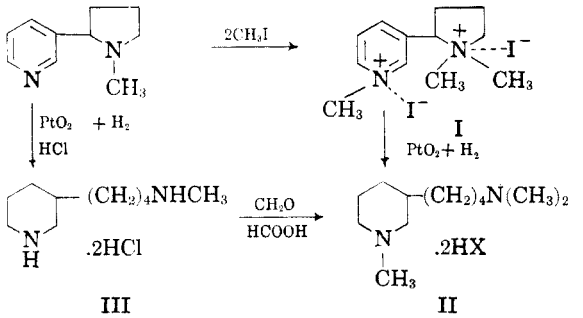
Catalytic hydrogenation of nicotine dimethiodide (I) with Adams catalyst gave good yields of 1-methyl-3-(4′-dimethylaminobutyl)piperidine (II) as its dihydriodide.[1]



Both II and its bis-metho quaternary salts have been found to be potent hypotensive ganglionic blocking agents in laboratory animals.[1,2]

An alternative route has now been devised for the preparation of II. Nicotine dihydrochloride is reduced to octahydrometanicotine (III)[1,3,4] which then is methylated by the Eschweiler[5]-Clarke[6] procedure to yield II.

The new synthesis has several advantages for the larger scale preparations which were necessary in order to obtain enough material for clinical evaluation. One of the limiting factors in larger runs is the amount of nicotine derivative which can conveniently be reduced at one time in the catalytic hydrogenation apparatus. The original route used the relatively costly and heavy methyl iodide which contributes more than half the weight of the intermediate I, as iodide. Since the *dihydriodide* of II is not suitable for clinical purposes, use of iodide was neither necessary nor desirable. Several attempts to circumvent the use of iodide by quaternizing nicotine with methyl chloride in an autoclave under pressure, prior to reduction, gave unsatisfactory results, presumably because of incomplete reaction with the methyl chloride.

The conversion of I to II or of nicotine to III requires, presumably, that the debenzylative-like cleavage of the pyrrolidine ring should *precede* hydrogenation of the pyridine ring. Both the pyrrolidine ring cleavage and the pyridine ring hydrogenation should be accelerated when the nitrogens are cationic. Quaternization seems to favor the preliminary debenzylative-like ring-opening somewhat more efficiently than does the making of the nitrogens cationic through simple salt formation with hydrochloric acid. Thus similar catalytic hydrogenations gave about 90% of II from I and only about 70% of the open chain product,[7] III, from nicotine dihydrochloride.

EXPERIMENTAL

Reduction of nicotine dihydrochloride. Catalytic hydrogenation of 16 g. (0.1 mole) of pure *l*-nicotine in 150 cc. of ethanol containing 0.3 mole of hydrogen chloride and 0.5 g. of Adams catalyst was carried out in a Burgess-Parr type machine at four atmospheres of hydrogen pressure and room temperature. Reduction was rapid and 0.35–0.4 mole of hydrogen was absorbed within three hours. The filtrates were concentrated after removal of the catalyst. The product, octahydrometanicotine dihydrochloride (III), was purified by recrystallizations from ethanol–ethyl acetate, and from isopropyl alcohol. The yield of pure product was 15–17 g. (60–70%); m.p. 202–203°.

Equally successful results were obtained on a much larger scale using a high pressure rocking-bomb hydrogenator.

Methylation of III. A 34-g. portion (0.2 mole) of the free base, liberated from the dihydrochloride, III, was mixed carefully and with cooling with 70 cc. of 98% formic acid.

(1) Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).
(2) Norton and Phillips, *Nature*, **172**, 867 (1953).
(3) Windus and Marvel, *J. Am. Chem. Soc.*, **52**, 2543 (1930).
(4) Harlan and Hixon, *J. Am. Chem. Soc.*, **52**, 3385 (1930).
(5) Eschweiler, *Ber.*, **38**, 880 (1905).
(6) Clarke, Gillespie ,and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(7) The authors of references (3) and (4) claim that catalytic hydrogenation of nicotine dihydrochloride gave 75% of octahydrometanicotine (III) and 25% of hexahydronicotine.