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.

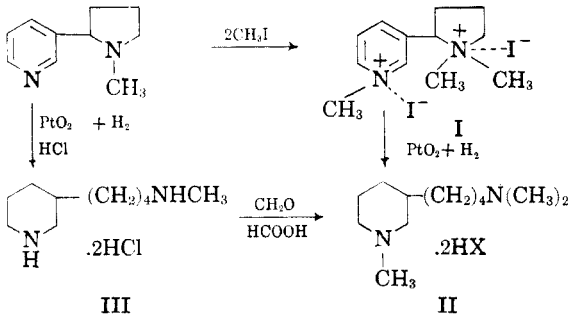
CHEMISTRY DEPARTMENT
TULANE UNIVERSITY
NEW ORLEANS 18, LOUISIANA

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

ARTHUR P. PHILLIPS

Received April 20, 1956

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.

After adding 60 cc. of 37% formalin the mixture was heated for four hours at 100°. Another 70 cc. of 98% formic acid and 50 cc. of 37% formalin were added and heating was continued for six hours. The reaction mixture was acidified with 60 cc. of concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The residue was purified by several recrystallizations from isopropyl alcohol and gave 50–52 g. (90–95%) of II dihydrochloride, m.p. 239–240°.

WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

Steric Factors in the Hydrolysis of Potassium Dinitrochlorobenzenesulfonates

JACK RADELL, LEONARD SPIALTER, AND RICHARD C. JARNAGIN

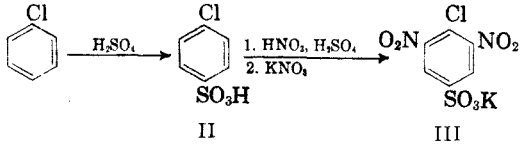
Received April 20, 1956

The sulfonate group in potassium 2-chloro-3,5-dinitrobenzenesulfonate, in contrast to its isomer potassium 4-chloro-3,5-dinitrobenzenesulfonate, hydrolyzes readily under nonequilibrium conditions. This was deduced from an examination of the mixture of these isomers obtained by the monosulfonation of chlorobenzene followed by subsequent dinitration. It is suggested that steric factors play an important role in the differential reactivity of these compounds.

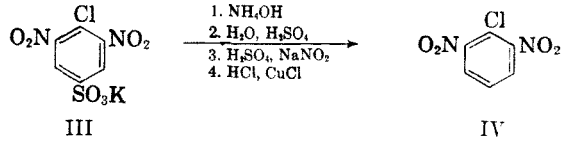
DISCUSSION

An attempt to prepare 2,6-dinitrochlorobenzene (IV) directly from potassium 4-chloro-3,5-dinitrobenzenesulfonate (III)[1] showed that the 4-chloro compound III contained significant amounts of the isomer, potassium 2-chloro-3,5-dinitrobenzenesulfonate (V). Upon refluxing with aqueous sulfuric acid, V but not III could be hydrolyzed under nonequilibrium conditions. However, refluxing under equilibrium conditions resulted in no detectable quantity of either dinitrochlorobenzene isomer.

In the recommended procedure[1,2] for the preparation of potassium 4-chloro-3,5-dinitrobenzenesulfonate (III), the first step involves the sulfonation of chlorobenzene, followed by dinitration and isolation of the potassium salt (III). 2,6-Dinitrochlorobenzene (IV) may be prepared[1,2] from III by the circuitous route involving conversion of the chlorine atom to an amino group, then hydrolysis of the sulfonate function followed by diazotization of the amino group and replacement with a chlorine atom.



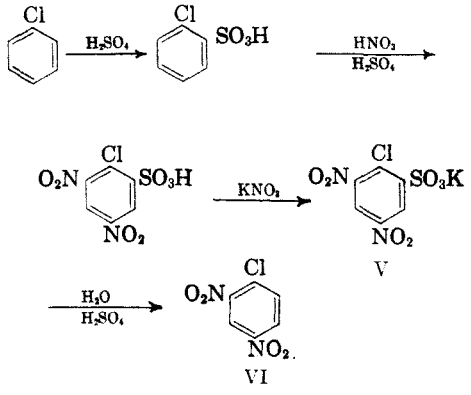
II III



III IV

Since hydrolysis of the sulfonate group in III would lead directly to the desired product, IV, this approach was undertaken. No information is reported on this hydrolysis in the literature.

From the refluxing aqueous sulfuric acid solution of potassium dinitrochlorobenzenesulfonates (I) was steam-distilled a light yellow water-insoluble solid, under nonequilibrium conditions, which was identified as 2,4-dinitrochlorobenzene. Most of the starting material (69.3%) could be accounted for by the recovery of pure III. These results indicate the sulfonation of chlorobenzene resulted in the formation of 2-chlorobenzenesulfonic acid as well as the 4-chlorobenzenesulfonic acid. The reactions converting 4-chlorobenzenesulfonic acid to III, which failed to hydrolyze, have been described above. The 2-chlorobenzenesulfonic acid that formed underwent a similar series of reactions. The latter was nitrated to 2-chloro-3,5-dinitrobenzenesulfonic acid which was isolated as a potassium salt (V). Compound V upon hydrolysis formed 2,4-dinitrochlorobenzene (VI).



The attempt to hydrolyze the same material (I) by simple refluxing with aqueous sulfuric acid failed. This indicated that the equilibrium is far on the side of the sulfonic acid and unfavorable for the hydrolysis of 2-chloro-3,5-dinitrobenzenesulfonate (V). However, under nonequilibrium conditions where the product is removed by steam-distillation as soon as it is formed, complete hydrolysis of V is accomplished. Although the equilibrium is not very favorable it must be established rather readily since the hydrolysis was complete in two hours.

No 2,6-dinitrochlorobenzene (IV) steam-distilled during the 26 hours the aqueous sulfuric acid solution was refluxed, nor could any be isolated from

(1) H. P. Schultz, *Org. Syntheses*, **31**, 45 (1951).
(2) F. D. Gunstone and S. H. Tucker, *Org. Syntheses*, **32**, 23 (1952).