Anal. Calcd. for $C_{16}H_{14}N_5Cl\cdot HCl$: C, 55.2; H, 4.3; N, 20.1. Found: C, 55.1; H, 4.5; N, 20.3.

2-(1-*p*-Chlorophenyl-3-guanidino)-6-chloro-4-methylquinazoline hydrochloride was obtained by method A as cream-colored micro-crystalline needles melting at 261–262.5° with decomposition in 40% yield.

Anal. Calcd. for $C_{16}H_{13}N_5Cl_2\cdot HCl$: C, 50.2; H, 3.7; N, 18.3. Found: C, 49.9; H, 3.9; N, 18.4.

Acknowledgment.—The authors wish to express their gratitude to Dr. J. D. Thayer of the Venereal Disease Experimental Laboratory, U. S. Public Health Service, Chapel Hill, North Carolina, for chemotherapeutic evaluation of certain of these compounds, the results of which are in preparation for publication elsewhere. Appreciation is also expressed to the American Cyanamid Company for gifts of chemicals used in portions of this work.

CHAPEL HILL, NORTH CAROLINA

RECEIVED NOVEMBER 5, 1951

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MIAMI]

The Preparation of Sperimidine Trihydrochloride (1,8-Diamino-4-azaoctane Trihydrochloride)

BY MORRIS DANZIG[1] AND HARRY P. SCHULTZ

Spermidine trihydrochloride has been prepared in 11% over-all yield through the formation of γ-aminobutyronitrile, N-(2-cyanoethyl)-γ-aminobutyronitrile and spermidine trihydrochloride.

Recent work[2–6] has redirected attention to spermidine. Although two syntheses[7,8] have already been reported, the processes are long, arduous and give low yields. The purpose of this investigation was to develop a shorter synthesis of spermidine trihydrochloride with a better over-all yield.

This three-step synthesis consists of ammonolysis of γ-bromobutyronitrile to γ-aminobutyronitrile (I), the cyanoethylation of γ-aminobutyronitrile to N-(2-cyanoethyl)-γ-aminobutyronitrile (II), followed by reduction of N-(2-cyanoethyl)-γ-aminobutyronitrile hydrochloride to spermidine trihydrochloride (III).

$$H_2N(CH_2)_3CN \quad \text{I}$$

$$NC(CH_2)_2NH(CH_2)_3CN \quad \text{II}$$

$$H_2N(CH_2)_3NH(CH_2)_4NH_2\cdot 3HCl \quad \text{III}$$

Most of the γ-aminobutyronitrile used was prepared by mixing a 30 to 1 molar ratio of liquid ammonia and γ-bromobutyronitrile in a steel bomb; the reaction was completed in 48 hours at room temperature. Ammonolysis of γ-chlorobutyronitrile gave no γ-aminobutyronitrile. A small amount of γ-aminobutyronitrile was also prepared by the hydrolysis of γ-phthalimidobutyronitrile according to the procedure of Goldberg and Kelly.[9]

The cyanoethylation of γ-aminobutyronitrile proceeded readily in ether solution at room temperature. Since the hydrochloride salt of N-(2-cyanoethyl)-γ-aminobutyronitrile was to be reduced this salt was prepared by adding alcoholic hydrogen chloride to the ether solution of N-(2-cyanoethyl)-γ-aminobutyronitrile, and was reduced in ethanolic hydrogen chloride over platinum oxide catalyst. Reduction was initiated at room temperature at approximately 4 atmospheres after which it was brought to completion at 70°. Deviations from this procedure yielded no spermidine trihydrochloride, only high melting solids, although in all cases the theoretical amount of hydrogen was always absorbed by the reaction mixture.

Experimental Procedures

γ-Aminobutyronitrile.—Into a glass cylinder were placed 26.1 g. (0.18 mole) of γ-bromobutyronitrile[10] and about 90 g. (5.3 moles) of liquid ammonia. The glass container was sealed into a stainless steel bomb[11] and kept at room temperature for 48 hours occasionally rocked by hand. At the end of the reaction time the residue in the bomb was placed in 50% sodium hydroxide solution then extracted with three 75-ml. portions of ether. The ether solution was dried and distilled. The yield of γ-aminobutyronitrile, boiling at 80–82° (10 mm.), was 6.3 g. (42%). The hydrochloride of a small sample of γ-aminobutyronitrile was made and was found to melt at 143–145°. Goldberg and Kelly[9] reported a boiling point of 95–97° (20 mm.) for γ-aminobutyronitrile and a melting point of 138–140° for γ-aminobutyronitrile hydrochloride.

N-(2-Cyanoethyl)-γ-aminobutyronitrile.—A 200-ml. flask was fitted with stirrer, condenser and addition funnel, and 6.3 g. (0.075 mole) of γ-aminobutyronitrile and 10 ml. of ether were placed in it. Acrylonitrile (4.0 g., 0.075 mole) was added dropwise for two hours to the stirred solution, temperature being maintained at 30°. After all acrylonitrile had been added, the solution was stirred at room temperature for 14 hours and for 1 hour on a steam-bath. Ethanolic hydrogen chloride was then added to the cooled ether solution until precipitation was complete. The precipitate was filtered and recrystallized from 90 ml. of absolute ethanol, giving 11.5 g. (88.5% of theory) of N-(2-cyanoethyl)-γ-aminobutyronitrile hydrochloride melting at 133–134°.

Anal. Calcd. for $C_7H_{12}N_3Cl$: N, 24.2. Found: N, 24.3, 24.2.

Spermidine Trihydrochloride.—A 500-ml. glass Parr pressure flask was charged with 5.0 g. (0.029 mole) of N-(2-cyanoethyl)-γ-aminobutyronitrile hydrochloride, 0.2 g. of platinum oxide catalyst,[12] 20 ml. of ethanolic hydrogen

(1) Abstracted in part from a thesis by Morris Danzig, presented to the Graduate Faculty of the University of Miami in partial fulfillment of the requirements for the degree of Master of Science in Chemistry, June, 1951.

(2) M. Silverman and E. Evans, *J. Biol. Chem.*, **150**, 265 (1943).

(3) M. Silverman and E. Evans, *ibid.*, **154**, 521 (1944).

(4) A. Miller and L. Peters, *Arch. Biochem.*, **6**, 281 (1945).

(5) E. Snell and E. Herbst, *J. Biol. Chem.*, **176**, 989 (1948).

(6) W. Jadassohn, H. Fierz-David and H. Vollenweider, *Helv. Chem. Acta*, **27**, 1384 (1944).

(7) H. Dudley, O. Rosenheim and W. Starling, *Biochem. J.*, **21**, 97 (1927).

(8) J. V. Braun and W. Pinkernelle, *Ber.*, **70**, 1230 (1937).

(9) A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1372 (1947).

(10) C. Derrick and R. Hess, THIS JOURNAL, **40**, 547 (1918).

(11) H. Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wisconsin, 1937, p. 32. The authors are indebted to Mr. William Clark for making this steel bomb in the machine shop of the Engineering Department, University of Miami.

(12) R. Adams, V. Voorhees and R. Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 463.

chloride (0.12 mole of hydrogen chloride) and 0.5 ml. of distilled water. The flask was placed under a hydrogen pressure of 60 p.s.i. and shaken for one hour at room temperature. The flask was then heated to 70° and at the end of the second hour an almost quantitative amount of hydrogen had been taken up. Water was added to the cooled reduction mixture, dissolving the precipitate in the reduction vessel. The catalyst was filtered off, and the filtrate of alcohol, water and spermidine trihydrochloride was evaporated to dryness on a steam-bath. The residue was triturated three times with 30-ml. portions of absolute ethanol, then recrystallized from a solution of 2 ml. of concentrated hydrochloric acid in 65 ml. of absolute ethanol, yielding 2.1 g. (28.7%) of spermidine trihydrochloride melting at 256–258°.

Anal. Calcd. for $C_7H_{22}N_3Cl_3$: N, 16.5. Found: N, 16.4, 16.3.

The chloroaurate and the picrate derivatives were prepared and found to melt at 219.5-220.5° and 210–212°, respectively. Dudley, Rosenheim and Starling[7] reported a melting point of 220–222° for spermidine chloroaurate and a melting point of 210–212° for spermidine picrate.

CORAL GABLES, FLORIDA RECEIVED OCTOBER 10, 1951

[CONTRIBUTION NO. 247 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

Reverse Addition of Lithium Aluminum Hydride to Nitroölefins

BY R. T. GILSDORF[1] AND F. F. NORD

The reverse addition of lithium aluminum hydride to 1-phenyl-2-nitropropene-1 was studied in detail in order to correlate this method with those previously recorded in the literature for the reduction of nitroölefins. A variety of products was isolated by varying the reaction temperature and the ratio of reactants. Among them was 1-phenyl-2-nitropropane, arising from the selective reduction of the double bond. By employing acidic hydrolysis of the intermediate organometallic complex, phenylacetone was obtained *via* a modified Nef reaction. Several other α-aryl ketones were similarly prepared. A study on the reverse addition of lithium aluminum hydride to ω-nitrostyrene, led to the development of a novel method of converting benzaldehyde to its next higher homolog.

A. Reduction of 1-Phenyl-2-Nitropropene-1

Introduction

It has been shown[2,3] that when compounds of the type ArCH=CRX, where X is a polar group such as CHO, COOH or NO_2, are treated with lithium aluminum hydride *via* normal addition, the double bond, as well as the functional group, is reduced. However experiments[4] on the reverse addition of the above reagent to cinnamaldehyde demonstrated that the carbonyl function could be selectively reduced by such a method. In view of the above findings and of the fact that nitroölefins prepared from aromatic aldehydes conform to the type, ArCH=CRX, where X is NO_2, the reverse addition of lithium aluminum hydride to nitroölefins was studied, as a continuation of our earlier investigation,[3] to correlate this method with those previously reported[5] for the reduction of nitroölefins. In these latter cases a wide variety of products has been obtained but at no time has any uncondensed[6] β-aryl nitroalkane been isolated.

The nitroölefin chosen for study was 1-phenyl-2-nitropropene-1.

Experimental

Reduction of 1-Phenyl-2-nitropropene-1 to β-Phenylisopropylamine and N-(β-Phenylisopropyl)-hydroxylamine.—In a three-necked two-liter flask equipped with a mechanical stirrer, dropping funnel and a condenser through which was suspended a low temperature thermometer (openings protected with calcium chloride tubes), a solution of 12.2 g. (0.075 mole) of 1-phenyl-2-nitropropene-1 in 300 ml. of absolute ether was cooled to below −30° with an acetone–Dry Ice-bath. During rapid stirring, a solution of 4.25 g. (0.112 mole, the calculated amount for the reduction of the nitro group) of lithium aluminum hydride in 100 ml. of absolute ether, was added at such a rate that the temperature of the reaction mixture was maintained between −30 and −40°. Exothermic reaction progressed during the addition and the color of the nitroölefin was discharged. The temperature in the reaction flask was then allowed to fall below −40°, the freezing bath was removed and the temperature allowed to rise to 15°. Hydrolysis was carried out with 400 ml. of 20% aqueous sodium potassium tartrate. The addition of the first few drops of this solution caused slight reaction indicating that the hydride had not been completely utilized. The aqueous layer was extracted with two additional 50-ml. portions of ether and the combined ethereal extracts, after drying over Drierite, yielded, on rectification, 4.4 g. (44%) of β-phenylisopropylamine, b.p. 72–74° (4.0 mm.) and 2.6 g. (23%) of N-(β-phenylisopropyl)-hydroxylamine, b.p. 116–118° (4.0 mm.). The latter substance readily solidified. Recrystallization from light petroleum ether afforded a white crystalline solid, m.p. 63–64°.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.42; H, 8.66. Found: C, 71.69; H, 8.42.

The β-phenylisopropylamine isolated was characterized as its hydrochloride and phenylthioureide: The hygroscopic hydrochloride, prepared by bubbling anhydrous hydrogen chloride through a solution of the amine in absolute ether, after recrystallization from an absolute alcohol–ether combination, had a m.p. of 147–148°. In the literature,[7] the m.p. is listed as 145–147°.

Anal. Calcd. for $C_9H_{14}ClN$: N, 8.15. Found: N, 8.30.

The phenylthioureide, prepared in the usual way,[8] had a m.p. of 131.5–132.5° after recrystallization from alcohol.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 71.07; H, 6.71. Found: C, 71.30; H, 6.38.

The previously unreported N-(β-phenylisopropyl)-hydroxylamine readily reduced Tollens reagent at room temperature. It had the same melting point as, and did not depress the melting point of, N-(β-phenylisopropyl)-hy-

(1) Condensed from a part of the dissertation submitted to the Graduate Faculty of Fordham University in partial fulfillment for the degree of Doctor of Philosophy.

(2) (a) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947); (b) **69**, 2548 (1947); (c) **70**, 3738 (1948).

(3) R. T. Gilsdorf and F. F. Nord, *J. Org. Chem.*, **15**, 807 (1950).

(4) F. A. Hochstein and W. G. Brown, THIS JOURNAL, **70**, 3484 (1948).

(5) (a) G. Alles, *ibid.*, **54**, 271 (1942); (b) O. Schales, *Ber.*, **68**, 1579 (1935); (c) J. Kindler, E. Brandt and E. Geglhaar, *Ann.*, **511**, 209 (1934); (d) B. Reichert and W. Koch, *Arch. der Pharm.*, **273**, 265 (1935); (e) L. Beauvault and A. Wahl; *Compt. rend.*, **134**, 1145 (1902); (f) A. Sonn and A. Schellenberg, *Ber.*, **50**, 1513 (1917); (g) H. Cerf de Mauney, *Bull. soc. chim.*, [5] **7**, 133 (1940); (h) E. P. Kohler and N. L. Drake, THIS JOURNAL, **45**, 1281 (1923).

(6) The reduction of ω-nitrostyrene to 2,3-diphenyl-1,4-dinitrobutane has been reported.[5f]

(7) D. H. Dey, *J. Chem. Soc.*, 18 (1930).

(8) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 206.