75–76° (10 mm.) was taken as the pure aldehyde. A mixture of 480 g. (4 moles) of freshly distilled phenylacetaldehyde, 720 g. (7 moles) of acetic anhydride, and 73.5 g. (0.75 mole) of crystalline potassium acetate was refluxed in an oil-bath kept at 160° for two hours. The reaction mixture was then allowed to cool and excess acid washed out several times with water and finally with 5% sodium carbonate solution. The resultant oil was dried over sodium sulfate and distilled. The fraction boiling at 113–117° (10 mm.) was taken as the enol acetate of phenylacetaldehyde; yield 390 g. (61%): redistilled enol acetate, b. p. 113–115° (10 mm.), $n^{25}D$ 1.550; d^{25}_4 1.061. Semmler[10] working with 10 g. of phenylacetaldehyde reported the following constants: b. p. 119–21 (10 mm.), d_{20} 1.065, n_D 1.5483, and yield of enol acetate, 80%.

Bromination of Enol Acetate.—A solution of 80.5 g. (0.5 mole) of enol acetate and 200 ml. of carbon tetrachloride was cooled in an ice-bath and bromine diluted with an equal volume of carbon tetrachloride was added slowly with constant shaking, care being taken not to allow the temperature to rise above 10°. The theoretical amount of bromine was absorbed in about thirty minutes.

Formation of Dimethyl Acetal.—To the above brominated mixture was added 200 ml. of methyl alcohol (99.5–100%) with shaking and cooling. The mixture was allowed to stand for two days with occasional shaking, and then diluted with 1 l. of water. The separated oil was dried and fractionated in the presence of a small amount of sodium carbonate. The fraction boiling at 130–135° (10 mm.) was taken as dimethyl acetal; yield, 202 g. (82%). Redistilled α-bromophenylacetaldehyde dimethyl acetal, b. p. 133–135° (10 mm.), $n^{25}D$ 1.5395; d^{25}_4 1.343.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 48.96; H, 5.34; Br, 32.64. Found: C, 48.76; H, 5.28; Br, 32.40.

Hydrolysis of Acetal.—Considerable difficulty was experienced in hydrolyzing the acetal, since the liberated aldehyde polymerized rapidly on heating. The yields varied with experimental conditions but in no case were they higher than 25%. On gently heating a mixture of 24.5 g. (0.1 mole) of the acetal with 25 ml. of 50% citric acid for fifteen minutes and allowing the liberated methyl alcohol to distil off, a partially hydrolyzed oil was obtained. This, upon distillation under vacuum with a small quantity of sodium carbonate, gave about 5 g. (25%) of α-bromophenylacetaldehyde, b. p. 108–9° (10 mm.), $n^{25}D$ 1.5900; d^{25}_4 1.521; 2,4-dinitrophenylhydrazone, m. p. 139°.

Anal. of α-bromophenylacetaldehyde, C_8H_7BrO: Calcd., C, 48.24; H, 3.54; Br, 40.15. Found: C, 48.76; H, 3.85; Br, 39.51.

Anal. of 2,4-dinitrophenylhydrazone, $C_{14}H_{11}BrO_4N_4$: Calcd., N, 14.78. Found: N, 14.72.

(10) Semmler, *Ber.*, **42**, 584 (1909).

Summary

A general method for the synthesis of α-bromoaldehyde acetals has been developed, based upon the bromination of enol acetates with subsequent reaction of the brominated product with methyl alcohol. The method has the advantage of simplicity and higher yields as compared with previously reported syntheses.

Isobutyraldehyde, heptaldehyde and phenylacetaldehyde were considered representative of various types of aldehydes and were chosen to test the general applicability of this procedure The yield of enol acetates ranged from 40–60%, and the α-bromoaldehyde dimethyl acetals were obtained from these in 75–80% yields. Hydrolysis of acetals gave α-bromoaldehydes of varying yields (25–95%).

During the course of this investigation, the following new compounds were prepared in pure state and their constants determined: enol acetate of isobutyraldehyde, α-bromoheptaldehyde dimethyl acetal, α-bromophenylacetaldehyde dimethyl acetal, α-bromophenylacetaldehyde, and the 2,4-dinitrophenylhydrazones of α-bromoisobutyraldehyde, α-bromoheptaldehyde and α-bromophenylacetaldehyde.

MONTREAL, CANADA RECEIVED NOVEMBER 24, 1943

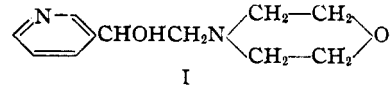
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

Amino Alcohol Studies. 3-Piperidyl Derivatives

BY ALFRED BURGER, ROBERT W. ALFRIEND[1] AND ADOLPH J. DEINET

In the course of investigations of amino alcohols in saturated cyclic systems, we planned to prepare a number of such 3-substituted derivatives of piperidine. This work had to be interrupted for external reasons, and we are reporting our method for the synthesis of such compounds.

3-Diazoacetylpyridine, prepared by a modification of the method of Dornow,[2] reacted with hydrobromic acid in ether to yield 3-bromoacetylpyridine hydrobromide which was converted to the corresponding morpholino ketone by treatment with morpholine. Reduction with aluminum isopropoxide furnished 1-(3-pyridyl)-2-(4-morpholino)-ethanol (I). The pyridine ring was then saturated by catalytic hydrogenation (II).



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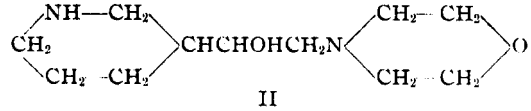

II

Experimental

The formation of tars in the reaction with diazomethane was minimized when free nicotinyl chloride instead of its hydrochloride[2] was used.

Nicotinyl chloride was prepared according to the directions of Douglass and Forman[3] but was purified by distillation over quinoline. The pure acid chloride was obtained in a yield of 90% as a colorless liquid, b. p. 75–77° (7 mm.), of an odor similar to that of benzoyl chloride.

(1) Eli Lilly Research Fellow.

(2) Dornow *Ber.*, **73**, 156 (1940).

(3) Douglass and Forman, THIS JOURNAL, **56**, 1609 (1934).

It is easily hydrolyzed by traces of moisture but can be preserved unchanged when stored in a closed vessel in a dry atmosphere. The formation of nicotinic acid hydrochloride upon exposure to moisture may account for some of the discrepancies in recent descriptions of nicotinyl chloride.[4]

3-Bromoacetylpyridine Hydrobromide.—A solution of 60 g. of nicotinyl chloride in 150 cc. of dry benzene was stirred into a solution of 54 g. of diazomethane in 1500 cc. of ether at 0°. Stirring was continued for three hours at room temperature until the evolution of nitrogen had ceased, a copious resinous precipitate was filtered off, the filtrate cooled in ice, and 48% hydrobromic acid was added with stirring until acid to congo red. 3-Bromoacetylpyridine hydrobromide precipitated as a yellow crystal powder. It was washed with acetone, and the crude product used in the reaction with morpholine. The yield was 98.4 g. (82%).

3-(4-Morpholino)-acetylpyridine.—Thirty grams of the crude bromoketone hydrobromide was added in small portions to a cooled solution of 27.9 g. (3 moles) of morpholine in 200 cc. of dry ether. When the vigorous reaction had subsided the mixture was allowed to stand overnight, the separated morpholine hydrobromide was filtered, the filtrate concentrated under reduced pressure, and the oily residue heated at 70° and 5 mm. for five hours to remove any unchanged morpholine. The crude morpholino ketone crystallized on standing; the yield was 18.4 g. (83%). A small sample was sublimed at 100° and 1 mm. The colorless sublimate melted at 64–68°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: N, 13.6. Found: N, 13.9.

The colorless **dihydrochloride** was prepared in acetone solution and recrystallized from absolute ethanol–ether. It melted at 197–205°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot 2HCl$: Cl, 25.4. Found: Cl, 25.4.

The orange-yellow **dipicrate** crystallized from ethanol, m. p. 158–162°.

Anal. Calcd. for $C_{23}H_{20}N_8O_{16}$: N, 16.9. Found: N, 16.5.

(4) Tamayo and Vargas, *Anales fis. quim.*, **38**, 179 (1942); *Chem. Abst.*, **37**, 5064[2] (1943).

1-(3-Pyridyl)-2-(4-morpholino)-ethanol.—The reduction of the morpholino ketone with aluminum isopropoxide was carried out essentially according to the procedure described previously.[5] The rate of the reaction was greatly increased, and the yield improved, when the free amino ketone, and not its salt, was used. After distilling the excess isopropyl alcohol, the residue was shaken with cold 10 *N* sodium hydroxide solution, and the morpholino alcohol extracted into ether. The colorless **dihydrochloride,** prepared in acetone solution, and recrystallized from ethanol–ether, melted at 211°. The yield was 25%.

Anal. Calcd. for $C_{11}H_{16}N_2O_2 \cdot 2HCl$: Cl, 25.2. Found: Cl, 25.1.

The yellow **dipicrate** melted at 166°.

Anal. Calcd. for $C_{23}H_{22}N_8O_{16}$: N, 16.8. Found: N, 17.1.

1-(3-Piperidyl)-2-(4-morpholino)-ethanol.—A solution of 0.65 g. of 1-(3-pyridyl)-2-(4-morpholino)-ethanol hydrochloride in 200 cc. of ethanol containing 0.6 g. of hydrogen chloride was hydrogenated under ordinary pressure in the presence of 0.2 g. of Adams catalyst. Ninety per cent. of the calculated amount of hydrogen was absorbed within twenty hours. The catalyst was filtered, and the solvent removed under reduced pressure. The remaining oily hydrochloride crystallized after standing for several days. It was washed with a mixture of acetone and ether and recrystallized from ethanol–ether. The colorless prisms melted at 256–257°. The yield was 0.3 g. (45%).

Anal. Calcd. for $C_{11}H_{22}N_2O_2 \cdot 2HCl$: C, 46.0; H, 8.4; Cl, 24.7. Found: C, 46.9; H, 8.5; Cl, 25.0.

Summary

3-Bromoacetylpyridine and morpholine yielded 3-(4-morpholino)-acetylpyridine which was reduced to 1-(3-pyridyl)-2-(4-morpholino)-ethanol by the Ponndorf reaction. Hydrogenation of the pyridine nucleus furnished 1-(3-piperidyl)-2-(4-morpholino)-ethanol.

(5) Burger and Harnest, THIS JOURNAL, **65**, 2382 (1943).

CHARLOTTESVILLE, VA. RECEIVED MARCH 13, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Preparation of N-(*d*-Ribityl)-3,4-dimethylaniline

BY M. TISHLER, N. L. WENDLER,[1] K. LADENBURG AND J. W. WELLMAN[2]

As none of the known syntheses of *d*-ribose[3] is simple and economical, a synthesis of riboflavin without the use of this sugar is of practical interest. Accordingly, we have developed two different syntheses of N-(*d*-ribityl)-3,4-dimethylaniline, V—a key intermediate in the riboflavin synthesis[4]—which do not involve *d*-ribose.

One method starts with *d*-ribonic acid, readily prepared from *d*-arabonic acid. In this synthesis 3,4-dimethylaniline reacts with *d*-ribonolactone and the resulting anilide, I, is acetylated to 3,4-dimethyl-(tetraacetyl-*d*-ribonyl)-aniline, II. The reduction of the amide group was accomplished by converting the anilide to the chloroimine, III, and reducing the latter by catalytic methods.[5] The resulting secondary amine, IV, is deacetylated catalytically to V.

The catalytic hydrogenation of the chloroimine occurs readily providing the chloride is pure and anhydrous conditions are maintained. The

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(2) Present address: Enka Rayon Corp., Enka, North Carolina.

(3) V. Ekenstein and Blanksma, *Chem. Weekblad*, **10**, 664 (1913); Karrer, Becker, Benz, Frei, Solomon and Schopp, *Helv. Chim. Acta*, **18**, 1440 (1935); Bredereck and Rother, *Ber.*, **71**, 408 (1938); Richtmyer, Hann and Hudson, THIS JOURNAL, **61**, 343 (1939).

(4) Karrer and Meerwein, *Helv. Chim. Acta*, **18**, 1130 (1935); Tishler and Wellman, U. S. Patent 2,261,608.

(5) This scheme of reducing substituted anilides has been applied to the preparation of other secondary amines and our results will be reported later. Since the completion of this work, T. S. Work, *J. Chem. Soc.*, 429 (1942), reported the preparation of a few secondary amines from chloroimines by reduction with stannous chloride and ethereal hydrogen chloride. Very recently in *C. A.*, **38**, 1247 (1944) (British Patent 550,169) the preparation of N-(*d*-tetraacetylribityl)-3,4-dimethylaniline, IV, is reported by a scheme similar to ours but details are lacking.