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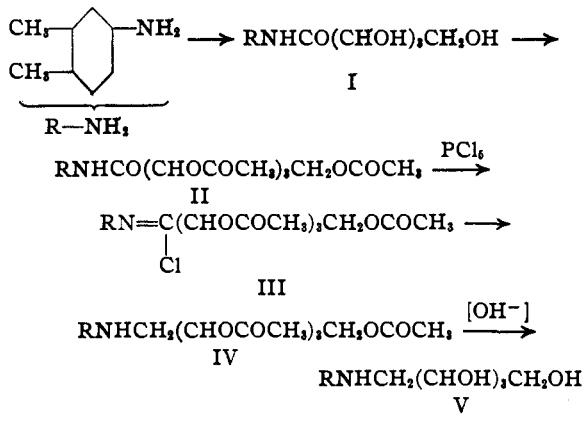
(2) Present address: Enka Rayon Corp., Enka, North Carolina.

(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.



presence of phosphorus compounds inhibits the reduction.

Attempts to reduce the amide grouping directly (I → V) by the catalytic methods employed for the simpler amides[6] were unsuccessful. Under conditions where hydrogenation actually occurred (copper chromite catalyst 160–180°, 200 lb. pressure) hydrogenolysis takes place as indicated by the fact that 3,4-dimethylaniline is formed in appreciable amounts.

The second method consists of the reductive coupling of 3,4-dimethylaniline and tetraacetyl-*d*-ribonitrile. The preparation of some unsymmetrical secondary amines by the reductive coupling of nitriles and primary amine has been reported previously by Kindler and Hess.[7] These investigators recommended that such reductive couplings be carried out by adding the nitrile slowly to two equivalents of the amine in the presence of catalyst and hydrogen. In our case, this procedure offered no advantages; about the same yield was obtained when equivalent amounts of the reactants were catalytically reduced in the usual manner. The reductive coupling is best carried out in methanol in the presence of a small amount of aqueous acetic acid. The presence of the latter appears to have a beneficial effect, possibly because of its ability to combine with the ammonia formed during the reduction. The reduction proceeds better at low pressures (0.5 to 2 atmospheres pressure) than at high pressures (10 to 100 atmospheres pressure).

Acknowledgment.—The authors wish to thank Dr. R. T. Major and Dr. J. R. Stevens for their interest and suggestions.

Experimental

3,4-Dimethyl-*d*-ribonylaniline, I.—A mixture of 12.1 g. of 3,4-dimethylaniline, 15 g. of *d*-ribonic acid lactone, and 0.05 g. of hydroquinone is heated on the steam-bath with occasional shaking for one-and-one-half hours, during which time the mixture solidifies. The straw-colored solid is essentially pure anilide and may be used for the next step directly. Further purification may be effected by recrystallization from ethanol whereby the product is obtained as fluffy needles melting at 164–165° with slight decomposition.

Anal. Calcd. for $C_{13}H_{19}O_5N$: C, 57.99; H, 7.06; N, 5.20. Found: C, 58.14; H, 7.09; N, 5.34.

3,4-Dimethyl-(tetraacetyl-*d*-ribonyl)-aniline, II.—The crude ribonanilide from above is powdered and added to a mixture of 60 cc. of acetic anhydride and 40 cc. of pyridine. On shaking the solid dissolves with liberation of heat. The mixture is cooled with tap water occasionally so that the inside temperature does not rise above 45°. After all the solid is dissolved, the light brown reaction mixture is stored for fifteen hours in the refrigerator. At the end of this time, the reaction mixture is treated with norite, filtered and the filtrate added to about 200 g. of cracked ice with stirring. The product separates as a gum which soon solidifies. About 39 g. of white product is obtained which is suitable for the subsequent step.

The product may be recrystallized from ethanol or cyclohexane. It separates as needles melting at 114–115° $[\alpha]^{25}D$ 16 ± 1°, in $CHCl_3$ (*C*, 1%).

Anal. Calcd. for $C_{21}H_{27}O_9N$: C, 57.66; H, 6.18; N, 3.21. Found: C, 57.51; H, 6.26; N, 3.21.

3,4-Dimethyl-(tetraacetyl-*d*-ribimidochloro)-benzene, III.—To a suspension of 30.6 g. of the anilide in 200 cc. of alcohol-free chloroform is added 15 g. of phosphorus pentachloride. After stirring the mixture for one hour the solution is concentrated to dryness under reduced pressure and the residue is dissolved in 150 cc. of dry xylene. The solution is concentrated again to an oil under reduced pressure and the residue is dissolved in 50 cc. of dry xylene, filtered and cooled to 0°. After crystallization starts, 200 cc. of petroleum ether is added. The product is collected on a filter, washed well with petroleum ether and used as such in the next step; dried weight 30 g., m. p. 68–70°.

Anal. Calcd. for $C_{21}H_{26}O_8NCl$: C, 55.02; H, 6.32. Found: C, 55.50; H, 6.33.

The chloroimine is sensitive to moist air and is converted to the anilide II by treatment with water.

N-(*d*-Tetraacetylribityl)-3,4-dimethylaniline,[8] IV.—A. From the Chloroimine, III.—A mixture of the above chloroimine, 100 cc. of dry ethyl acetate (or dry dioxane) and 10 g. of 5% Pd-$BaCO_3$ (or 5% Pd-$CaCO_3$) at 50–55° is shaken with hydrogen at 15–30 lb. pressure. The calculated quantity of hydrogen is absorbed in three to four hours. The catalyst is separated by filtration, the solution is concentrated to dryness under reduced pressure and the residue is dissolved in 25 cc. of methanol. The product (wt. 18.5 g.) separated as white, fluffy needles, m. p. 94–95°) is obtained by diluting the filtrate with 10 cc. of water.

If the imidochloride is not thoroughly washed from phosphorus-containing compounds, the reduction is sluggish. In such instances, replacement of the spent catalyst (when the reduction slows down perceptibly) with a fresh portion is beneficial.

B. From Tetraacetyl-*d*-ribonitrile.—A mixture of 0.5 g. of palladium chloride, 1 g. of acid-washed norite in 30 cc. of methanol is shaken with hydrogen until the chloride is reduced. To this mixture is added 5 g. of tetraacetyl-*d*-ribonitrile,[9] 1.9 g. of 3,4-dimethylaniline, 5 cc. of acetic acid, 2 cc. of water and 30 cc. of methanol, and the mixture is shaken with hydrogen at 5–10 lb. pressure. The reduction is completed in about one hour, somewhat more than the calculated quantity of hydrogen (2.5 eq.) being absorbed. The mixture is filtered, concentrated to dryness and the white, crystalline residue slurried with 20% methanol-water; weight 3.75 g., m. p. 94–95°. The product is best purified by recrystallizing from methanol or methylcyclohexane and melts when pure at 99–100°.

Anal. Calcd. for $C_{21}H_{29}O_8N$: C, 59.65; H, 6.88; N, 3.32. Found: C, 59.90; H, 6.91; N, 3.17.

(6) Adkins and Wojcik, THIS JOURNAL, **56**, 247, 2419 (1934); Adkins and Paden, *ibid.*, **58**, 2487 (1936).

(7) Kindler and Hess, *Arch. Pharm.*, **271**, 439 (1933).

(8) Since the completion of this work, the preparation of this compound from aldehydo-tetraacetyl-*d*-ribose and 3,4-dimethylaniline has been described in British Patent 551,491.

(9) For the preparation of the nitrile, see Ladenburg, Tishler, Wellman and Babson, THIS JOURNAL, **66**, 1217 (1944).

3,4-Dimethyl-(*d*-ribityl)-aniline, V.—The hydrolysis of IV is best carried out by catalytic *trans*-esterification procedures using barium methylate or sodium methylate in methanol. In a typical experiment, 5 g. of IV in 15 cc. of methanol containing 0.1 g. of sodium methylate is gently heated to reflux for one hour. On cooling the product separates in essentially pure form melting at 142–143° (wt. 2.3 g.). On diluting the filtrate with an equal volume of water, 0.5 g. of somewhat less pure product is obtained.

Summary

N-(*d*-Ribityl)-3,4-dimethylaniline was prepared by two methods without the use of *d*-ribose. In one method, 3,4-dimethyl-(tetraacetyl-*d*-ribonyl)-anilide is converted to the chloroimine and the latter is reduced and then deacetylated. In the second procedure 3,4-dimethylaniline and tetraacetyl-*d*-ribonitrile are subjected to catalytic reductive coupling and the resulting acetylated amine deacetylated.

RAHWAY, NEW JERSEY RECEIVED MAY 5, 1944

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF GEORGIA]

The Hydrolysis of Some Quinone Oximes

BY W. T. SUMERFORD AND D. N. DALTON

Compounds of the *p*-benzoquinone series have recently become of more than academic interest due to their vitamin K activity,[1] their use as intermediates in the synthesis of tocopherols,[2] and their potent fungicidal properties.[3]

Quinones may be obtained in varying yields by oxidizing under stated conditions the appropriate: (1) hydrocarbon, (2) dihydric phenol, (3) aromatic amine, (4) aminophenol, or (5) aromatic diamine with: (1) chromium trioxide, (2) ceric sulfate, (3) sodium dichromate, (4) ferric chloride, and (5) manganese dioxide, respectively.

The hydrolysis of quinone monoximes to the corresponding quinones and hydroxylamine would seem to offer an attractive route to the production of quinones since the tautomeric nitrosophenols can usually be prepared conveniently and in good yields. In fact this method has not been entirely overlooked. Henrich, Taubert and Birkner[4] obtained 2-chloro-5-hydroxy-tolu-3,6-quinone in an unstated yield by treating the monoxime of this compound with diluted sulfuric acid and potassium dichromate. More recently Karrer and Hoffmann[5] used a 30% solution of hydrogen peroxide to destroy the hydroxylamine in a similar reaction, and thereby were able to hydrolyze 2,6-dimethyl-3-ethylbenzoquinone-1-oxime to obtain a 70% yield of the corresponding quinone.

Lapworth[6] found that certain aldehydes aid in the hydrolysis of oximes by removing hydroxylamine from the sphere of the reaction. Tseng[7] claims to have hydrolyzed three quinone monoximes by refluxing them with 8% hydrochloric acid and formaldehyde to obtain yields of the corresponding quinones up to 90% of the theoretical. Attempts to duplicate the results of Tseng[7] with thymoquinone monoxime were unsuccessful, but a 36% yield of the quinone was obtained with the use of acetone in place of the formaldehyde.[8]

Since Tseng's results fell far short of duplication, and the Karrer and Hoffmann method[5] was found to be inapplicable to some homologous oximes, other oxidizing agents known to react with hydroxylamine were tried in this reaction. Preliminary trials showed that ferric chloride and cupric sulfate could be used advantageously here, but cuprous salts, which were tried because of the relative position of Cu^{++} and Cu^{+} in the electromotive series, proved superior to anything used in the reaction. A method using cuprous chloride and a carbonyl compound for the hydrolysis of quinone oximes was worked out, and applied to a series of tautomeric *p*-nitrosophenols $\rightleftarrows$ quinone monoximes. The results are given in Table I, and are compared there with the results obtained by subjecting the same oximes to the Karrer and Hoffmann method.

Experimental Part

Preparation of the Oximes.—All of the quinone oximes listed in Table I except 2-methylnaphthoquinone monoxime were prepared by treating the appropriate phenol with sodium nitrite and hydrochloric acid as described by Kremers and Wakeman.[9] The 2-methylnaphthoquinone monoxime was obtained by heating equivalent amounts of the quinone and hydroxylamine hydrochloride in ethanol containing hydrochloric acid. The thymoquinone dioxime was prepared by refluxing 2-methyl-5-isopropylbenzoquinone-1-oxime with hydroxylamine hydrochloride in ethanol.

Hydrolysis of the Oximes. Method I.—A mixture of 0.01 mole of the quinone oxime, 20 ml. of diluted hydrochloric acid (1 to 5), and 3 ml. of Superoxol (assay 26%) was refluxed for one and one-half hours. The mixture was then steam distilled, the distillate extracted with diethyl ether, the ether extract dried over Drierite, and finally allowed to evaporate spontaneously with the aid of a small electric fan. In one or two instances it was necessary to complete the drying process by placing the quinone in a desiccator over phosphorus pentoxide for an hour or

(1) Fieser, Campbell and Fry, THIS JOURNAL, **61**, 2206 *et seq.* (1939).

(2) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 318 (1939).

(3) Ter Horst and Felix, *Ind. Eng. Chem.*, **35**, 1255 (1943).

(4) Henrich, Taubert and Birkner, *Ber.*, **45**, 303 (1912).

(5) Karrer and Hoffmann, *Helv. Chim. Acta*, **22**, 654 (1939).

(6) Lapworth, *J. Chem. Soc.*, **91**, 1133 (1907).

(7) Tseng, Hu and Chu, *J. Chinese Chem. Soc.*, **2**, 136 (1934).

(8) Sumerford and Hartung, *J. Am. Pharm. Assoc.*, **29**, 65 (1940).

(9) Kremers and Wakeman, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 511.