[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF COLORADO]

The Pyridylthioacetmorpholides and Pyridylacetic Acids[1]

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While studying intermediates leading to the synthesis of certain azabicyclics, a scheme was devised whereby quinuclidine might be prepared from 4-pyridylacetic acid. This acid could be esterified, and the ester reduced to 4-piperidylethanol, an intermediate used by Loeffler and Stietzel[3] and Meisenheimer[4] in preparing quinuclidine. Similarly, 3-piperidylethanol, an intermediate for 1-aza-bicyclo[1.2.3]octane as synthesized by Prelog,[5] might be prepared from 3-pyridylacetic acid.

No description of 4-pyridylacetic acid was found in a search of the available literature. Oparina[6] described the synthesis of 2-pyridylacetic acid from 2-phenacylpyridine in 1934. Miescher and Kagi[7] prepared 3-pyridylacetic acid in 1941 indirectly by the Arndt–Eistert[8] reaction from quinolinic acid-2-methyl ester-3-chloride. In the same year Hartman and Bosshard[9] prepared the 3-isomer from 3-acetylpyridine by the Willgerodt[10] reaction. Late in 1946, after the work in this investigation had been completed, Pattison and Carmack[11] described the preparation of the 2-isomer by the Willgerodt reaction.

In this investigation the Schwenk[12] modification of the Willgerodt reaction was used to prepare the 4-, 3- and 2-pyridylthioacetmorpholides. Late in 1946, after the work in this investigation had been completed, Schwenk and Papa[13] described the preparation of 3-pyridylthioacetmorpholide and its subsequent hydrolysis. In our work, the thiomorpholides were hydrolyzed to the corresponding pyridylacetic acids. The ethyl esters of the 4- and 3-pyridylacetic acids were reduced to the corresponding piperidylethanols. These reactions may be illustrated as follows, using the 4-isomer as an example: 4-methylpyridine → isonicotinic acid → ethyl isonicotinate → 4-acetylpyridine → 4-pyridylthioacetmorpholide → 4-pyridylacetic acid → ethyl 4-pyridylacetate → 4-piperidylethanol.

Picolinic acid hydrochloride was prepared by the method of Singer and McElvain.[14] Isonicotinic acid was prepared by our modification of this method. Ethyl isonicotinate and ethyl picolinate were synthesized by the method of LaForge.[15] Commercially available (Eastman Kodak Company) ethyl nicotinate was used. The acetylpyridines were prepared by the method of Kolloff and Hunter.[16]

Experimental[17]

Isonicotinic Acid.—In a 5-liter flask mounted on a steam-bath and fitted with a reflux condenser and a mechanical stirrer, were placed 2500 ml. of water, 93 g. (1.0 mole) of 4-methylpyridine (Eastman Kodak Company), and 182 g. of potassium permanganate. The mixture was refluxed with stirring until the purple color disappeared. A second portion of 150 g. of potassium permanganate (2.1 moles in all) was added then with 1000 ml. of water. The mixture was refluxed again until no purple color remained. The warm solution was filtered, and the residue washed with 500 ml. of hot water. The filtrate and washings were evaporated under reduced pressure on a steam-bath to a volume of approximately 300 ml. The residual liquid was filtered and cooled. The filtrate was acidified carefully with concentrated hydrochloric acid (100–110 ml.) using congo red paper. The mixture was cooled, and the precipitate collected and dried. The yield of crude acid was 74–86 g. (60–70% of the theoretical amount). The melting point of the crude acid was 308–310° (sealed tube). The crude acid was purified by dissolving in approximately 25 times its weight of hot water, treating with decolorizing carbon, filtering, and cooling. The yield was 62–74 g. (50–60%) of a colorless acid, melting at 314–316° (sealed tube).

The Pyridylthioacetmorpholides.—In the synthesis of 4-pyridylthioacetmorpholide, 227 g. (1.88 moles) of 4-acetylpyridine, 60.5 g. (1.88 moles) of sulfur, and 164 g. (1.88 moles) of morpholine were mixed in a liter flask equipped with a reflux condenser. The mixture was heated gradually, and refluxed gently for about twelve hours. The warm solution was poured into 500 g. of ice which contained enough water to make the mixture stirrable. The combined mixture was stirred until the oil crystallized. The crystalline material was filtered, washed with a little ice-water, and dried. The yield was 320 g. (76.5% of the theoretical amount). A sample recrystallized from absolute ethanol melted at a temperature of 104–105.5°. A picrate melted at 184–186° (dec.).

The 3-pyridylthioacetmorpholide was prepared in the same way from 3-acetylpyridine. However, this isomer was more difficult to crystallize when poured into the ice and water mixture. A crude yield of 80% of the theoretical amount was obtained. A sample upon recrystallizing from absolute ethanol melted at 78–80°. A picrate melted at the temperature of 167–169°.

Analyses. Calcd. for $C_{11}H_{14}ON_2S$, %

	Carbon	Hydrogen	Nitrogen	Sulfur
Calcd.	59.46	6.31	12.61	14.41
4-Isomer	59.27	6.30	12.11	13.90
3-Isomer	59.35	6.60	12.65	14.29
2-Isomer	59.19	6.50	12.43	14.34

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(2) Present address: Eastman Kodak Company, Rochester, N. Y.

(3) Loeffler and Stietzel, *Ber.*, **42**, 124 (1909).

(4) Meisenheimer, Nereschеimer, Finn and Schneider, *Ann.*, **420**, 190–239 (1920).

(5) Prelog, Heimbach and Cerkovnikov, *J. Chem. Soc.*, 677 (1939).

(6) Oparina, *Chem. Zentr.*, **106**, I, 2531 (1935).

(7) Miescher and Kagi, *Helv. Chim. Acta*, **24**, 1471 (1941).

(8) R. Adams, Editor-in-Chief, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 38–62.

(9) Hartman and Bosshard, *Helv. Chim. Acta*, **24**, 28–35E (1941).

(10) Willgerodt, *Ber.*, **20**, 2467 (1887); **21**, 534 (1888).

(11) Pattison and Carmack, THIS JOURNAL, **68**, 2034 (1946).

(12) Schwenk and Block, *ibid.*, **64**, 3051 (1942).

(13) Schwenk and Papa, *J. Org. Chem.*, **11**, 801 (1946).

(14) Singer and McElvain, THIS JOURNAL, **57**, 1135 (1935).

(15) LaForge, *ibid.*, **50**, 2477 (1928).

(16) Kolloff and Hunter, *ibid.*, **63**, 490 (1941).

(17) All melting points and boiling points reported in this paper are uncorrected.

The 2-isomer was prepared similarly from 2-acetylpyridine. However, this isomer was very difficult to crystallize when poured into the ice and water mixture. When crystalline, it was necessary to filter while cold, and to recrystallize the whole yield from absolute ethanol at once. A crystallized yield of 63% of the theoretical amount was obtained, m. p. 65–67°. A picrate melted with slight decomposition at 178–180°.

The Pyridylacetic Acids.—Forty-four and four-tenths grams (0.2 mole) of 4-pyridylthioacetmorpholide, 12 g. of potassium hydroxide and 200 ml. of 95% ethanol were placed in a 500-ml. flask equipped with a reflux condenser. The mixture was refluxed gently on a steam-bath for seventy-two hours. At the end of that time, the mixture was poured into two volumes of water. The resulting solution was distilled at reduced pressure to approximately one-third volume, and another volume of water was added. The mixture was distilled again under reduced pressure, this time nearly to dryness. The residue was acidified with hydrochloric acid and evaporated to dryness under reduced pressure. The residue was extracted with three 200-ml. portions of absolute ethanol. The alcohol mixture was decolorized with carbon, filtered, evaporated to one-half volume, filtered, cooled and added to an excess of ether. The yield of white 4-pyridylacetic acid hydrochloride, m. p. 130–131°, was 30 g., or 86% of the theoretical amount. It formed a picrate which melted at 114–116°.

Anal. Calcd. for $C_7H_8NO_2Cl$: C, 48.43; H, 4.65; N, 8.07; Cl, 20.43. Found: C, 48.34; H, 4.75; N, 8.33; Cl, 20.34.

3-Pyridylacetic acid was prepared in the same manner. It was isolated both as the hydrochloride, m. p. 153–155°, and as the free acid, m. p. 144–146°, the latter in 74% yield. It formed a picrate which melted at 99–101°.

2-Pyridylacetic acid was synthesized similarly, but in very small yield. It was identified as the picrate, m. p. 140–142°.

The Ethyl Pyridylacetates.—The 3- and 4-pyridylacetic acids were esterified by the method of LaForge.[15] Ethyl 3-pyridylacetate, b. p. 121–122° at 10 mm., was obtained in 60% yield. This boiling point corresponds to that obtained by Hartman and Bosshard.[9] The ester forms a picrate which melts at a temperature of 110–112°.

Ethyl 4-pyridylacetate, b. p. 107–108° at 3 mm., was obtained in 49% yield. A picrate melted at a temperature of 121–123°.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.41; H, 6.75; N, 8.40.

The Piperidylethanols.—The ethyl pyridylacetates were reduced by the procedure of Sandborn and Marvel[18] for ethyl nicotinate. The 3-piperidylethanol was obtained in 25% yield as a thick oil, b. p. 121–123° at 6 mm., $n^{25}D$ 1.4920. This boiling point is the same as that obtained by Merchant and Marvel,[19] however, they obtained an index of refraction of $n^{25}D$ 1.4888.

The 4-piperidylethanol[20] was obtained as a thick oil in 10% yield, b. p. 138–140° at 12 mm., $n^{25}D$ 1.5082. This boiling point corresponds to that obtained by Meisenheimer.[4]

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Summary

The pyridylthioacetmorpholides were synthesized and then hydrolyzed to the corresponding pyridylacetic acids. The ethyl esters of 3- and 4-pyridylacetic acids were reduced to the corresponding piperidylethanols.

(18) Sandborn and Marvel, THIS JOURNAL, **50**, 563 (1928).

(19) Merchant and Marvel, *ibid.*, **50**, 1197 (1928).

(20) Much of the work of this investigation had been completed when Reilly Tar and Chemical Corporation announced the commercial availability of 4-pyridylethanol of 95% purity. A redistilled sample of their material gave the same compound as above when reduced with sodium and alcohol.

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CONTRIBUTION FROM THE BIOCHEMISTRY LABORATORY, DIVISION OF FOOD SCIENCE AND TECHNOLOGY, NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

Color Formation in Furfural Systems[1]

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Introduction

Furfural has been suspected for some time to be an important intermediate involved in the "browning" of sugar solutions and various food products.[3] Since the literature contains no specific information concerning the factors involved in the coloration of originally colorless furfural solutions, a study of this reaction was undertaken. Dunlop, *et al.*,[4] studied the decomposition of furfural and concluded that color and acid formation in furfural at room temperature were due to autoxidation. Schenck[5] proposed a somewhat similar mechanism for the oxidative decomposition of furan and 2,5-dimethylfuran. These investigators did not deal with water solutions of the compounds in question.

Materials and Methods

Eastman Kodak Co. technical furfural served as the source of furfural for most of these experiments. This material was fractionated using an all-glass apparatus. The fraction used was nearly colorless and had a boiling point of 160–161° (cor.).

The amino acids obtained for this work were: Pfanstiehl C. P. glycine, ammonia free: Amend Drug and Chemical Company *d*-arginine monohydrochloride, C. P.; and Eimer and Amend *dl*-aspartic acid, C. P., m. p. 280° (dec.).

Samples of biacetyl, crotonaldehyde and purified

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(3) H. Schiff, *Ann.*, **239**, 352 (1887).

(4) A. P. Dunlop, P. R. Stout and S. Swadesh, *Ind. Eng. Chem.*, **38**, 705 (1946).

(5) G. O. Schenck, *Ber.*, **77**, 661 (1945).