[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ILLINOIS
AND THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

REARRANGEMENT OF THE ALPHA-FURFURYL GROUP. 2-FURYLACETIC ACID AND 5-METHYLFUROIC ACID

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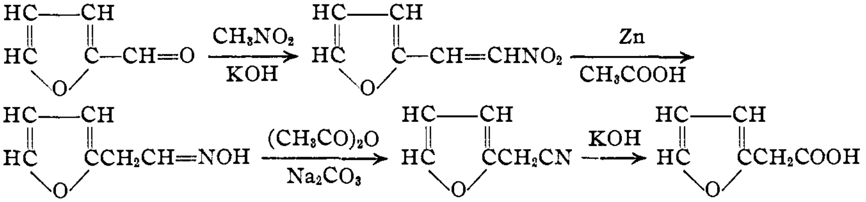
During the past few years the chemistry of furan derivatives has been developed considerably due to the availability of pure furfural in large amounts. The furan analogs of many of the well-known benzene derivatives have been prepared and their properties investigated. The present work was undertaken with the object of synthesizing 2-furylacetic acid and a few related compounds.

The methods of synthesis which may be employed in the furan series are limited to some extent by the fact that furan and many of the simpler furan derivatives are relatively sensitive to strong mineral acids, particularly the halogen acids. For this reason it seemed advisable to devise a method for producing 2-furylacetic acid from furfural without using any reaction which involves such acids. The series of reactions indicated below was selected for this purpose and the desired product, 2-furylacetic acid, was obtained as a white crystalline solid, m. p. 67.3–67.5°.



Starting with α-furfuryl chloride, Kirner and Richter[1] recently synthesized an acid which was considered to be 2-furylacetic acid and described the substance as a white, crystalline solid which melted at 108.5–109.5°. A nitrile, supposedly 2-furylacetonitrile (α-furfuryl cyanide), was obtained by the action of α-furfuryl chloride upon an aqueous solution of sodium cyanide, and this was hydrolyzed by means of aqueous potassium hydroxide solution to the corresponding acid. The observation that the nitrile and the acid obtained by the method of synthesis used in the present work did not agree in physical properties with the compounds obtained from α-furfuryl chloride led to an investigation of the latter. The fact that 5-methylfuroic acid, a structural isomer of 2-furylacetic acid, is described in the literature as a white crystalline solid which melts at 108–109°,[2] suggested the possibility that a molecular rearrangement had occurred in the series of reactions involving α-furfuryl chloride. In order

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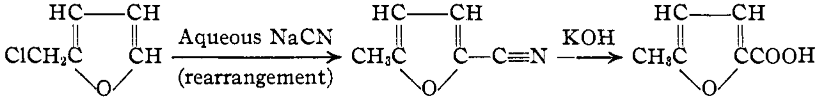
[1] Kirner and Richter, THIS JOURNAL, **51,** 3131 (1929).

[2] Hill and Jennings, *Am. Chem. J.*, **15,** 167 (1893).

to test this point a specimen of authentic 5-methylfuroic acid was prepared by using as a starting material the methylpentose, rhamnose. The latter was converted into 5-methylfurfural by the usual method of ring closure, and the aldehyde was oxidized by means of silver oxide to the corresponding acid. The 5-methylfuroic acid obtained in this way had exactly the same melting point as the acid obtained by the method of Kirner and Richter from α-furfuryl chloride, and the melting point of a mixture of the two substances in equal amounts was exactly the same as that of the original pure substances. The identity of the acids was confirmed by microscopical studies of the crystals of both specimens.[3]

This result leads to the conclusion that a rearrangement of the α-furfuryl group into the 5-methylfuryl group occurred during one of the reactions involved in the synthesis of Kirner and Richter. It seems probable that this rearrangement takes place in the treatment of α-furfuryl chloride with aqueous sodium cyanide solution, so that the resulting nitrile is 5-methylfuronitrile and not 2-furylacetonitrile (α-furfuryl cyanide). Evidence in favor of this view is the fact that although the conditions for hydrolysis of the nitriles were practically the same in both syntheses, two different acids resulted. One might assume that rearrangement occurred in both cases or in only one, but it is more reasonable to suppose that rearrangement did not occur in either instance during the alkaline hydrolysis. It appears that the synthesis of Kirner and Richter follows the reactions given below.



α-Furfuryl chloride 5-Methylfuronitrile 5-Methylfuroic acid

The possibility that the chloride obtained from α-furfuryl alcohol[4] might not be α-furfuryl chloride but the isomeric 5-methyl-2-chlorofuran was also considered. The great reactivity of the chlorine atom in the chloride prepared from α-furfuryl alcohol makes this alternative quite unlikely, since one would not expect the chlorine atom of 5-methyl-2-chlorofuran to be highly reactive.[5]

In order to test the correctness of this view and to elucidate the mechanism of the rearrangement, further work is being carried on with the nitrile obtained from α-furfuryl chloride, and with other compounds that are

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[3] The authors wish to express their thanks to Professor C. W. Mason and Mr. P. P. McClellan for carrying out the microscopical studies reported in this paper.

[4] Kirner, This Journal, 50, 1955 (1928).

[5] Investigations of the simple halogenated furans, such as 2-chloro-, 3-chloro-, 2-bromo- and 3-bromofuran, indicate that a chlorine or bromine atom attached to the furan ring is inert toward reagents that react quite readily with α-furfuryl chloride. The preparation and properties of the simple halogenated furans will be described in a forthcoming publication by Shepard, Winslow and Johnson.

obtained from this chloride by replacement reactions. The fact that α-furfuryl alcohol undergoes rearrangement in the course of ring opening in the presence of hydrochloric acid, with the formation of levulinic acid and methyl levulinate,[6] has a direct bearing on the rearrangement dealt with in the present work, since both rearrangements involve migration of a hydrogen from the carbon atom in the 5-position of the ring to the methylene group attached in the 2-position.

Experimental Part

Synthesis of 2-Furylacetic Acid

2-Furylacetaldoxime, $C_4H_3O—CH_2CH{=}NOH$.—Pure freshly distilled furfural was condensed with nitromethane according to the procedure of Thiele and Landers,[7] and the resulting furylnitroethylene was reduced by means of zinc and aqueous acetic acid as described by Bouveault and Wahl.[8] Since the purification of the oxime by distillation results in a considerable loss through decomposition, the crude oxime was converted directly into furylacetonitrile. The yields of the crude oxime were 65–70% of the calculated amount. Preliminary experiments indicated that the improved yield obtained by using the purified oxime did not compensate for the loss entailed in its purification.

2-Furylacetonitrile (α-Furfuryl Cyanide), $C_4H_3O—CH_2CN$.—The method employed for the dehydration of 2-furylacetaldoxime was similar to that used by Dollfus[9] for the conversion of phenylacetaldoxime into phenylacetonitrile. A trial experiment with the lower homolog of furylacetaldoxime, furfuraldoxime, indicated that the corresponding nitrile could be obtained in satisfactory yield by the use of this method. Fifty grams of crude 2-furylacetaldoxime (0.4 mole) was dissolved in 80 g. of acetic anhydride (0.8 mole) and the solution was boiled gently for two to three minutes. After cooling, the dark colored solution was poured carefully into a slight excess of aqueous sodium carbonate solution and the mixture was subjected to steam distillation. The 2-furylacetonitrile was extracted from the distillate with pure ether and the ethereal solution was dried over anhydrous calcium chloride. After removal of the solvent, the residual 2-furylacetonitrile was distilled under diminished pressure, b. p. 78–80°, at 20 mm. The yields were 5–6 g. (12–15%, calculated on the basis that the crude oxime was 100% pure).

2-Furylacetonitrile is a colorless liquid when freshly distilled but rapidly becomes yellow on standing, even in sealed tubes. It is appreciably soluble in water and is extremely soluble in alcohol and ether; it has a pleasant aromatic odor resembling that of phenylacetonitrile. The physical constants of the redistilled material were: b. p. 78–80° at 20 mm., n_D^{25} 1.4715, d_4^{25} 1.0854; MR_D (calcd.)[10] 28.24, MR_D (obs.) 27.60.

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[6] Pummerer and Gump, *Ber.*, **56**, 999 (1923). These authors converted α-furfuryl alcohol into levulinic acid in 40% yields by heating with aqueous 0.5 *N* hydrochloric acid or 10% aqueous oxalic acid. In anhydrous methyl alcohol containing 0.1% of hydrogen chloride, α-furfuryl alcohol gave δ-methoxylevulinic acetal and methyl levulinate.

[7] Thiele and Landers, *Ann.*, **369**, 303 (1909).

[8] Bouveault and Wahl, *Bull. soc. chim.*, [3] **29**, 526 (1903).

[9] Dollfus, *Ber.*, **25**, 1917 (1892).

[10] The molecular refraction of this compound was calculated from the revised values of Eisenlohr for the atomic refractions [Landolt-Börnstein, "Physikalisch-chemische Tabellen," Julius Springer, Berlin, 5th ed., Vol. II, **1923**, p. 985]. The observed molecular refraction was obtained by the Lorentz–Lorenz formula.

Kirner and Richter reported the following physical constants for the nitrile obtained from α-furfuryl chloride, after four fractionations under diminished pressure: b. p. 74–75° at 27 mm., n_D^{20} 1.4833, d_4^{20} 1.04627; MR_D (calcd.)[11] 28.173; MR_D (obs.) 29.236.

Anal. Subs., 0.2243: CO_2, 0.5539; H_2O, 0.0944. Calcd. for C_6H_5ON: C, 67.27; H, 4.71. Found: C, 67.34; H, 4.71.

2-Furylacetic Acid, $C_4H_3O—CH_2COOH$.—The nitrile described above was hydrolyzed by refluxing for several hours with an 18% aqueous solution of potassium hydroxide. The resulting dark colored solution was cooled, treated with decolorizing charcoal and filtered. The filtrate was added slowly while stirring vigorously to a 20% excess of ice-cold 50% sulfuric acid which was covered with a layer of ether, in order to extract the organic acid from the aqueous layer as soon as it was liberated. The ethereal solution was separated, washed with a small volume of cold water and dried over anhydrous calcium chloride. After removal of the solvent the crude 2-furylacetic acid crystallized in yellow leaflets. After three crystallizations from petroleum ether, b. p. 25–40°, the melting point remained constant at 67.3–67.5° (uncorr.), and the product formed beautiful glistening white leaflets. This acid is slightly soluble in petroleum ether, appreciably soluble in water, and very soluble in alcohol and ether.

Anal. Subs., 0.2054: CO_2, 0.4282; H_2O, 0.0877. Calcd. for $C_6H_6O_3$: C, 57.13; H, 4.80. Found: C, 57.35; H, 4.82. Neutralization value: calcd., 126.1; found. 125.2.

Microscopical Examination.—The substance can be crystallized from water or petroleum ether; both solvents give rise to the same crystal habit. Crystals from petroleum ether were used for this study.

The substance crystallizes in six-sided plates or in long thin tablets which in no way resemble needles. Examination shows these tablets to be elongated modifications of the six-sided plates. Edges of the crystals indicate the possibility of fine, lamellar twinning.

The angles at the ends of the crystals are about 122° with adjacent edges seldom of equal length. The crystals exhibit a very slight oblique extinction of between 2 and 3°, accompanied by dispersed, extinction. Birefringence is moderately weak. Due to the solubility of the substance in water and organic liquids, the indices of refraction could not be determined.

The interference figure indicates that the crystals are optically negative and that the observed crystal faces are perpendicular to a line drawn somewhere between the acute bisectrix and an optic axis, *i. e.*, they are inclined to the acute bisectrix. The optic axial angle was judged to be about 40° ($2V = 40° \pm$), assuming $n = 1.5$. The optic plane is nearly normal to the elongation direction of the crystals. Apparently, these belong either to the monoclinic or triclinic system.

Anilide of 2-Furylacetic Acid, $C_4H_3O—CH_2CONHC_6H_5$.—One gram of pure furylacetic acid was boiled gently with 3 g. of freshly distilled aniline in a small test-tube. The latter was provided with a cork bearing a small bent glass tube which allowed the water to distil out of the reaction mixture. After cooling, the contents of the tube

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[11] In a private communication Dr. Kirner stated that the value 30.571 which was published in his paper should be corrected to 28.173.

were treated with water and the product was taken up in ether. The ethereal solution was extracted successively with dilute hydrochloric acid and dilute potassium hydroxide solution to remove excess aniline and unreacted furylacetic acid. The solvent was distilled off and the residual anilide was crystallized from 50% alcohol. The purified 2-furylacetanilide formed grayish-white leaflets, m. p. 79–80° (uncorr.).

Anal. Subs., 0.1334: CO_2, 0.3468; H_2O, 0.0682. Calcd. for $C_{12}H_{11}O_2N$: C, 71.61; H, 5.51. Found: C, 70.90; H, 5.72.

Decarboxylation of 2-Furylacetic Acid. 2-Methylfuran.—In order to follow this reaction in an approximately quantitative way, a weighed sample of the acid was heated in a test-tube provided with a tared receiver and an ascarite bulb to absorb the evolved carbon dioxide. A slow stream of nitrogen was passed through the apparatus to displace the products of decomposition from the reaction tube. A sample of 2.009 g. of pure 2-furylacetic acid (0.0158 mole) on heating in an oil-bath at 250–260° for thirty minutes gave 0.559 g. of carbon dioxide (0.0127 mole) and 1.065 g. of 2-methylfuran (0.0130 mole). These quantities correspond, respectively, to 80 and 82% of the theoretical. The 2-methylfuran was dried over metallic sodium and redistilled; b. p. 62.8–63.5° at 737 mm. Wolff[12] reported b. p. 62.5–63° at 746 mm. for pure 2-methylfuran obtained by heating furfural hydrazone with sodium methylate.

Synthesis of 5-Methylfuroic Acid

Preparation from Rhamnose.—In a 1-liter flask connected through a short distilling column with condenser set for distillation, 50 g. of rhamnose was heated with 300 cc. of 10% hydrochloric acid containing 50 g. of sodium chloride. The methylfurfural steam distilled during the course of heating (one and one-half to two hours) and was extracted from the distillate with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. After distilling off the solvent, the residual 5-methylfurfural (2.3–2.6 g.) was oxidized to the corresponding acid by means of silver oxide, in the presence of barium hydroxide.[13] The resulting 5-methylfuroic acid was crystallized twice from water, once from a mixture of benzene and petroleum benzine and finally from petroleum benzine, b. p. 100–110°; it formed white needles, m. p. 107–108.5° (108.3–109.8°, corr.).

Preparation from α-Furfuryl Alcohol.—The synthesis from α-furfuryl alcohol was effected through the preparation of α-furfuryl chloride,[4] reaction of the latter with aqueous sodium cyanide and hydrolysis of the resulting nitrile by means of 25% potassium hydroxide solution, according to the directions of Kirner and Richter.[1] The resulting acid was crystallized twice from water and twice from petroleum benzine, b. p. 100–110°; it formed white needles, m. p. 107–108.5° (108.3–109.8°, corr.). Kirner and Richter reported m. p. 108.5–109.5 (uncorr.).

The acid obtained in this way was mixed thoroughly with an equal quantity of the authentic 5-methylfuroic acid obtained from rhamnose and the mixture was found to melt at 107–108.5° (108.3–109.8°, corr.), which is exactly the same temperature as that of the original acids. The identity of the two specimens was confirmed further by a microscopical study of the crystals.

Microscopical Examination.—Both substances crystallize from water in the same crystal habit. The crystals are rectangular tablets or elongated six-sided tablets, the rectangular tablets being preponderant. Both types show beveled edges. Since the substances were soluble in water and most organic liquids, it was impossible to determine the refractive

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[12] Wolff, *Ann.*, **394**, 102 (1912).

[13] Delépine and Bonnet, *Bull. soc. chim.*, [4] 5, 883 (1909).

indices. The crystals exhibit strong birefringence and are either of the orthorhombic or the monoclinic system.

The rectangular tablets are perpendicular to the optic normal, as indicated by their interference figure, and show parallel extinction.

The six-sided tablets are perpendicular to the acute bisectrix and extinguish parallel to the elongation. This plane of extinction contains the axial plane. The crystals exhibit marked dispersion of the optic axes ($v > \rho$) and are optically negative. The apparent optic axial angle is greater than 120° ($2E > 120°$). The angles at opposite ends of the crystals are about 106° (determined, 105.5°, 106.2°).

Summary

1. 2-Furylacetic acid has been synthesized from furfural by a series of reactions which does not involve the use of mineral acids.

2. It has been shown that an acid prepared by the nitrile synthesis from α-furfuryl chloride, and described as 2-furylacetic acid, is actually the isomeric 5-methyl-2-furoic acid. It appears probable that rearrangement of the α-furfuryl group into the 5-methylfuryl group occurred in the reaction of α-furfuryl chloride with aqueous sodium cyanide solution.

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

CERTAIN DIALKYL ACETIC ACIDS CONTAINING 12, 13 AND 14 CARBON ATOMS AND THEIR BACTERICIDAL ACTION TOWARD B. LEPRAE. XVIII[1,2]

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In a previous paper a comparison of a complete series of octadecanoic acids and a complete series of hexadecanoic acids of the general formula $RCH(CO_2H)R'$ were prepared in which R and R' were alkyl groups of the proper size to give the desired molecular weight. The various octadecanoic acids gave irregular bactericidal values but the hexadecanoic acids showed values which increased regularly as the carboxyl group was moved toward the middle of the chain. The conclusion was drawn that the bactericidal action was due to the particular physical properties of the acids and that among these properties molecular weight appeared to be very important. In several of the series of acids studied which contained a ring structure, compounds containing less than 16 carbon atoms were

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[1] Three previous papers in this field are XV, Stanley, Jay and Adams, THIS JOURNAL, **51**, 1261 (1929); XVI, Ford and Adams, *ibid.*, **52**, 1259 (1930); XVII, Browning, Woodrow and Adams, *ibid.*, **52**, 1281 (1930).

[2] This communication is in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.