[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

FURYLANGELIC ACID[1]

BY ALBERT S. CARTER

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In proving the structure of furfural, Baeyer[2] studied the condensation of furfural and sodium acetate, yielding furylacrylic acid in a manner exactly analogous to the condensation of benzaldehyde to yield cinnamic acid. Upon reduction, furylacrylic acid gave furylpropionic acid, which upon treatment with bromine and subsequent oxidation by silver oxide was converted into a so-called *furonic acid*, having the structure indicated by the formula $HOOCCH{=}CHCOCH_2CH_2COOH$. This was reduced by hydriodic acid to yield a dibasic acid identified as pimelic.

In the same general manner used to prepare furylacrylic acid, Baeyer[3] successfully prepared a so-called furylangelic acid from sodium butyrate and furfural, to which he assigned the structure $C_4H_3OCH{=}CHCH_2CH_2COOH$. Tönnies[4] reported the conversion of furylangelic acid into furylvaleric, butyrofuronic and finally azelaic acids in a manner analogous to the conversion of furylacrylic into pimelic acid. The azelaic acid thus obtained did not agree exactly in melting point with any of the known isomers of the formula $C_9H_{16}O_4$, but approximated most nearly that of *n*-azelaic acid. The literature definitely states that the resulting acid possesses a normal chain. The structure $C_4H_3OCH{=}CHCH_2CH_2COOH$ does not agree with the present conception of the course of the Perkin condensation, for in the light of the formation of α-methylcinnamic acid from benzaldehyde and sodium propionate and other similar condensations, we should be led to expect that Baeyer's furylangelic acid would have the structure represented by $C_4H_3OCH{=}C(C_2H_5)COOH$. This would lead to the formation of α-ethylpimelic acid instead of *n*-azelaic acid in the course of the reactions carried out by Tönnies, but this ethylpimelic acid has been prepared[5] and found to differ from the product which Tönnies reported.

Furylangelic acid was prepared and found to be identical with the product obtained by Baeyer. By treatment with ozone and hydrolysis of the ozonide, the products included carbon dioxide, propionic acid and possibly α-ketobutyric acid. It is impossible to obtain these products

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[1] From an investigation, carried out under the direction of Professor Richard Fischer, which constituted a part of a thesis presented by A. S. Carter to the Graduate School Faculty of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

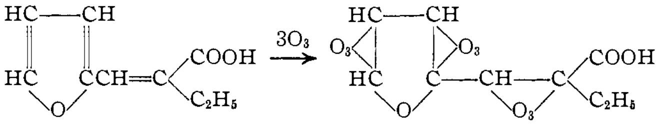
[2] Baeyer, *Ber.*, **10**, 355, 395, 1358 (1877).

[3] Baeyer, *Ber.*, **10**, 1364 (1877).

[4] Tönnies, *Ber.*, **12**, 1200 (1879).

[5] Carter, THIS JOURNAL, **50**, 1967 (1928).

from Baeyer's formula for furylangelic acid (δ-furylallylacetic acid), but they might, however, be the expected products from α-ethyl-β-furylacrylic acid, as shown below. This evidence indicates that furylangelic acid is an ethylacrylic acid derivative and the ozone oxidation proceeds as follows



the ring breaking to form HCOOH, CHOCHO and CHOCOOH, and the side chain giving $C_2H_5COCOOH$, which subsequently decomposes to form C_2H_5COOH, CO_2 and H_2O. The evidence throughout the remainder of this paper substantiates this view.

The products of permanganate oxidation of furylangelic acid included furoic acid, acetic acid and propionic acid, and from a study of the oxidation it was concluded that it could be understood only through the use of the ethylacrylic acid structure for furylangelic acid, oxidizing at the side-chain double bond to give ketobutyric acid, which decomposed in two ways to form acetic acid and propionic acid.

In an endeavor to correlate these facts with those of Tönnies, his work was repeated as exactly as possible. Having established the structure of furylangelic acid as possessing a branched chain, it was considered improbable that any means of reduction and ring opening could yield *n*-azelaic acid.

Reduction of furylangelic acid gave furylvaleric acid, which was undoubtedly the same as that obtained by Tönnies, though no analytical results or physical data can be found by which his product might be recognized. The composition of this product indicated that the reduction consisted in the addition of one molecule of hydrogen, which would be expected to enter at the most vulnerable point, namely, the double bond in the side chain. The reduction would then be analogous to the reduction of cinnamic to hydrocinnamic acid.

Furylvaleric acid was converted into butyrofuronic acid through the use of bromine and subsequent oxidation with silver oxide

$$C_4H_3OC_4H_6COOH \xrightarrow[H_2O]{Br_2} OCHCH{=}CHCOC_4H_6COOH + 2HBr \xrightarrow{Ag_2O} HOOCCH{=}CHCOC_4H_6COOH$$

The product of this reaction was carefully purified and found to possess a melting point slightly higher than that recorded by Tönnies, but analysis indicated the same compound. The name given to this acid is misleading. In accord with his structure of furylangelic acid, butyrofuronic acid would be heptene-1-one-3-dicarboxylic acid-1,7; in accord with the structures established in this paper it should be heptene-1-one-3-dicarboxylic acid-1,5.

Upon hydriodic acid reduction of butyrofuronic acid, *n*-azelaic acid was not obtained. Instead, the products of the reduction were ethylpimelic acid and heptanone-3-dicarboxylic acid-1,5. The results of this work seem to warrant the conclusion that an acid melting at 117° similar to azelaic acid cannot be obtained by the method of hydriodic acid reduction employed. The melting point of the butyrofuronic acid used by Tönnies might indicate that it was impure and this might lead to the explanation of his different results. To speculate upon the hydriodic acid reduction; in the light of such anomalous results as the reduction of dibenzylcarbonyl to the phosphoric acid ester of the corresponding alcohol, as obtained by Gräbe[6] and Johnson and Hodge,[7] it would not be highly improbable to expect the reduction of butyrofuronic acid to ethylacetone diacetic acid (heptanone-3-dicarboxylic acid-1,5) and the corresponding hydroxy compound which Tönnies found to be unstable, as intermediate reduction products. Heptanone-3-dicarboxylic acid-1,5 was evidenced by the products obtained by reduction at 190° for four hours; further reduction might next produce the hydroxyl group and subsequent decomposition of this acid take place, thus accounting for the water-insoluble resin and the low yields of the final product, ethylpimelic acid, mentioned in the experimental part of this paper.

Marckwald[8] subjected furylacrylic acid to the action of dry hydrogen chloride in alcoholic solution and obtained a diethyl ester of acetone diacetic acid. In a manner similar to this, the diethyl ester of heptanone-3-dicarboxylic acid-1,5 was prepared, which upon hydrolysis yielded the previously unprepared acid. Marckwald was unsuccessful in carrying out a similar reaction upon furylpropionic acid; the same failure to obtain results was found when the reaction was applied to furylvaleric acid. It is probable, therefore, that the double bond plays an important part in this reaction, which is essentially the addition of two molecules of water to furylangelic acid.

Heptanone-3-dicarboxylic acid-1,5 was successfully reduced to ethylpimelic acid by means of hydriodic acid. In all, fifteen reductions were made on butyrofuronic acid and heptanone-dicarboxylic acid and in no case was an acid similar to azelaic obtained, proving conclusively that furylangelic acid has the furylethylacrylic structure indicated by its oxidation products.

Experimental Part

Furylangelic Acid.—Forty g. of dry sodium butyrate, 40 cc. of freshly distilled furfural and 100 g. of butyric anhydride were heated under an air condenser for eighteen hours at 135–160°. The product, while warm, was washed out of the reaction flask

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[6] Gräbe, *Ber.*, **7**, 1624 (1874).

[7] Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913).

[8] Marckwald, *Ber.*, **20**, 2811 (1887); **21**, 1398 (1888).

with 450–500 cc. of water, was neutralized with sodium carbonate and then treated for two or three hours with absorbent charcoal without boiling. Upon filtration, most of the tar and much of the color was removed; this was then again treated with charcoal, boiled for twenty minutes, allowed to settle and filtered, giving a light yellow solution. Boiling the solution during the first treatment causes the solution of some of the tar, which is otherwise carried down with the charcoal in the cold. Boiling the solution for twenty minutes during the second treatment was found to replace satisfactorily steam distillation of the excess furfural from the reaction mixture. Ice was then added and the free acid precipitated with dilute sulfuric acid. An excess of sulfuric acid is to be avoided, for it tends to bring out remaining furfural, contaminating the product. The cold solution was filtered by suction and the furylangelic acid dried; yield, 45–48 g. (80%) of crude, slightly colored product melting at 85–90°. For much of the work this crude acid could be used without further purification but it was readily purified by dissolving in ethyl alcohol and precipitating with ice water or by crystallization from hot petroleum ether. The pure substance melted at 95.5–97° after drying at 40° in vacuum for six hours; it was soluble in alcohol, chloroform, hot petroleum ether and slightly in hot water.

Anal. Subs. 0.1500: CO_2, 0.3577; H_2O, 0.0806. Calcd. for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found: C, 65.04; H, 5.94.

The melting point recorded above is higher than that observed by Baeyer (87–88°). The melting point of the crude acid before purification checked more closely that of Baeyer. Two stereoisomeric forms are possible. Liebermann[9] isolated two forms of furylacrylic acid which were found to melt at 103 and 82–86°.

It was found impossible to obtain satisfactory yields of furylangelic acid using acetic anhydride as the condensing agent, as furylacrylic acid was the predominant product of the reaction in every case.

Ozone Oxidation of Furylangelic Acid.—Ten g. of dry furylangelic acid was dissolved in 200 cc. of dry chloroform in a tall cylinder, packed in ice and subjected to 5% ozonized oxygen at the rate of 10 liters per hour for four hours. The substance became yellow and then darkened to a brown with a definite green fluorescence and a brown, oily product separated on the sides of the tube. The ozonide was a thick, brown, tarry mass, insoluble in water and only partially soluble in chloroform, with a strong pungent odor resembling acetic acid. The chloroform was removed under diminished pressure after transferring the product to a 500-cc. flask. The ozonide was hydrolyzed by refluxing for three hours with 300 cc. of water. The product consisted of an acid solution and a tar from which nothing could be resolved. The acid solution was neutralized with dilute sodium hydroxide and evaporated to 2 cc. under diminished pressure. This solution was made acid with hydrochloric acid and a small amount of insoluble tar filtered off; the filtrate was treated with 1 cc. of a solution containing one part of phenylhydrazine to eight of a 50% solution of acetic acid. After standing for several hours, an oily hydrazone precipitated out, which was filtered off and recrystallized from chloroform; m. p. 138–142°. Upon standing for a few days, this hydrazone became liquid and underwent decomposition. Its behavior and properties resembled the phenyl hydrazone of α-ketobutyric acid, melting[10] at 144–145° which is probably the primary product of the hydrolysis.

It was found that the hydrolysis product was much more strongly acid if a small quantity of ferric chloride was added before hydrolyzing. The tar was filtered from this solution; it was made alkaline with ammonium hydroxide and again filtered to remove

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[9] Liebermann, *Ber.*, **27**, 283 (1894); **28**, 129 (1895).

[10] Wislicenus, *Ann.*, **246**, 333 (1888).

ferric hydroxide. The solution was treated with ammoniacal silver nitrate and warmed to 40–50° for six hours; the resulting reduced silver was filtered from the warm solution, leaving a more completely oxidized product which was free from formaldehyde. This was made strongly acid with phosphoric acid, filtered and distilled to a volume of 30 cc. The acid distillate was redistilled and used for Duclaux determinations of the acid present. The values determined on two runs were 11.4, 11.2, 11.4 and 11.6, 11.6, 11.6 on the first three 10-cc. fractions. These values indicate propionic acid, which was checked by the preparation of propiono-*p*-toluide from the sodium salts obtained by evaporating the neutralized distillates from the Duclaux determinations.

Permanganate Oxidation.—Ten g. of furylangelic acid was dissolved in 150 cc. of water containing 10 g. of sodium hydroxide; this was rapidly titrated with saturated potassium permanganate (about 680 cc.), the manganese dioxide was filtered off and the solution was boiled down to a volume of 100 cc. Upon acidifying the solution with sulfuric acid, a white precipitate resulted, which was filtered off, dried and identified as furoic acid.

Anal. Subs. 0.2000: CO_2, 0.3916; H_2O, 0.0635. Calcd. for $C_5H_4O_3$: C, 53.57; H, 3.57. Found: C, 53.40; H, 3.53.

The acid solution was still found to reduce permanganate, so 100 cc. of the saturated permanganate solution was added and the mixture distilled until salts began to crystallize out. The distillate was redistilled after addition of 10 cc. of sulfuric acid and an equal volume of permanganate, leaving about 20 cc. in the distilling flask to insure that no sulfuric acid was in the product. This was used for Duclaux determination of the acids present, the first four fractions giving the following values: 9.9+, 9.9−, 9.8−, 9.7+. These values do not check either propionic acid or acetic acid, but fall between them. The neutral solutions were evaporated and the resulting sodium salts were used for the preparation of *p*-toluides. The melting point of the resulting toluide was 104–120°, indicating a mixture. This was dissolved in 3 cc. of hot benzene and, upon cooling, aceto-*p*-toluide, melting at 146–147°, was obtained and a more soluble toluide remained in the benzene, which was recrystallized from petroleum ether, giving a product melting at 120–125°, probably indicating propiono-*p*-toluide (m. p. 123–124.5°).

Upon carrying out a similar run in which the furylangelic acid was dissolved in hot, concentrated sulfuric acid, considerable carbon dioxide was evolved during the addition of the oxidizing agent and no furoic acid was left at the end, indicating that the furane ring had been oxidized. The acid distillate, however, gave the same toluides and Duclaux values as had been found in the case of the basic oxidation. If phosphoric acid was substituted for sulfuric acid, the Duclaux values were lower, that is, 8.0, 8.2, 8.5, and the relative amount of the propiono-*p*-toluide obtained was very small. This evidence seems to indicate that acetic and propionic acids are both formed from some intermediate oxidation product, probably ketobutyric acid, for it was found that propionic acid was not oxidized to acetic acid under the conditions of this work.

Furylvaleric Acid.—Fifty grams of furylangelic acid was suspended in 2 liters of water and 800 g. of 3% sodium amalgam was added; frequent small additions of sulfuric acid hastened the action of the amalgam. The basic solution was separated from mercury, filtered and acidified with sulfuric acid, giving an oil which was collected in ether, dried over sodium sulfate and finally, upon evaporation of the ether, gave 50 g. of an oily acid (98% of the theoretical). This acid was distilled under diminished pressure; b. p. about 174° at 46 mm.

Anal. Subs. 0.2000: CO_2, 0.4698; H_2O, 0.1274. Calcd. for $C_9H_{12}O_3$: C, 64.3; H, 7.14. Found: C, 64.05; H, 7.08.

Butyrofuronic Acid.—By means of violent mechanical stirring, 4.5 g. of furylvaleric acid was suspended in one liter of water. To this was added 4.5 g. of bromine dissolved in water; stirring was stopped and the brominated mixture was immediately poured upon washed silver oxide, freshly precipitated from 28.5 g. of silver nitrate. Again the product was mechanically stirred and heated in a water-bath at 35–40° for two hours. The silver was precipitated with hydrochloric acid, filtered and the butyrofuronic acid extracted with ether. Continuous ether extraction for twenty-four hours was necessary because of the solubility of butyrofuronic acid in water. Evaporation of the ether gave brown crystals which were purified by dissolving in water, boiling with absorbent charcoal and evaporating to dryness in a vacuum desiccator over calcium chloride. This product was further purified by precipitating from warm ether by means of petroleum ether. Butyrofuronic acid was soluble in water, alcohol, warm chloroform and ether; m. p. 149–150° (Tönnies gives 140–142° with previous softening); yield about 1 g. (18–19%).

Anal. Subs. 0.1350: CO_2, 0.2669; H_2O, 0.0714. Calcd. for $C_9H_{12}O_5$: C, 54.0; H, 6.00. Found: C, 53.90; H, 5.88.

Reduction of Butyrofuronic Acid.—One g. of butyrofuronic acid, 8 g. of hydriodic acid (sp. gr. 1.70) and 0.5 g. of red phosphorus were sealed in a Pyrex bomb tube and heated at 195–200° for six hours. Upon opening the tube there was slight pressure and an inflammable gas escaped; the contents were decolorized with sulfurous acid and extracted with ether. Evaporation of the ether left brown, tarry material, a part of which was soluble in hot water. This portion was precipitated from hot water three times, giving a colorless product which was further purified by precipitation from hot benzene. This entire oily mass crystallized upon the introduction of a crystal of ethylpimelic acid and proved to be identical with ethylpimelic acid (heptane-dicarboxylic acid-1,5), melting at 41–43°, and the silver salt corresponded to silver ethylpimelate.

Anal. Subs. 0.2000: AgCl, 0.1430. Calcd. for $C_9H_{14}O_4Ag_2$: Ag, 53.73. Found: Ag, 53.81.

The temperature and the duration of heating were varied in a number of runs but in no case was a product melting at 117° obtained. By adding only 0.3 g. of phosphorus and heating for four hours, a very small amount of heptanone-3-dicarboxylic acid-1,5 was recognized in the product.

Heptanone-3-dicarboxylic Acid-1,5.—Thirty g. of furylangelic acid was dissolved in 100 cc. of 95% alcohol and subjected to dry hydrogen chloride until a turbid solution was obtained (twenty-five minutes). Continuing the current of hydrogen chloride, this was refluxed on a water-bath for one hour, then treated with the gas for two hours longer, during which period it was allowed to cool. The alcohol and hydrogen chloride were distilled off on a water-bath, leaving a thick, brown oil possessing a pleasant aromatic odor. This ester was shaken with an equal volume of saturated sodium carbonate solution, collected in a small volume of ether and fractionated under diminished pressure. The major portion of the product distilled at 198–200° (25 mm.), giving 45 g. (96%) of colorless ester. Free heptanone-3-dicarboxylic acid-1,5 was obtained by refluxing with 150 cc. of 20% potassium hydroxide solution until the hydrolysis was complete. This solution was acidified with sulfuric acid and continuously extracted with ether for a period of forty-eight hours. Evaporation of the ether gave 32.5 g. (92.4%) of crystalline acid from 45 g. of the ester. Heptanone-dicarboxylic acid was readily obtained in a high degree of purity by recrystallizing from hot benzene; m. p. 83–84.5°. The silver salt was prepared and analyzed.

Anal. Subs. 0.3000: AgCl, 0.2061. Calcd. for $C_9H_{12}O_5Ag_2$: Ag, 51.9. Found: Ag, 51.7.

Heptanone-dicarboxylic acid was soluble in water, ether, acetone, chloroform and hot benzene; insoluble in cold benzene and petroleum ether; it crystallized in small white rosets from the sirup resulting by evaporation of a water solution.

Reduction of Heptanone-3-dicarboxylic Acid-1,5.—As before in the reduction of butyrofuronic acid, 9 g. of the acid was reduced by means of 1.8 g. of phosphorus and 60 cc. of hydriodic acid for eight hours at 190–200°. The product, extracted from the reduction mixture after decolorizing with sulfur dioxide and purifying by precipitation from hot water and benzene, consisted of 1 g. of colorless liquid which crystallized upon the introduction of a crystal of ethylpimelic acid. Analysis and melting point indicated that the reduction product was identical with that obtained from butyrofuronic acid, namely, ethylpimelic acid. The analysis of the silver salt gave the following results.

Anal. Subs. 0.5000: AgCl, 0.3601. Calcd. for $C_9H_{14}O_4Ag_2$: Ag, 53.73. Found: Ag, 54.20.

Summary

1. A method has been developed whereby furylangelic acid can be produced in yields of over 80% of the theoretical from furfural, sodium butyrate and butyric anhydride.

2. The structure of furylangelic acid and the course of the Perkin reaction when applied to furfural and butyric acid have been established through the isolation and identification of the products of oxidation of furylangelic acid.

3. Furylvaleric acid has been prepared and the ring opened by bromination and oxidation to yield heptene-1-one-3-dicarboxylic acid-1,5.

4. Butyrofuronic acid has been reduced to heptane-dicarboxylic acid-1,5 and heptanone-3-dicarboxylic acid-1,5.

5. The previously unprepared heptanone-3-dicarboxylic acid-1,5 and its ethyl ester have been prepared from furylangelic acid, and this product has been reduced to heptane-dicarboxylic acid-1,5.

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

THE ACIDIC AND BASIC CATALYSIS OF ACETYLATION REACTIONS

BY JAMES B. CONANT AND GEORGE M. BRAMANN

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The acetylation of hydroxy compounds by means of acetic anhydride is frequently catalyzed by the addition of sulfuric acid, sodium acetate or pyridine. Since acetic acid is often the initial solvent and is always formed by the reaction, the behavior of these catalysts in this solvent may afford the clue to the explanation of their action. Sulfuric acid is obviously an acid catalyst which furnishes hydrogen ions in excess of those provided by acetic acid itself. Sodium acetate and pyridine are examples of basic catalysts, since it has been shown[1] that these substances are strong bases in acetic acid.

The development of methods of studying the hydrogen ion activity

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[1] Hall and Conant, THIS JOURNAL, **49**, 3047 (1927).