[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Synthesis of 3,4-Dicarboxy-2-furanvaleric Acid and Some of Its Derivatives

BY KLAUS HOFMANN[1]

Synthetic work on substances related to biotin, which is at present under way in this Laboratory called for the preparation of 3,4-dicarboxy-2-furanvaleric acid. Alder and Rickert[2] have described a procedure for the preparation of furan-3,4-dicarboxylic acid which we have successfully applied to the synthesis of 3,4-dicarboxy-2-furanvaleric acid. The starting material for the present investigation was 2-furanvaleric acid which was prepared by a modification of the method of Asano and Nakatomi.[3] Furylacrolein (I) and malonic acid were condensed to 4-(2-furyl)-1,3-butadiene-1,1-dicarboxylic acid (II). Attempts to decarboxylate this substance according to the procedure of the Japanese workers resulted in the formation of tarry products and in no instance was it possible to obtain 4-(2-furyl)-1,3-butadiene-1-carboxylic acid (III). The original procedure was therefore modified. The crude condensation product (II) was dissolved in methanol and was hydrogenated with palladium black as the catalyst until approximately 3 moles of hydrogen had been absorbed. Decarboxylation of the resulting product in pyridine solution at 130–140° resulted in the formation of 2-furanvaleric acid (IV) which was obtained in 50% yield as a white crystalline mass melting at 42–43°. The acid was further characterized by the preparation of its anilide which melted at 75–76°.

When equimolar amounts of this acid and diethyl-acetylene-dicarboxylate were heated on the steam-bath the diene addition compound (V) was obtained as a viscous oil. This oil when hydrogenated in the presence of palladium black, absorbed one mole of hydrogen and was transformed into the partially hydrogenated substance (VI). Heating of this product to 190–200° caused its decomposition into ethylene and 3,4-dicarbethoxy-2-furanvaleric acid (VII) which was obtained in 60–70% yield as a viscous oil boiling at 204–206° at 0.02 mm. Saponification of (VII) yielded 3,4-dicarboxy-2-furanvaleric acid (VIII) melting at 188–190°. The presence of the furan nucleus in this acid was demonstrated spectroscopically. The ultraviolet absorption spectrum of (VIII) was compared with the absorption curve of 3,4-dicarboxy-furan prepared according to Reichstein, *et al.*[4] As may be seen from Fig. 1 the two absorption curves are almost identical, demonstrating the furan nature of the tricarboxylic acid (VIII).

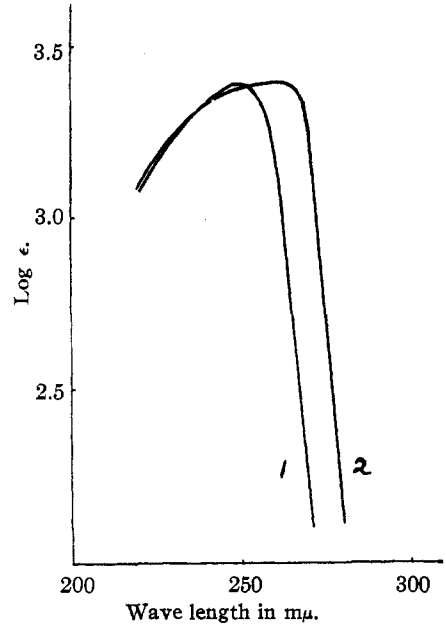


Fig. 1.—Ultraviolet absorption spectra of 3,4-dicarboxy-furan (curve 1) and 3,4-dicarboxy-2-furanvaleric acid (curve 2) in absolute alcohol.

The application of the Alder–Rickert synthesis made it possible to prepare derivatives of 3,4-dicarboxy-2-furanvaleric acid containing various substituents at the furan carboxyls as well as at the acid group at the end of the aliphatic side-chain. Thus treatment of the ester acid (VII) with thionyl chloride gave the acid chloride (X) which, when coupled with piperidine, formed the oily ester piperidide (XI). Treatment of this derivative with alcoholic potassium hydroxide removed the ester groups in positions 3 and 4 with the formation of 3,4-dicarboxy-2-furanvaleric acid piperidide (XII) melting at 133–134°. In contrast to the aliphatic carboxyl group, which is blocked by the piperidine residue, the ring carboxyl groups in compounds (XI) and (XII) are available for further transformations.

As may be seen in the experimental section, the triethyl ester (IX) of (VIII) has likewise been prepared.

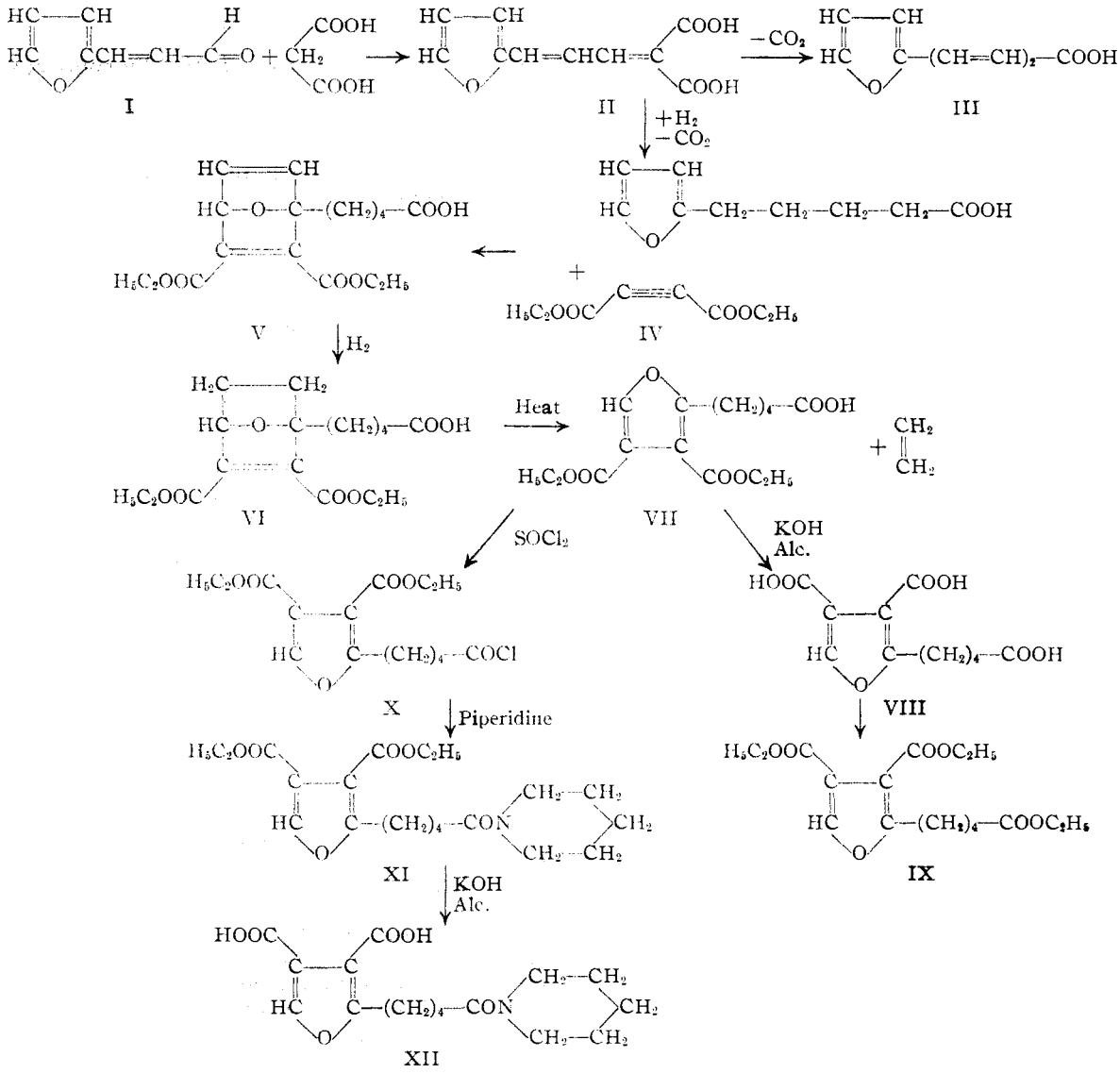
It has been possible to hydrogenate some of the above compounds and thus to prepare the corresponding tetrahydrofuran derivatives. The results of these studies will be presented in a forthcoming publication from this Laboratory.

(1) The author wishes to express his thanks to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for their generous support of this work.

(2) Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(3) Asano and Nakatomi, *J. Pharm. Soc.* (Japan), **53**, 176 (1933).

(4) Reichstein, Grüssner, Schindler and Hardmeier, *Helv. chim. acta*, **16**, 276 (1933).



Experimental

All melting points are corrected.

4-(2-Furyl)-1,3-butadiene-1,1-dicarboxylic Acid (II).—325 grams of furyl-acrolein, prepared according to Burdick and Adkins,[5] and 600 g. of malonic acid were dissolved in 890 cc. of pyridine; 1 cc. of piperidine was then added and the solution was heated on the steam-bath for four hours in a stream of carbon dioxide. The resulting dark red solution was poured on cracked ice and acidified to congo red with concentrated hydrochloric acid. The reaction product began to crystallize and the crystallization was complete after the solution was kept in the refrigerator overnight. The crystalline material was then collected on a Buchner funnel, was washed with dilute hydrochloric acid and water and was dried at 100° *in vacuo*; 337 g. of the crude product was obtained in the form of orange needles. This material, which consists of a mixture of isomers, was used for the next step without further purification. A sample was recrystallized from dilute methanol. Red needles were obtained, which decomposed at 190–195° without melting.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.68; H, 3.87. Found: C, 57.80; H, 4.01.

(5) Burdick and Adkins, THIS JOURNAL, **56**, 441 (1934).

2-Furanvaleric Acid (IV).—Fifty grams of the above acid was dissolved in 400 cc. of methanol and was hydrogenated in the presence of palladium black at a pressure of 0.1 atmosphere until 13 liters of hydrogen had been consumed. The catalyst was then filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting sirup was dissolved in 100 cc. of pyridine and the solution was heated to 130–140° until the vigorous evolution of carbon dioxide had stopped. The cooled mixture was then dissolved in ether. The ether solution was washed with dilute hydrochloric acid and water, and was dried over sodium sulfate. The ether was removed on the steam-bath and the residue was distilled *in vacuo*. The fraction boiling at 110–130° at 0.02 mm., solidified on cooling and represents almost pure 2-furanvaleric acid. A sample which was recrystallized from petrol ether melted at 42–43°. The yield was 20 g. (50% of the theoretical yield).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.18. Found: C, 64.02; H, 7.31.

Anilide of 2-Furanvaleric Acid.—3.3 grams of the above acid and 6 cc. of freshly distilled aniline were heated to 180° for twelve hours. The excess of aniline was removed *in vacuo*, the residue was taken up in ether and the ethereal solution was extracted with 3 *N* hydrochloric acid and water, and was dried over sodium sulfate. Sublimation

of the reaction product at 170° and 0.02 mm. yielded a white solid which was recrystallized from a mixture of ether and petrol ether; 3.7 g. of colorless needles melting at 75–76° was obtained.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.07; H, 7.04; N, 5.75. Found: C, 73.75; H, 6.83; N, 5.81.

3,4-Dicarbethoxy-2-furanvaleric Acid (VII).—54 grams of 2-furanvaleric acid (IV) and 62 g. of diethyl-acetylenedicarboxylate were heated on the steam-bath for twelve hours. The oily addition compound (V) was then dissolved in 300 cc. of ethyl acetate and was hydrogenated in the presence of palladium black until 1 mole of hydrogen had been absorbed. The catalyst was then removed by filtration and the ethyl acetate was evaporated. The residue which consists of the partially hydrogenated compound (VI) was then heated at 16 mm. pressure to 190–200° until the evolution of ethylene had stopped. The substance was then distilled and the fraction boiling at 205–210° at 0.02 mm. was collected; 68 g. (68% of the theoretical yield) of 3,4-dicarbethoxy-2-furanvaleric acid was obtained.

3,4-Dicarboxy-2-furanvaleric Acid (VIII).—21.6 grams of the above compound was dissolved in 80 cc. of 5 *N* potassium hydroxide and the solution was heated on the steam-bath for two hours; 80 cc. of water was then added and the solution was acidified to congo red with concentrated hydrochloric acid. The crystalline acid which separated out was collected, washed with water, and dried at 100° *in vacuo*; 16.8 g. (95% of the theoretical yield) of the crude acid melting at 180–182° was obtained. The material was purified by crystallization from a mixture of methanol and ethyl acetate. Needles melting at 188–190° were obtained.

Anal. Calcd. for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72. Found: C, 51.45; H, 4.90.

3,4-Dicarbethoxy-2-furanvaleric Acid Ethyl Ester (IX).—13.5 grams of the above acid, 200 cc. of absolute ethanol and 20 cc. of concentrated sulfuric acid were refluxed for twelve hours. The solution was then concentrated *in vacuo* to one-third of its volume. The residue was diluted with ice-cold water and was extracted with ether. The ether solution was washed with 2 *N* sodium carbonate and water and was dried over sodium sulfate. The ether was removed on the steam-bath and the residue was distilled *in vacuo*; 12.5 g. (70% of the theoretical yield) of the ester boiling at 165–166° at 0.02 mm. was obtained: $n^{24}D$ 1.4741; d^{24} 1.124. The same ester was obtained in 90% yield when 3,4-dicarbethoxy-2-furanvaleric acid (VII) was esterified in the manner described above.

3,4-Dicarbethoxy-2-furanvaleryl Chloride (X).—11.8 grams of 3,4-dicarbethoxy-2-furanvaleric acid (VII) was mixed with 15 cc. of thionyl chloride and the mixture was heated on the steam-bath until the vigorous reaction was over. The excess of thionyl chloride was removed *in vacuo* and the residue was distilled; 9.4 g. (74% of the theoretical yield) of the acid chloride, boiling at 177–178° at 0.02 mm., was obtained.

3,4-Dicarbethoxy-2-furanvaleric Acid Piperidide (XI).—9.4 grams of the above acid chloride (X) was dissolved in 50 cc. of dry ether and this solution slowly added to a solution of 8 g. of freshly distilled piperidine in 50 cc. of ether. The mixture was kept at room temperature for thirty minutes, then washed with 3 *N* hydrochloric acid, 2 *N* sodium carbonate and water and dried over sodium sulfate. The ether was removed and the resulting oil was distilled *in vacuo*; 9.72 g. (90% of the theoretical yield) of the piperidide boiling at 210–211° at 0.02 mm. was obtained: $n^{24}D$ 1.5006; d^{24} 1.132.

3,4-Dicarboxy-2-furanvaleric Acid Piperidide (XII).—9.5 grams of the above ester piperidide (XI) was dissolved in 20 cc. of 5 *N* potassium hydroxide and 40 cc. of methanol and the mixture refluxed for two hours. The solution was then concentrated *in vacuo* and the residue was acidified to congo red with concentrated hydrochloric acid. The resulting oil crystallized on cooling and scratching with a glass rod. The material was collected, was washed with water and was dried. Crystallization of the material from dilute alcohol yielded 6.4 g. (79% of the theoretical yield) of whetstone shaped needles melting at 132–133°.

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 59.45; H, 6.55; N, 4.33. Found: C, 59.33; H, 6.72; N, 4.31.

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Summary

1. 3,4-Dicarboxy-2-furanvaleric acid as well as some of its derivatives have been prepared.

2. A satisfactory procedure for the preparation of 2-furanvaleric acid has been described.

3. The ultraviolet absorption curves of 3,4-dicarboxy-2-furanvaleric acid as well as 3,4-dicarboxy-furan have been given.

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Unsaturated Synthetic Glycerides. III. Unsaturated Symmetrical Mixed Diglycerides[1]

BY B. F. DAUBERT AND H. E. LONGENECKER

Of the several reliable methods for the synthesis of diglycerides, all involve the use of a glycerol derivative with two free hydroxyls and one temporarily blocked or potential hydroxyl group. Thus, in the Fisher[2] method 1-iodohydrin (Alival) is treated with an excess of an acid chloride, producing 1-iodo-2,3-diacylglycerol. During the subsequent replacement of the iodine by an hydroxyl group, acyl migration from the 2(beta) to the 1(alpha) position of glycerol is known to occur with the resulting production of a symmetrical diglyceride. Similarly, when the 2,3-diacyl derivatives of either the 1-trityl ether of glycerol or 1-carbobenzyloxyglycerol are hydrolyzed, acyl migration occurs to yield the more stable 1,3-diglycerides.[3,4,5,6] These three independent methods have been useful

(1) The authors are indebted to Swift and Company and the Buhl Foundation for grants in support of this investigation.

(2) Fisher, *Ber.*, **53**, 1621 (1920).

(3) Jackson and King, THIS JOURNAL, **55**, 678 (1933).

(4) Daubert and King, *ibid.*, **61**, 3328 (1939).

(5) Verkade, van der Lee and Meerburg, *Rec. trav. chim.*, **51**, 850 (1932); **54**, 716 (1935).

(6) Verkade and van der Lee, *ibid.*, **55**, 267 (1936).