[CONTRIBUTION NO. 549 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Furan and Tetrahydrofuran Derivatives. II. The Synthesis of 3,4-Dicarboxy-2-furanpentanol and Some of its Derivatives[1]

BY KLAUS HOFMANN[2]

In continuation of investigations directed toward the synthesis of biotin analogs, certain derivatives of 3,4-dicarboxy-2-furanpentanol were required. The synthesis of such compounds is described in the present communication.

2-Furanvaleric acid,[3] the starting material for the present work, was esterified with cold alcoholic hydrochloric acid, and the resulting ethyl ester (II) was reduced by the Bouveault–Blanc method to give 2-furanpentanol (III) which was characterized by the preparation of its α-naphthylurethan. The Alder–Rickert procedure[4] was then used to introduce the carboxyl groups into the molecule. Thus, 2-furanpentanol (III) was heated with diethyl acetylenedicarboxylate, and the addition compound (IV) was reduced catalytically and decomposed in the manner described for the preparation of 3,4-dicarbethoxy-2-furanvaleric acid.[3] Hydrolysis of the resulting 3,4-dicarbethoxy-2-furanpentanol (V) with an excess of alcoholic potassium hydroxide removed both ester groups with the formation of 3,4-dicarboxy-2-furanpentanol (VI) which melted at 124–126°. Mild saponification with one equivalent of dilute sodium hydroxide, however, selectively removed one of the ester groups with the formation of an oily ester-acid (probably VII) the homogeneity of which was established by its transformation through the following reactions into the crystalline monoanilide (XI). Substance (VII) was acetylated, and the acetate (VIII) was converted into (XI) (m. p. 157–157.5°) through the acid chloride (IX), and the anilide acetate (X). The above observations established the greater lability toward saponification of one of the ester groups in 3,4-dicarbethoxy-2-furanpentanol (V).[5] In view of the fact that the ester group at carbon atom 3 is located between two substituents which may provide some "steric hindrance," compound (VII) is postulated as 3-carbethoxy-4-carboxy-2-furanpentanol. Further work is under way to offer direct chemical proof for the structure of compound (VII). Attempts to prepare 4-carboxymethyl-3-carboxy-2-furanpentanol from the acid chloride (IX) by the Arndt–Eistert reaction were unsuccessful, and afforded only gummy reaction products.

(1) Communication No. I appeared in THIS JOURNAL, **66**, 51 1944).

(2) The author wishes to express his appreciation to Ciba Pharmaceutical Products, Inc., Summit, N. J., for their generous support of this work.

(3) Hofmann, THIS JOURNAL, **66**, 51 (1944).

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

(5) It should be mentioned that 2-methyl-3,4-dicarbethoxyfuran can likewise be selectively hydrolyzed. Hofmann, unpublished experiments.

3,4-Dicarboxy-2-furanpentanol was the starting material for further experimentation. This material was acetylated with acetic anhydride in pyridine and the resulting acetate (XII) on treatment with thionyl chloride was converted to the diacid chloride (XIII). Aqueous alkali transformed (XIII) into 3,4-dicarboxy-2-furanpentanol, whereas treatment with aniline followed by alkaline hydrolysis afforded the corresponding dianilide (XIV). These results demonstrate that treatment of 3,4-dicarboxy-2-furanpentanol acetate with thionyl chloride gave the desired dichloride, and that no anhydride formation had taken place. Acid chlorides of this general type are valuable starting materials for the preparation of substituted aminofuran derivatives, the preparation of which will be the subject of a forthcoming communication from this Laboratory.

Experimental

All melting points are corrected.

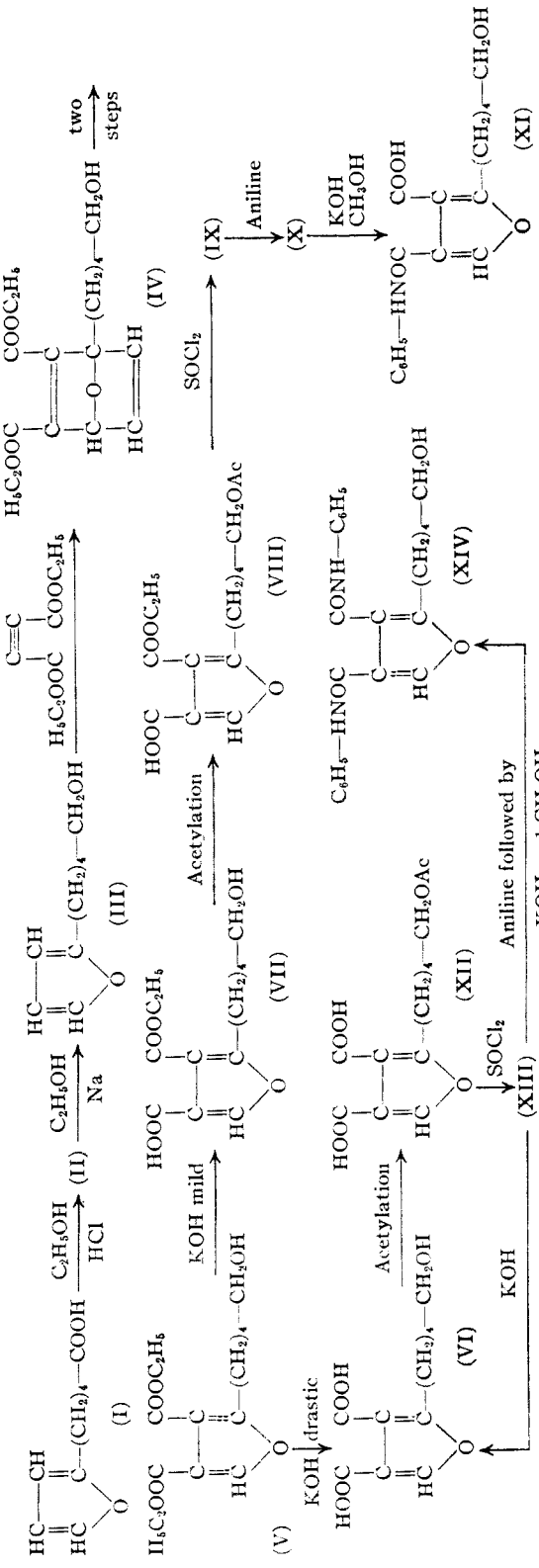
Ethyl-2-furanvalerate (II).—A solution of 46.7 g. of 2-furanvaleric acid in 500 cc. of 4% absolute ethanolic hydrochloric acid was kept at room temperature for twelve hours, and was then concentrated *in vacuo* to a small volume. The residue was dissolved in ether, the ethereal solution was washed with 2 *N* sodium carbonate and water, dried over sodium sulfate, and the ether was removed on the steam-bath. Distillation of the residue yielded 49 g. (89.9% of the theoretical yield) of the desired ester as a colorless liquid which boiled at 130–133° at 16 mm.

2-Furanpentanol (III).—A solution of 30 g. of ethyl 2-furanvalerate (II) and 20 g. of phenol in 200 cc. of absolute alcohol was added rapidly to 60 g. of sodium. Absolute alcohol (400 cc.) was added slowly, and the mixture was refluxed until all of the sodium had disappeared. The solution was cooled, the sodium ethylate was decomposed by the addition of 200 cc. of water and refluxing was continued for an additional hour. Most of the alcohol was then removed by steam distillation, the residue was cooled, and extracted with three portions of ether. The ether extracts of two such runs were combined, washed with water, dried over sodium sulfate, and the ether removed on the steam-bath. Distillation of the residue yielded 40.1 g. (85% of the theoretical yield) of 2-furanpentanol as a colorless liquid which boiled at 125–130° at 16 mm.

α-Naphthylurethan of 2-furanpentanol.—One gram of 2-furanpentanol and 1.1 g. of α-naphthyl isocyanate were heated on the steam-bath for one hour, and the mixture placed in the refrigerator overnight. Recrystallization of the resulting solid from petroleum ether (b. p. 30–60°) gave silky needles which melted at 58–58.5°.

Anal. Calcd. for $C_{20}H_{21}O_3N$: C, 74.27; H, 6.54; N, 4.33. Found: C, 73.97; H, 6.46; N, 4.41.

3,4-Dicarbethoxy-2-furanpentanol (V).—A mixture of 30.8 g. of 2-furanpentanol (III) and 37.6 g. of diethyl acetylenedicarboxylate was heated on the steam-bath for twelve hours. The resulting yellow addition product (IV) was dissolved in 200 cc. of ethyl acetate, and was hydrogenated in the presence of palladium black until 1 mole of hydrogen had been absorbed, at which point the hydrogenation came to an end. The catalyst was removed by filtration, the ethyl acetate was evaporated *in vacuo*, and



the residue was decomposed by heating to 190–200° at 16 mm. pressure. Distillation of the reaction product yielded 40.3 g. (67.6% of the theoretical yield) of the desired product as a yellow oil which boiled at 174–178° at 0.02 mm.: $n^{25}D$ 1.4855; d^{25} 1.119.

3,4-Dicarboxy-2-furanpentanol (VI).—A solution of 20.0 g. of the above ester (V) in 55 cc. of 5 *N* potassium hydroxide and 100 cc. of methanol was refluxed for four hours, and the methanol was removed *in vacuo*. The residue was acidified with concentrated hydrochloric acid and the resulting acid was extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulfate, filtered, and concentrated to a small volume on the steam-bath; 13.5 g. (83.1% of the theoretical yield) of needles melting at 124–126° was obtained. A sample of the acid was recrystallized from ethyl acetate for analysis.

Anal. Calcd. for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.75; H, 5.69.

3-Carbethoxy-4-carboxy-2-furanpentanol (VII).—To a solution of 10.0 g. of (V) in 200 cc. of absolute alcohol, 336 cc. of 0.1 *N* sodium hydroxide was added slowly with stirring. The mixture was kept at room temperature overnight, and the alcohol was removed *in vacuo* at a bath temperature of 40°. The residual aqueous solution was extracted with ether, and from the ether extracts 653 mg. of starting material was recovered. The water layer was acidified to congo red with concentrated hydrochloric acid and extracted with ether. The ether solution was washed with water, dried over sodium sulfate and the ether was removed on the steam-bath. After drying at 100° *in vacuo*, 8.0 g. (88.2% of the theoretical yield) of acidic ester was obtained.

3-Carbethoxy-4-carboxy-2-furanpentanol Acetate (VIII).—Eight grams of the above ester acid (VII) was dissolved in 40 cc. of pyridine, and 24 cc. of acetic anhydride, and the solution was kept at room temperature overnight. The solvents were then removed *in vacuo*, the residue was dissolved in ethyl acetate, and the ethyl acetate solution was washed with 2 *N* hydrochloric acid and water. The acidic material was extracted with 10% sodium bicarbonate, and was isolated from the extract by acidification and extraction with ethyl acetate. The ethyl acetate extracts were dried over sodium sulfate, evaporated on the steam-bath, and the residue was distilled *in vacuo*, 6.2 g. (67.0% of the theoretical yield) of the desired product was obtained as a viscous oil, boiling at 187–190° at 0.02 mm.

3-Carboxy-4-anilidocarboxy-2-furanpentanol (XI).—One cc. of the above ester acid (VIII) was heated to 70–80° with 2 cc. of thionyl chloride until the vigorous reaction was over. The excess of thionyl chloride was removed *in vacuo*, the resulting mono acid chloride (IX) was dissolved in 10 cc. of dry ether, and the solution was added to an ether solution of 2 cc. of aniline. The mixture was kept at room temperature for thirty minutes, washed with 2 *N* hydrochloric acid and water, dried over sodium sulfate, and the ether removed on the steam-bath. The resulting compound (X) was refluxed for two hours with 3 cc. of 5 *N* potassium hydroxide and 6 cc. of methanol, and the methanol was removed *in vacuo*. The residue was acidified to congo red with concentrated hydrochloric acid and the insoluble anilide (XI) was collected, washed with water, and dried over phosphorus pentoxide *in vacuo*. Recrystallization from a mixture of ethyl acetate and methanol gave 627 mg. of needles which melted at 157–157.5°.

Anal. Calcd. for $C_{17}H_{19}O_5N$: C, 64.36; H, 6.03; N, 4.41. Found: C, 64.28; H, 6.14; N, 4.44.

3,4-Dicarboxy-2-furanpentanol-acetate (XII).—A solution of 5.0 g. of 3,4-dicarboxy-2-furanpentanol (VI) in 20 cc. of dry pyridine and 12 cc. of acetic anhydride was kept at room temperature overnight. The solvents were removed *in vacuo*, the residue was dissolved in ethyl acetate, and the solution was washed with 2 *N* hydrochloric acid and 10% sodium bicarbonate. The bicarbonate extracts were acidified to congo red with concentrated hydrochloric acid and were then extracted with ethyl acetate. The ethyl acetate was washed with water, dried over sodium sulfate, and removed on the steam-bath. The resulting crystalline material was purified by recrystalliza-

tion from benzene; 5.5 g. (93.7% of the theoretical yield) of the desired product was obtained as needles which sintered at 96° and melted at 102–103°.

Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.91; H, 5.67. Found: C, 54.88; H, 5.84.

Acid Chloride of 3,4-Dicarboxy-2-furanpentanol-acetate (XIII).—Five grams of the above compound (XII) was heated for one hour to 90° with 10 cc. of thionyl chloride. The excess of thionyl chloride was evaporated and the residue was distilled *in vacuo;* 5.2 g. (92% of the theoretical yield) of the desired acid chloride was obtained as a colorless oil which boiled at 160–165° at 0.03 mm.

A small amount of the acid chloride was hydrolyzed with an excess of 5 *N* potassium hydroxide and the resulting acid was isolated and recrystallized from ethyl acetate. Needles which melted at 124–126° were obtained which did not depress the melting point when mixed with an authentic sample of 3,4-dicarboxy-2-furanpentanol (VI).

Dianilide of 3,4-Dicarboxy-2-furanpentanol (XIV).—A solution of 900 mg. of the above acid chloride (XIII) was added to an ether solution of 2 cc. of aniline. The mixture was kept at room temperature for thirty minutes and was then washed with 2 *N* hydrochloric acid, 10% sodium bicarbonate and water, was dried over sodium sulfate and the ether removed on the steam-bath. The crystalline residue was refluxed for one hour with 10 cc. of methanol and 2 cc. of 5 *N* potassium hydroxide. The methanol was removed *in vacuo* and the residue was acidified with concentrated hydrochloric acid, and extracted with a large amount of ethyl acetate. The ethyl acetate solution was washed with water, dried over sodium sulfate, filtered, and concentrated on the steam-bath. The resulting crystals of the anilide were purified by recrystallization from methanol; 1.2 g. of silky needles melting at 99–101° was obtained.

Anal. Calcd. for $C_{23}H_{24}O_4N_2$: C, 70.39; H, 6.16; N, 7.13. Found: C, 70.17; H, 6.35; N, 6.84.

The author wishes to express his thanks to Mrs. Florence Baker for technical assistance.

Summary

1. The preparation of 2-furanpentanol and of 3,4-dicarboxy-2-furanpentanol has been described.

2. 3,4-Dicarboxy-2-furanpentanol was characterized by a number of derivatives.

3. 3,4-Dicarbethoxy-2-furanpentanol was selectively hydrolyzed and the structure of a 3-carbethoxy-4-carboxy-2-furanpentanol was suggested for the reaction product.

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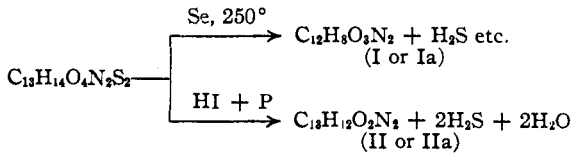
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin. V. The Structure of Certain Indole Derivatives Related to Gliotoxin[1,2]

BY JOHN R. JOHNSON, RICHARD B. HASBROUCK,[3] JAMES D. DUTCHER[4] AND WILLIAM F. BRUCE

The antibiotic substance gliotoxin is produced by at least two microörganisms other than *Gliocladium fimbriatum*—it has been isolated from cultures of *Aspergillus fumigatus*[5] and of a species of *Penicillium* not yet definitely identified.[6] Investigations of the chemical constitution of the crystalline antibiotic principle have led to the isolation of two crystalline primary degradation products which are free of sulfur and have been identified definitely as derivatives of indole-2-carboxylic acid. Gliotoxin on heating with selenium[1] loses one carbon atom and gives a yellow crystalline compound, m. p. 253–255°, having the formula $C_{12}H_8O_3N_2$. The latter on hydrolysis gives oxalic acid and a colorless compound, $C_{10}H_{10}ON_2$, which has been shown to be the N-methylamide of indole-2-carboxylic acid. A milder degradation is accomplished by reduction with hydriodic acid and red phosphorus in glacial acetic acid,[7] which leads to a colorless crystalline compound, m. p. 122°, having the formula $C_{13}H_{12}O_2N_2$ and containing all of the carbon and nitrogen atoms of the gliotoxin molecule. This product on mild hydrolysis gives a 13-carbon monobasic acid of the formula $C_{13}H_{14}O_3N_2$, which on further hydrolytic cleavage breaks down into indole-2-carboxylic acid and *dl*-α-N-methylalanine. Although gliotoxin is optically active, $[\alpha]^{26}D$ −255°, both of the primary degradation products are optically inactive.



The selenium degradation product has been synthesized previously from the methylamide of indole-2-carboxylic acid and ethoxalyl chloride, and the hydriodic acid reduction product has been prepared from indole-2-carbonyl chloride and an ester of *dl*-α-N-methylalanine. Although these syntheses represent an important advance toward elucidation of the constitution of the primary degradation products, they do not suffice to establish the structures unambiguously. Both syntheses involve the ring closure of a substituted amide of indole-2-carboxylic acid, and it is known

(1) This is a continuation of a series previously entitled "Gliotoxin, the Antibiotic Principle of *Gliocladium fimbriatum*," the last instalment of which appeared in THIS JOURNAL, **66**, 619 (1944).

(2) Presented before the New York Section of the American Chemical Society, June 9, 1944.

(3) Abbott Laboratories Fellow in Chemistry, 1940–1941; Allied Chemical and Dye Corporation Fellow, 1941–1942.

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(5) Menzel, Wintersteiner and Hoogerheide, *J. Biol. Chem.*, **152**, 419 (1944); Glister and Williams, *Nature*, **153**, 651 (1944); also private communication from Dr. Neville F. Stanley, The Prince Henry Hospital, Sydney, Australia.

(6) Professor Harold Raistrick (London), private communication to J. R. J., October 1943; *cf.* Johnson, McCrone and Bruce, THIS JOURNAL, **66**, 501 (1944).

(7) Dutcher, Johnson and Bruce, *ibid.*, **66**, 617 (1944).