The sodium salt of 2-aminopyrimidine does not react satisfactorily with ethylene chlorohydrin, γ-chlorobutyronitrile, trimethylene chlorobromide, trimethylene bromide or trimethylene chlorohydrin.

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Furan and Tetrahydrofuran Derivatives. III. The Synthesis of Certain 3,4-Diaminofuran Derivatives[1]

BY KLAUS HOFMANN AND ANNA BRIDGWATER

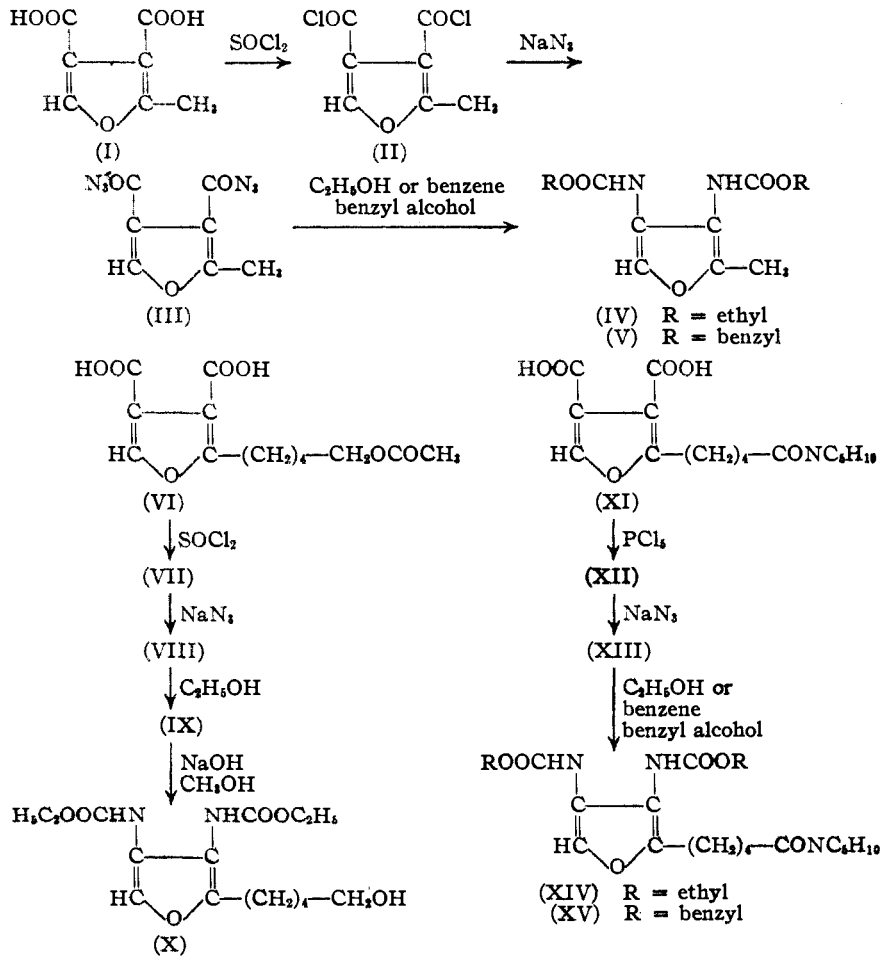
In recent communications[2,3] suitable procedures have been described for the preparation of a number of 3,4-dicarboxyfurans. These studies are being continued and the present report deals with the preparation of certain 3,4-diaminofuran derivatives which are needed for synthetic work on biotin analogs.

Aminofurans are very unstable unless they contain carboxy or nitro groups attached to the furan nucleus, and only two alkyl aminofurans have been described in the literature.[4]

For the present our attention has been focused on the preparation of urethans of 3,4-diaminofurans which should be stable, crystalline compounds. Blomquist and Stevenson[5] have synthesized a number of simple aminofuran derivatives by the Curtius degradation of the corresponding carboxylic acids, and this approach seemed applicable to the 3,4-dicarboxyfurans. The easily available 3,4-dicarboxy-2-methylfuran (I)[6] was chosen as a model compound for a study of the Curtius degradation of 3,4-dicarboxyfurans.

Many unsuccessful attempts were made to prepare the dihydrazide of 3,4-dicarboxy-2-methylfuran. Treatment of its dimethyl ester with hydrazine hydrate under a variety of experimental conditions did not afford the desired dihydrazide, and the standard Curtius method was therefore abandoned. A modification of the Curtius procedure, which involves treatment of acid chlorides with sodium azide and decomposition of the corresponding azides has been applied successfully to the preparation of a number of furyl isocyanates and urethans.[7]

This procedure seemed promising since 3,4-dicarboxyfurans are smoothly converted into their acid chlorides. Thus, 3,4-dicarboxy-2-methyl-



(1) The authors wish to express their appreciation to Ciba Pharmaceutical Products, Inc., and to The Buhl Foundation for their generous support of this work.

(2) Hofmann, THIS JOURNAL, 66, 51 (1944).

(3) Hofmann, *ibid.*, 67, 421 (1945).

(4) Stevenson and Johnson, *ibid.*, 59, 2525 (1937).

(5) Blomquist and Stevenson, *ibid.*, 56, 146 (1934).

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

(7) Singleton and Edwards, THIS JOURNAL, 60, 540 (1938).

furan (I) was converted into its acid chloride (II) and an ethereal solution of (II) was stirred with an aqueous solution of sodium azide. Evaporation of the ether solution gave the crystalline azide (III), which when decomposed in absolute alcohol in an atmosphere of nitrogen yielded the desired 3,4 - diaminocarbethoxy - 2 - methylfuran (IV).

The results of these model experiments were encouraging and the above procedures were therefore applied to some of the more complicated 3,4-dicarboxyfurans. 3,4-Dicarboxy-2-furanpentanol acetate (VI)[8] was the next compound which was studied, and its acid chloride (VII) was treated with sodium azide. The resulting oily azide (VIII) was decomposed in absolute alcohol and 3,4 - diaminocarbethoxy - 2 - furanpentanolacetate (IX) was obtained. This compound was extremely difficult to purify and since it might be expected that the acetyl group could be selectively removed without affecting the aminocarbethoxy groups, the crude material was treated with one equivalent of cold methanolic sodium hydroxide and the desired 3,4-diaminocarbethoxy-2-furanpentanol (X) was isolated.

A similar transformation of 3,4-dicarboxy-2-furanvaleric acid piperidide (XI)[2] was also accomplished. The crystalline acid chloride (XII) was obtained when a chloroform solution of (XI) was treated with phosphorous pentachloride, and an ethereal suspension of this compound was stirred with aqueous sodium azide. The resulting oily azide (XIII) was decomposed in absolute alcohol and 3,4-diaminocarbethoxy-2-furanvaleric acid piperidide (XIV) was obtained in prismatic crystals which melted at 89–91°. Decomposition of the azides (III) and (XIII) in benzene solution in the presence of benzyl alcohol[8] gave the 3,4-diaminocarbobenzyloxy compounds (V) and (XV). Hydrogenation of some of the aforementioned 3,4-diaminocarbethoxyfurans has led to most interesting results which will be described in a forthcoming communication.

Experimental[9,10]

Acid Chloride of 3,4-Dicarboxy-2-methylfuran (II).—A mixture of 5.0 g. of 3,4-dicarboxy-2-methylfuran, prepared according to Alder and Rickert,[6] and 20 cc. of thionyl chloride was heated to 70–80° for one hour, and the excess of thionyl chloride was removed *in vacuo*. Distillation of the residue gave 5.8 g. (95% of the theoretical yield) of the desired acid chloride (II) as a colorless liquid which boiled at 150–151° at 25 mm.

Diazide of 3,4-Dicarboxy-2-methylfuran (III).—A solution of 30.3 g. of the above acid chloride (II) in 380 cc. of ether was added to an ice cold solution of 38.0 g. of sodium azide in 90 cc. of water, and the mixture was stirred in an ice-bath for two hours. The ether layer was then separated, washed with ice cold 10% sodium bicarbonate and dried over sodium sulfate. The ether was removed *in vacuo* at room temperature and the resulting crystalline azide (III) was used directly without further purification.

3,4-Diaminocarbethoxy-2-methylfuran (IV).—A solution of the above azide, prepared from 30.3 g. of the acid chloride (II), in 400 cc. of absolute alcohol, was placed in a round-bottomed flask, equipped with a gas inlet tube and a reflux condenser. The end of the reflux condenser was connected to a calcium chloride tube and a gas-washing bottle filled with concentrated sulfuric acid, and a slow stream of nitrogen was passed through the apparatus. The flask was then heated slowly to 45–50°, and maintained at this temperature until the initial rapid evolution of nitrogen had almost ceased. The temperature was then raised to the boiling point of the alcohol, and the solution was refluxed for two hours. The alcohol was removed *in vacuo* and the yellow oil which resulted crystallized when placed in a refrigerator overnight. The crystals were collected, washed with methanol at −20°, and were recrystallized from methanol at −20°; 29 g. (77% of the theoretical yield based on the acid chloride) of colorless needles was obtained which melted at 105–107°.

Anal. Calcd. for $C_{11}H_{16}O_6N_2$: C, 51.56; H, 6.30; N, 10.93. Found: C, 51.63; H, 6.30; N, 11.33.

3,4-Diaminocarbobenzyloxy-2-methylfuran (V).—Two grams of the acid chloride (II) was converted into the azide (III) and the azide was decomposed in 25 cc. of dry benzene and 2.5 g. of benzyl alcohol, as described for the preparation of (IV). The solvents were evaporated *in vacuo* and the yellow oil which was obtained solidified on standing in the refrigerator. The crystals were collected, washed with ice cold methanol, and recrystallized from the same solvent; 2.9 g. (79% of the theoretical yield) of needles was obtained which melted at 122–124°.

Anal. Calcd. for $C_{21}H_{20}O_6N_2$: C, 66.30; H, 5.30; N, 7.36. Found: C, 66.14; H, 5.46; N, 7.63.

3,4-Diaminocarbethoxy-2-furanpentanolacetate (IX).—A solution of 11.0 g. of the acid chloride (VII),[8] in 100 cc. of ether, was stirred for two hours in an ice-bath with a solution of 10 g. of sodium azide in 25 cc. of water. The ether layer was then separated, washed with 10% sodium bicarbonate and dried over sodium sulfate. The oily azide (VIII) which was obtained on evaporation of the ether solution was dissolved in 100 cc. of absolute alcohol and decomposed as described above. The alcohol was removed *in vacuo*, and the residue was chilled at −20° overnight. The crystal mass which resulted was collected and washed with methanol at −20°; 7.3 g. (57% of the theoretical yield) of colorless crystals was obtained which melted at 56–58°. The compound was difficult to crystallize and liquefied when exposed to room temperature for a period of time.

3,4-Diaminocarbethoxy-2-furanpentanol (X).—To a solution of 5.8 g. of the above acetate (IX), in 58 cc. of methanol, 15.8 cc. of *N* sodium hydroxide was added, and the solution was kept at room temperature overnight. The methanol was then removed *in vacuo* and the residue was extracted with ether. The ether extract was washed with 2 *N* hydrochloric acid and water, dried over sodium sulfate, and the ether was removed on a steam-bath. The crude material was purified by recrystallization, first from ether and then from dilute methanol; 2.5 g. (48% of the theoretical yield) of needles was obtained which melted at 80–82°.

Anal. Calcd. for $C_{15}H_{24}O_6N_2$: C, 54.89; H, 7.37; N, 8.53. Found: C, 54.87; H, 7.34; N, 8.54.

Acid Chloride of 3,4-Dicarboxy-2-furanvaleric Acid Piperidide (XII).—To an ice cold solution of 5.0 g. of 3,4-dicarboxy-2-furanvaleric acid piperidide (XI),[2] in 25 cc. of chloroform, 9.6 g. of powdered phosphorous pentachloride was added slowly. The mixture was shaken for thirty minutes, filtered and concentrated to dryness *in vacuo* at a bath temperature of 40°. The resulting oil, after it was washed with three portions of dry ether, was placed in an ice-bath where crystallization soon occurred. The crystals were washed with dry ether, and dried over potassium hydroxide *in vacuo*. The yield was 5.5 g. (98% of the theoretical yield).

3,4-Diaminocarbethoxy-2-furanvaleric Acid Piperidide (XIV).—A suspension of 5.0 g. of the above acid chloride

(8) Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936).

(9) The microanalyses were performed by the Microchemical Laboratory, California Institute of Technology, Pasadena, California.

(10) All melting points are corrected.

(XII) in 50 cc. of ether was cooled in an ice-bath and a solution of 5.0 g. of sodium azide, in 20 cc. of water, was added slowly with vigorous stirring. The stirring was continued for an additional two hours, and the ether layer was separated and washed with ice cold 10% sodium bicarbonate and was dried over sodium sulfate. Evaporation of the ether *in vacuo* gave the oily azide (XIII) which was dissolved in 50 cc. of absolute alcohol and decomposed as described for the preparation of (IV). The alcohol was then removed *in vacuo*, the resulting oil was dissolved in a small amount of ether, and the ether solution placed in a refrigerator, where crystallization occurred. The crystals were washed with ether and recrystallized from a small volume of ethyl acetate; 2.6 g. (46% of the theoretical yield) of prismatic crystals was obtained, which melted at 89–91°.

Anal. Calcd. for $C_{20}H_{21}O_6N_3$: C, 58.68; H, 7.63; N, 10.25. Found: C, 58.40; H, 7.49; N, 10.33.

3,4-Diaminocarbobenzyloxy-2-furanvaleric Acid Piperidide (XV).—Nineteen grams of the acid chloride (XII) was transformed into the azide (XIII) and the azide was dissolved in a mixture of 100 cc. of benzene and 13.2 cc. of benzyl alcohol, and was decomposed under nitrogen as described above. The solvents were removed *in vacuo*, and the resulting oil was placed in the refrigerator where crystallization soon occurred. The crude material was washed with ether and was purified by recrystallization from methanol; 13.5 g. (48% of the theoretical yield) of needles was obtained, which melted at 129–131°.

Anal. Calcd. for $C_{30}H_{35}O_6N_3$: C, 67.52; H, 6.61; N, 7.87. Found: C, 67.58; H, 6.67; N, 7.86.

Acknowledgment.—The authors wish to express their appreciation to Mrs. Florence Baker and to Miss Lola Ward for their valuable assistance in certain phases of this work.

Summary

A method for the preparation of 3,4-diaminofuran derivatives has been described, and a number of these compounds have been prepared.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON & COMPANY]

Preparation of Phenyl Ketones from Bile Acids[1]

BY WILLARD M. HOEHN AND ROBERT BRUCE MOFFETT

The use of diphenylcadmium for the preparation of phenyl ketones from acid chlorides[2] has had no known application with the steroid acids.[3,4] The preparation of acid chlorides of bile acids has been described by Cortese and Bauman[5] in which the formates of hydroxylated bile acids were treated with thionyl chloride. In the present work it was found that formates of the bile acids studied could be crystallized directly from the formic acid reaction mixture in pure form. In most instances no further crystallization of formates was necessary.

These compounds together with their physical constants and analyses are given in Table I.

Several of the acid chlorides crystallized on removal of the thionyl chloride and in such cases they were recrystallized from dry ether (Table II).

The acid chlorides were dissolved in dry benzene and treated with a solution of diphenylcadmium prepared by adding cadmium chloride to phenylmagnesium bromide. The best results were obtained when a large excess of diphenylcadmium solution was added dropwise to the acid chloride solution with vigorous stirring at reflux temperature. A solid complex separated at once and could be filtered off, but usually the entire reaction mixture was decomposed by adding dilute hydrochloric acid.

The product was extracted with ether, which was removed by steam distillation. This steam distillation also served to remove biphenyl which was always a by-product of the preparation of the diphenylcadmium. The formate groups[6] were removed by hydrolysis and the phenyl ketone crystallized generally from methanol.

To further characterize these products the acetates were prepared from the hydroxyl-containing phenyl ketone. The formates of four of them were made. To establish the presence of the ketone group the oximes were prepared from four of the phenyl ketones. On mild oxidation the phenyl ketones from desoxycholic acid and from 3-hydroxy-12-ketocholanic acid gave the same triketone.

A Wolff–Kishner reduction on the phenyl ketone from desoxycholic acid gave 3,12-dihydroxy-24-phenylcholane, which failed to crystallize, but could be oxidized to the crystalline 3,12-diketo-24-phenylcholane.

Additional evidence of the structure of the phenyl ketones was obtained by the oxidation of their acetates to the next lower homolog of the bile acid from which they were prepared; thus on chromic acid oxidation followed by hydrolysis 3,12-diacetoxy-*nor*-cholanyl phenyl ketone gave *nor*-desoxycholic acid and 3-acetoxy-12-keto-*nor*-cholanyl phenyl ketone gave 3-hydroxy-12-keto-*nor*-cholanic acid.

(1) Reported in part at the April, 1944, meeting of the American Chemical Society at Cleveland, Ohio, and at the meeting of the Missouri Academy of Science, St. Louis, Missouri.

(2) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(3) Riegel and Kaye, THIS JOURNAL, **66**, 723 (1944), prepared isopropyl ketones from steroid acids by this method but no phenyl ketones were reported.

(4) Since the report of this paper at the A. C. S. meeting,[1] Jacobsen has published a communication to the Editor of THIS JOURNAL, **66**, 662 (1944), in which the phenyl ketone from cholic acid was prepared by this method.

(5) (a) Cortese and Bauman, THIS JOURNAL, **57**, 1393 (1935); (b) *J. Biol. Chem.*, **113**, 779 (1936).

(6) In one case (the phenyl ketone from 3-hydroxy-12-ketocholanic acid) the intermediate formate was isolated in pure form, showing that the diphenylcadmium does not react with these formic ester groups.