acid) (lit.[13] mp 261°). The ultraviolet spectrum in acetonitrile showed peaks at λ 276 mμ (ε 16,400) and 386 mμ (23,100).

3-Acetoxy-2,4,6-triphenylpyrylium perchlorate (16e) was obtained in 7.6-g yield, mp 230° (lit.[14] mp 230°).

(13) W. D. Dilthey and T. Bottler, *Ber.*, **52**, 2046 (1919).
(14) G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **83**, 1770 (1961).

Registry No.—Chalcone, 94-41-7; boron trifluoride etherate, 109-63-7; **5**, 1484-88-4; **8a**, 75696-46-5; **8b**, 15696-47-6; **8c**, 15696-48-7; **10**, 15707-55-8; **11**, 15707-56-9; **14**, 15707-57-0; **15**, 7654-52-6; **16a**, 3558-70-1; **16b**, 15707-60-5; **16c**, 15707-61-6; **16d**, 3558-71-2; **16e**, 15893-40-0.

Hydrolytic Dimerization of Ethyl 5-Amino-2-furoate[1]

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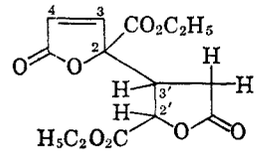
The acid hydrolysis of ethyl 5-amino-2-furoate (I) is shown to produce two stereoisomers of diethyl [(2,2′,3′,-4′,5,5′-hexahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate (II and IIa). A possible mechanism for this hydrolytic dimerization is proposed.

A number of nitrofurans have acquired considerable importance as chemotherapeutic agents.[3] In connection with biochemical studies concerning the metabolism of nitrofurans,[4,5] alkaline and acid hydrolyses of ethyl 5-amino-2-furoate (I) were investigated. The alkaline hydrolysis of I to give α-ketoglutaramic acid has been reported.[6] We now wish to report on a strikingly different reaction observed when I is treated with acid.

In aqueous–alcoholic hydrochloric acid at room temperature, I was found to undergo a rapid reaction resulting in the formation of the crystalline dilactone (II) as the major product. A higher melting isomer (IIa) was obtained simultaneously in low yield. The evidence for the structural assignments is presented.



II

The infrared spectra of II and IIa revealed intense lactone and ester absorptions at 5.55 and 5.73 μ, with a double-bond stretching band of low intensity at 6.25 μ. The 6.25-μ band was absent in the spectrum of the crystalline dihydro compound (III) obtained by catalytic hydrogenation of II in acetic acid over Adams catalyst. Treatment of III with aqueous–alcoholic sodium hydroxide at room temperature gave a saponification equivalent consistent with complete hydrolysis of the lactone and ester groups of III. The high value of the saponification equivalent of II may be due to incomplete hydrolysis of the unsaturated lactonic ester portion of II. The nmr spectrum of II is shown in Figure 1a. The pair of doublets at τ 2.51, and 3.62 may be attributed to the protons on the α,β-unsaturated carbonyl system of II. The doublet at τ 5.12 may be assigned to the proton on the oxygen-bearing carbon at 2′. The simple splitting pattern of the 2′ proton, as well as mechanistic considerations, suggest monosubstitution at C-3′. The 3′ and 4′ protons appear as complex multiplets centered at τ 6.50 and 7.50, respectively. The characteristic ethyl quartet and triplet are shown at 5.71 and 8.67. The nmr spectra of II and IIa are very similar and, since structure II contains three asymmetric centers, it is reasonable to assume that these two compounds are diastereoisomers. Both show a 4-cps coupling constant for the doublet at τ 5.12 (5.42 for IIa) indicating that both have a *trans* relationship between the 2′ and 3′ protons.[7] It would appear, therefore, that the two dilactones differ by their configuration at C-2.

Ultraviolet absorption studies of the reaction of I in aqueous–alcoholic hydrochloric acid show rapid disappearance of I and suggest the formation of an intermediate, which is converted into the final products at a slower rate. Hydrolysis of the amine group during the hydrolytic dimerization of I was determined by liberation of ammonia. The biphasic nature of this hydrolysis suggests the formation of the partially hydrolyzed intermediate V or VI, either of which could be formed *via* the reaction mechanism shown in Scheme I.

Dimerization of I may be considered to proceed *via* a nucleophilic addition of C-2 in one aminofuran molecule to the electrophilic site at C-3 of another. Hydrolysis of the 5′-amino or the 5-imino group of the initially formed intermediate (IV) would lead to V or VI. When the reaction is stopped at a time when most of I has disappeared and only about half the total ammonia has been liberated (2 min), a chloroform extract of the reaction mixture shows nmr signals at τ 3.12 and 3.59 (Figure 1b) which may be assigned to the protons on the α,β-unsaturated imino system of V. When the extracted material was hydrolyzed in the presence of deuterium oxide, II was formed without deuterium substitution. This observation supports the hypothesis that the hydrolytic dimerization of I proceeds *via* V rather than VI, since hydrolysis of the 5′-amino group of VI would result in deuterium substitution at C-4′.

Hydrolytic dimerization of I in a deuterated system results in a mixture of deuterated forms of II (Figure

(1) A preliminary report of this work has been presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966.
(2) (a) The Norwich Pharmacal Co.; (b) Cornell University.
(3) H. E. Paul and M. F Paul in "Experimental Chemotherapy," Vol. II, R. J. Schnitzer and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, p 307.
(4) H. E. Paul, V. R. Ells, F. Kopko, and R. C. Bender, *J. Med. Pharm. Chem.*, **2**, 563 (1960).
(5) J. Olivard, S. Valenti, and J. A. Buzard, *ibid.*, **5**, 524 (1962).
(6) G. M. Klein, J. P. Heotis, and J. A. Buzard, *J. Biol. Chem.*, **238**, 1625 (1963).
(7) H. Conroy, *Advan. Org. Chem.*, **2**, 311 (1960).

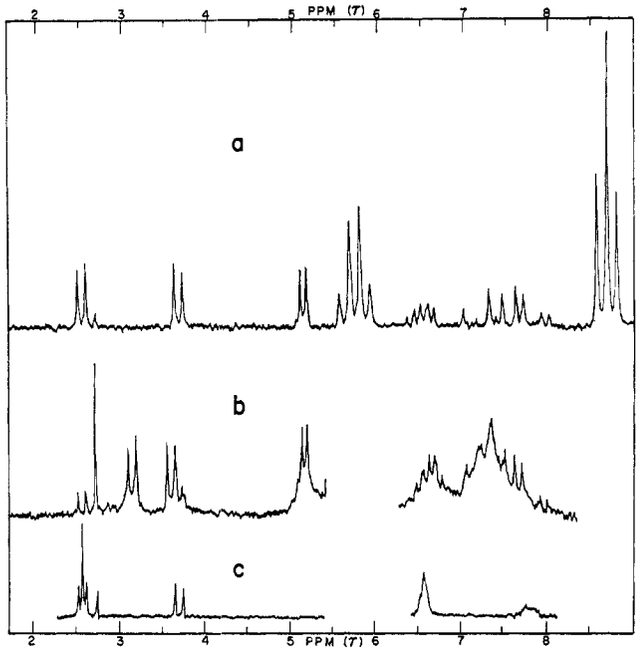
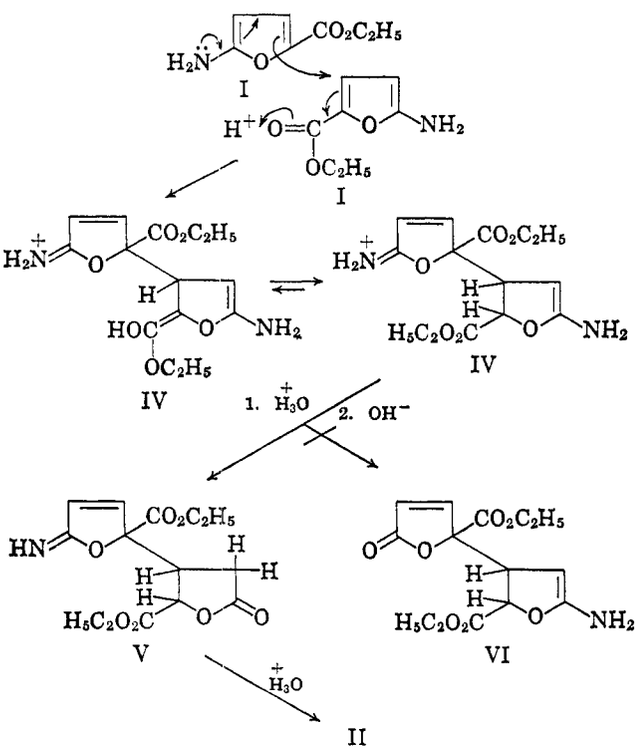


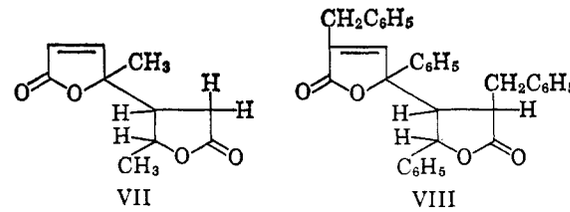
Figure 1.—Nmr spectra in $CDCl_3$ of (a) II, (b) partially hydrolyzed reaction mixture, and (c) II prepared in 0.5 *M* DCl in deuterium oxide–dioxane.

SCHEME I



1c). The absence of the τ 5.1 doublet indicates complete deuterium exchange at the 2′ position of II. This result is consistent with a reaction mechanism involving the enolic intermediate IV. The appearance of both a singlet at τ 2.51 and doublets at 2.51 and 3.65 indicates partial deuterium exchange at C-4, which probably occurred in the initial amino ester. On the basis of the relative areas of the peaks at τ 2.51 and 3.65, there is 67% deuterium exchange at C-4. The formation of II with partial deuteration at C-4 is consistent with our proposed reaction mechanism and indicates that, under the reaction conditions investigated, the rate of dimerization of I is competitive with the rate of deuterium exchange α to the amino group.

The 2,3′-bifuran, VII, has been obtained in 11% yield by mixing α-angelica lactone and potassium carbonate in a ball mill for 12 hr.[8] We prepared VII in 9% yield after stirring equal amounts of α- and β-angelica lactones with potassium carbonate for 1 hr. The nmr spectrum of VII shows a symmetrical pair of olefinic proton doublets at τ 2.51 and 3.83, a singlet at 8.47 (C-2 methyl), a doublet at 8.58 (C-2′ methyl), and multiplets at 5.50 and 7.40. The lithium aluminum hydride reduction of α-benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide has been reported to give VIII *via* a Michael-type condensation.[9]



Experimental Section

Melting points were determined on a micro hot stage (Fisher-Johns) apparatus and are corrected. Ultraviolet spectra were taken using a Beckman DB spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. The nmr spectra were determined using a Varian A-60 spectrometer.

Diethyl [(2,2′,3′,4′,5,5′-Hexahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate. Low-Melting Isomer (II).—A solution of 50 g of ethyl 5-amino-2-furoate in 500 ml of alcohol was added to 750 ml of 0.8 *M* hydrochloric acid. After 20 min, the solution was cooled for 2 hr and the product was collected. The crude product, mp 80–82°, was recrystallized from 600 ml of 95% ethanol resulting in 20 g (40%) of II, mp 95–96°. An analytical sample, mp 95–96°, was prepared by recrystallization from alcohol: $\lambda_{max}^{2\%\ EtOH}$ 200 mμ (ϵ 9600); infrared absorption (Nujol mull) at 5.55, 5.73, 6.25, 7.70, 7.93, 8.13, 8.65, 9.10, 9.30, 9.50, 10.35, 11.00, 12.05 μ; nmr spectrum ($CDCl_3$), doublets at τ 2.51, 3.62, 5.12, a triplet at 8.67, a quartet at 5.71, and complex multiplets at 6.5 and 7.5 with peak area ratios of 1:1:1:6:4:1:2.

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16; mol wt, 312. Found: C, 53.58; H, 4.96; mol wt (osmometer), 323; sapon equiv × 3, 370.

High-Melting Isomer (IIa).—The mother liquor from the preparation of II was cooled overnight at −10° resulting in 4 g of product melting at 81–82°. The mother liquor from the recrystallization of II was concentrated to 100 ml resulting in 7 g of product, mp 90–95°. The combined products were recrystallized from 95% ethanol (20 ml/g) at room temperature and the mother liquor was cooled at −10°. The product from the −10° crystallization was recrystallized four times as above resulting in 1.1 g, mp 106–108°. An analytical sample, mp 108–109°, was prepared by recrystallization from alcohol: infrared absorption (Nujol mull) at 5.58, 5.78, 6.25, 7.75, 7.95, 8.50, 9.30, 10.30, 11.00, 11.80, 11.98 μ; nmr spectrum ($CDCl_3$), doublets at τ 2.58, 3.67, 5.42, a triplet at 8.60, a quartet at 5.70, and complex multiplets at 6.5 and 7.3 with peak area ratios of 1:1:1:6:4:1:2.

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.85; H, 5.16; mol wt, 312. Found: C, 54.01; H, 5.14; mol wt (osmometer), 300.

Diethyl [(2,2′,3,3′,4,4′,5,5′-Octahydro-5,5′-dioxo)-2,3′-bifuran]-2,2′-dicarboxylate (III).—To a solution of 0.36 g of II in 5 ml of acetic acid was added 67 mg of platinum oxide and the mixture was stirred under a pressure of 70 mm for 18 hr. After filtration of the catalyst and evaporation of the solvent,

(8) R. Lukes and K. Syhora, *Collect. Czech. Chem. Commun.*, **19**, 1205 (1954).

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the residue was recrystallized from 5 ml of 95% ethanol resulting in 0.28 g of III, mp 107–108°. An analytical sample, mp 108–109°, followed by solidification and remelting at 112–113°, was prepared by recrystallization from alcohol: infrared absorption (Nujol mull) at 5.57, 5.75, 7.40 (shoulder), 7.65, 7.88, 8.03, 8.13, 8.33, 8.43, 8.70, 9.15, 9.30, 9.85, 10.20, 10.33, 10.85, 11.95, 13.20 μ; nmr spectrum ($CDCl_3$), a doublet at τ 5.18, a triplet at 8.62, a quartet at 5.70, and complex multiplets at 6.7 and 7.3 with peak area ratios of 1:6:4:1:6.

Anal. Calcd for $C_{14}H_{12}O_8$: C, 53.50; H, 5.77; mol wt, 314. Found: C, 53.24; H, 5.76; sapon equiv × 4, 316.

Reaction Intermediate.—To a solution of 2 g of I in 20 ml of 95% ethanol was added 20 ml of 1 *M* hydrochloric acid. After 2 min, the solution was added to 1750 ml of water and extracted three times with chloroform. The aqueous phase was neutralized with 40 ml of 1 *M* dipotassium phosphate and extracted three times with chloroform. The chloroform extract of the neutralized solution was dried over sodium sulfate and concentrated to 31 ml under reduced pressure. A 3-ml aliquot was evaporated to dryness under reduced pressure, dissolved in 2 ml of $CDCl_3$, evaporated, and dried for 10 min under oil pump vacuum. The residue (0.15 g) was immediately dissolved in $CDCl_3$ for determination of the nmr spectrum (Figure 1b). Absence of the τ 2.78 and 4.65 furanoid proton bands indicates that I is not present in this material. The infrared spectrum of the chloroform extract shows intense absorption at 5.62, 5.80, and 5.98 μ. Purification of the extracted material by crystallization or by thin layer chromatography was not successful. The remainder of the chloroform solution was evaporated, dissolved in 10 ml of dioxane, and treated with 15 ml of 0.8 *M* hydrogen chloride in deuterium oxide. After 15 min the solution was concentrated until an oil separated. After recrystallization from a mixture of chloroform and carbon tetrachloride, 0.35 g of product, mp 93–94°, was obtained. The nmr spectrum was identical with that of II.

Hydrolytic Dimerization of I in Deuterium Oxide.—To a solution of 1.7 g of I in 17 ml of dioxane was added 25 ml of 0.8 *M* deuterium chloride in deuterium oxide. After 15 min at room temperature, the solution was cooled at −10° for 1 hr. The yield of recrystallized product, mp 91–92°, was 0.7 g. The nmr spectrum was determined in $CDCl_3$ (Figure 1c). The peaks at τ 2.51 (triplet), 3.65 (doublet), and 6.55 (singlet) have relative areas of 1:0.33:1.

Ultraviolet Absorption Studies.—A solution of 0.624 g (4.03 mmol) of I in 10 ml of 95% ethanol was prepared. A 1-ml aliquot was added to 1 ml of 1 *M* hydrochloric acid in a 25-ml volumetric flask. After the desired reaction period, the solution was diluted to 25 ml with 1 *M* dipotassium phosphate. After diluting 1:100 with water, the ultraviolet absorption spectrum was determined. The half-life of I under these conditions is 0.5 min. The formation of a reaction intermediate is indicated by the appearance of a peak at 208 mμ. After a 15-min reaction period, only end absorption characteristic of II remains.

Hydrolysis Studies.—Hydrolysis of the amine group during the hydrolytic dimerization of I was determined by liberation of ammonia using the Van Slyke aeration procedure.[10] To a solution of 30 mg of I in 0.5 ml of 95% ethanol was added 0.5 ml of 1 *M* hydrochloric acid. Separate runs were made and in each run 5 ml of 1 *M* sodium hydroxide was added after the desired reaction period. Nitrogen was passed through the solution at 0.5 ft^3/hr for 90 min. The ammonia was absorbed in 10 ml of a 2% boric acid solution containing bromcresol green indicator and was titrated with 0.02 *N* sulfuric acid. The yields of ammonia after 0.5-, 1-, 2-, 5-, and 15-min reaction periods are 32, 40, 44, 57, and 77%.

Registry No.—I, 15856-35-6; II, 15814-68-3; IIa, 15814-69-4; III, 15856-36-7.

Acknowledgments.—The authors are grateful to Mr. Benjamin Stevenson for the preparation of compound I, to Mr. Grant Gustin and Mr. Marvin Tefft for the microanalyses, and to Mrs. Patricia Curtis for the nmr spectra.

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Kinetics of the Reaction of Chloroacetic Acid with Ammonia in an Aqueous Solution[1]

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The kinetics of the consecutive reactions between chloroacetic acid and ammonia in aqueous solutions to form glycine and iminodiacetic and nitrilotriacetic acids have been studied by following the produced chloride ion. The observed second-order rate law, $v = k$[chloroacetic acid][amino compound], together with the relation between the rate constant and the pH of the solution confirms the ordinary SN2 mechanism involving an attack of free ammonia or amino group on the chloroacetate ion. The reactivities of amino compounds are discussed in terms of their rate constants, activation parameters, and basicities of amino groups.

Treatment of chloroacetic acid with ammonia gave glycine, iminodiacetic acid, and nitrilotriacetic acid.

$$NH_3 + ClCH_2COOH \xrightarrow{-HCl} H_2NCH_2COOH \xrightarrow[-HCl]{ClCH_2COOH}$$

$$HN(CH_2COOH)_2 \xrightarrow[-HCl]{ClCH_2COOH} N(CH_2COOH)_3$$

A large excess (*ca.* 60-fold) of ammonia was found to be favorable for the preparation of glycine.[2-4] Cheronis and Spitzmuller have studied qualitatively the effect of pH of the solution on the yield of glycine; they suggested that the formation of secondary and tertiary amino compounds was reduced at pH below 10 and that the reactive species are probably free ammonia and chloroacetate ion.[5] Iminodiacetic acid has been prepared by the reaction of boiling aqueous chloroacetic acid with ammonia.[6] However, no report has appeared on the preparation of nitrilotriacetic acid from these materials. Few kinetic studies have been reported for this type of reaction.[7,8]

The present study was undertaken to obtain some information on the kinetics of the formation of glycine and iminodiacetic and nitrilotriacetic acids from chloroacetic acid and ammonia together with the effect of pH

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(7) J. D. Johnson and L. J. Edwards, *Trans. Faraday Soc.*, **45**, 286 (1949).
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