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# METHANOLYSIS AND HYDROLYSIS OF DERIVATIVES OF METHYL 2,5- AND 4,5-DIHYDROFURAN-2-CARBOXYLATES

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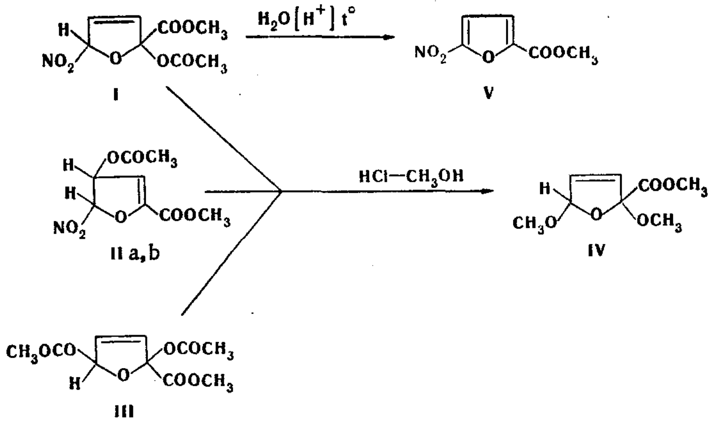
Methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate is formed in the reaction of HCl—$CH_3OH$ with methyl 5-nitro-2-acetoxy-2,5-, 5-nitro-4-acetoxy-4,5-, and 2,5-diacetoxy-2,5-dihydrofuran-2-carboxylates, whereas methyl 2,5-dioxo-3-pentenoate bis(2,4-dinitrophenylhydrazone) and 4-oxo-2-penten-1,5-dioic acid 2,4-dinitrophenylhydrazone are isolated in the presence of 2,4-dinitrophenylhydrazine. Methyl 5-nitrofuran-2-carboxylate is formed by treatment of methyl 5-nitro-2-acetoxy-2,5-dihydrofuran-2-carboxylate with aqueous solutions of acetic or phosphoric acid.

Acid hydrolysis with identification of the products in the form of hydrazones is frequently used for the establishment of the position of the substituents in the furan and dihydrofuran rings [1-4]. The possibilities of the method for the establishment of the structures of methyl esters of some 2,5- and 4,5-dihydrofuran-2-carboxylic acids (I-III) were determined in the present research [5].

We first found that esters I-III are not cleaved by the action of HCl in methanol but readily undergo nucleophilic substitution of the nitro and acetoxy groups by a methoxy group to give the same product (IV) — methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate. Moreover, isomerization to give a 2,5-dihydrofuran ring occurs in the case of II in the form of the cis and trans isomers (IIa, and IIb, respectively). We also obtained III in addition to methyl 5-nitrofuran-2-carboxylate (V) by a process similar to the isomerization we observed for IIb in [6] when it was treated with sodium acetate.

Despite the indications in [4], I was not converted to V by the action of HCl in methanol. We observed that I is capable of undergoing "aromatization" to V under the influence of acid reagents in the presence of water, for example, when it is heated with 1% acetic acid or 10% phosphoric acid.



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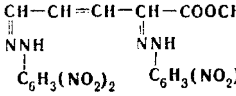
For comparison, we treated V and methyl furan-2-carboxylate with HCl—CH₃OH and found that their furan rings did not undergo opening (partial hydrolysis of the ester group is observed in the case of methyl furan-2-carboxylate).

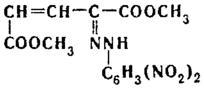
The reaction of I-III with HCl—CH₃OH in the presence of 2,4-dinitrophenylhydrazine (2,4-DNPH) proceeds in a more complex manner. Thin-layer chromatographic analysis of the reaction products showed that a multicomponent mixture, the composition of which depends primarily on the reaction conditions but not on the structure of the starting ester, is formed in this case. Brief reaction at room temperature leads to unstable substance A, which we were unable to isolate in individual form and therefore could not establish its structure. The formation of other reaction products (more than 10 spots on the thin-layer chromatogram) is observed when the reaction mixture is heated briefly, but the principal product is methyl 2,5-dioxo-3-pentenoate bis(2,4-dinitrophenylhydrazone) (VI).

When the reaction time is increased, dimethyl 4-oxo-2-pentene-1,5-dioate (4-ketoglutaconate) 2,4-dinitrophenylhydrazone (VII) is formed along with the other substances, evidently as a result of oxidative destruction of substance A rather than as a result of oxidation of VI, since the latter is extremely stable under the reaction conditions.



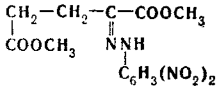
$\underset{\substack{\| \\ NNH \\ | \\ C_6H_3(NO_2)_2}}{CH}-CH=CH-\underset{\substack{\| \\ NNH \\ | \\ C_6H_3(NO_2)_2}}{CH}-COOCH_3$

VI



$\underset{\substack{| \\ COOCH_3}}{CH}=CH-\underset{\substack{\| \\ NNH \\ | \\ C_6H_3(NO_2)_2}}{C}-COOCH_3$

VII



$\underset{\substack{| \\ COOCH_3}}{CH_2}-CH_2-\underset{\substack{\| \\ NNH \\ | \\ C_6H_3(NO_2)_2}}{C}-COOCH_3$

VIII

We did not detect dimethyl 2-oxopentadionate (2-ketoglutarate) 2,4-dinitrophenylhydrazone (VIII) in the reaction mixture; its formation might have been expected from the results in [8].

It follows from the research accomplished that the method of acid hydrolysis with identification of the products in the form of hydrazones is not applicable for derivatives of methyl 2,5- and 4,5-dihydrofuran-2-carboxylates because of facile isomerization of the 4,5-dihydrofuran ring to a 2,5-dihydrofuran ring and the formation of a common intermediate, methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate (IV).

## EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Perkin—Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. The IR spectra were recorded with a UR-20 spectrometer. Compounds I-III and V were prepared by the method in [5]. Compound IV had bp 116-117°C (10 mm) and $n_D^{20}$ 1.4480 (bp 127-131°C (13-14 mm) and $n_D^{25}$ 1.4476 [7]). Compound VI was obtained by the method in [9] and had mp 272-274°C (264°C [9]). Compound VIII was obtained by the method in [10] and had mp 122-123°C (122-123°C [10]).

Reaction of HCl—CH₃OH with I-III. A mixture of 2.0 ml of 0.76 M HCl in CH₃OH and 10 mg of I-III was refluxed on a water bath for 30 min, after which the reaction products were investigated by thin-layer chromatography (TLC) on Silufol UV-254 plates. The solvent systems were cyclohexane—acetone (3:2) (a), benzene—heptane—ethyl acetate (33:4:3) (b), and benzene—ether (9:1) (c) (Table 1).

Compound IV. A mixture of 7.0 g (0.03 mole) of I and 50 ml of 0.76 M HCl in CH₃OH was refluxed for 1.5 h, after which it was neutralized with 2.5 g (0.03 mole) of NaHCO₃ and filtered. The solvent (30 ml) was removed from the filtrate by vacuum distillation, 50 ml of ether was added to the residue, and the mixture was filtered. The solvent was removed from the filtrate by distillation, and the residue was vacuum distilled to give 3.22 g (56%) of IV with bp 130°C (20 mm).

Methanolysis of I by the Method in [4]. Dry HCl was bubbled through a solution of 0.23 g of I in 2 ml of absolute methanol for 2 h, during which the course of the reaction was monitored by TLC (system b). Compounds I ($R_f$ 0.25) and IV ($R_f$ 0.17) were detected in the reaction mixture. The presence of V in the reaction products was not observed.

Hydrolysis of I. A) With 1% CH₃COOH. A mixture of 4.62 g of I and 6 ml of 1% acetic acid was refluxed for 20 min, after which it was cooled, and the precipitated bright crystals were removed by filtration, washed with water (2 ml), and dried in a vacuum desiccator over P₂O₅ to give 0.9 g of V with mp 79-80°C (from methanol).

TABLE 1. Chromatographic Characteristics of I-VIII

| Compound | $R_f$, system | | | Detection* | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | without treatment with a reagent | UV light | exposure in $NH_3$ vapors | after exposure in $NH_3$ vapors | | |
| | a | b | c | | | | in daylight | UV light | spraying with 0,1 N $KMnO_4$ |
| I | 0,35 | 0,25 | 0,43 | — | — | — | — | d | w |
| IIa | — | 0,33 | — | — | — | v | v | d | w |
| IIb | — | 0,37 | — | — | — | v | v | d | w |
| III | 0,30 | 0,16 | 0,31 | — | — | b | b | d | w |
| IV | 0,47 | 0,17 | 0,33 | — | — | — | — | — | w |
| VI | — | 0,33 | 0,59 | o | (d) | g | o | (d) | (y) |
| VII | — | 0,39 | 0,63 | y | dv | dv | y | dv | y |
| VIII | — | 0,32 | 0,56 | y | dv | y | y | dv | y |
| Substance A | — | 0,28 | 0,51 | yb | (d) | b | yb | (d) | (y) |
| 2,4-DNPH | — | 0,69 | 0,84 | y | db | y | y | db | y |

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*Spot colors: w is white, y is yellow, yb is yellow-brown, o is orange, b is blue, g is gray, d is dark spot, db is dark brown, dv is dark violet, and v is violet; a color abbreviation in parentheses indicates that the color is weakly expressed.

B) With 10% $H_3PO_4$. A solution of 2.3 g of I in 10 ml of chloroform was added slowly to 5 ml of 10% $H_3PO_4$ with simultaneous removal of the reaction product by steam distillation. The distillate (100 ml) was extracted with ether (three 50-ml portions), and the ether solution was washed with ice water (two 30-ml portions) and dried over $MgSO_4$. The solvent was removed to give 0.26 g of light-yellow V.

Reaction of Methyl Furan-2-carboxylate with $HCl—CH_3OH$. A mixture of 10 g of methyl furan-2-carboxylate and 250 ml of 0.76 M methanolic HCl solution was refluxed for 4 h, during which the course of the reaction was monitored by TLC in system a. The solvent was removed by distillation, and the residue was fractionated. The unchanged starting ester (7 g) distilled at 35-37°C (3 mm). The crystalline residue (mp 127-130°C) was furan-2-carboxylic acid (no melting-point depression was observed for a mixture with an analytical sample).

Cleavage of I by Means of $HCl—CH_3OH$ in the Presence of 2,4-DNPH. A 0.23-g sample of I was refluxed for 15 min with 10 ml of 0.76 M $HCl—CH_3OH$, after which a solution of 0.4 g of 2,4-DNPH in 10 ml of 0.76 M $HCl—CH_3OH$ was added to the reaction mixture. After 24 h, the resulting precipitate was removed by filtration and washed with methanol and water to give 0.23 g (44%) of VI with mp 272-274°C (from nitromethane).

Cleavage of IV by Means of $HCl—CH_3OH$ in the Presence of 2,4-DNPH. An 0.94-g sample of IV was dissolved in 10 ml of $CH_3OH$, and a solution of 1.0 g of 2,4-DNPH in 25 ml of 0.76 M $HCl—CH_3OH$ was added. After 24 h, the precipitated crystals were removed by filtration and washed with methanol and water to give 0.9 g of hydrazone VI with mp 272-273°C (from nitromethane).

When the filtrate was allowed to stand, it yielded a yellow crystalline precipitate, which was removed by filtration, and washed with a small amount of methanol to give 0.17 g of VII with mp 167-168°C. Found, %: C 46.0; H 3.5; N 16.0. $C_{13}H_{12}N_4O_8$. Calculated, %: C 44.3; H 3.4; N 15.9. PMR spectrum ($CDCl_3$, $\delta$): 10.05 (s, 1H, NH), 9.23 (d, 1H, 3-$H_{arom}$), 8.29 (q, 1H, 5-$H_{arom}$), 7.05 (d, 1H, vinyl H), 6.39 (d, 1H, 6-$H_{arom}$), 5.55 (d, 1H, vinyl H), 3.93 (s, 3H, $COOCH_3$), and 3.70 ppm (s, 3H, $COOCH_3$).

TLC Analysis of the Products of the Reaction of I-IV with $HCl—CH_3OH—2,4\text{-}DNPH$. A reagent prepared from 0.1 g of 2,4-DNPH and 4 ml of 0.76 M $HCl—CH_3OH$ was used for the cleavage. A 10-mg sample of I-IV and three drops of the $HCl—CH_3OH—2,4\text{-}DNPH$ reagent were heated on a water bath for 10 min, after which the mixture was cooled and chromatographed after 1 h (Table 1).

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# SYNTHESIS OF 1-(2-FURYL)-2-NITROPROPEN-3-ONES

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and A. L. Fridman*

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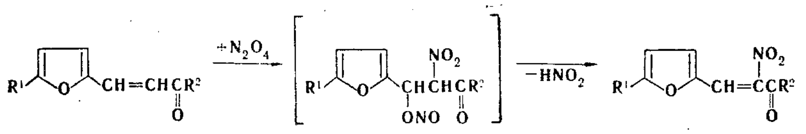
1-(2-Furyl)-2-nitropropen-3-ones were synthesized by reaction of nitrogen tetroxide with a number of α,β-unsaturated furylcarbonyl compounds. The 5-nitrofuryl derivative was obtained from 1-(2-furyl)-3-(4-methoxyphenyl)propen-3-one when the excess amount of $N_2O_4$ was increased. Replacement of bromine by a nitro group in the furan ring is observed in the case of the 5-bromofuryl derivative.

It is known that 1-(5-nitrofuryl)propen-3-ones have strong bactericidal and bacteriostatic properties [1]. In addition, 1-furyl-2-nitroethylene is a good repellent for application to clothing to protect against salt marsh mosquitoes and gnats and also protects leather clothing from mildew [2]. It therefore seemed of interest to synthesize 1-furyl-(substituted furyl)propen-3-ones and -propen-3-als with a nitro group in the side chain in the 2 position. Only a few of these compounds have been described [3, 4]. In order to synthesize other representatives we studied the reaction of nitrogen tetroxide with some α,β-unsaturated furylcarbonyl compounds (Ia-g).

Compounds Ia-f are converted smoothly to nitro derivatives IIa-f.



I a-f A II a-f

I-II a $R^1=CH_3$, $R^2=H$; b $R^1=R^2=CH_3$; c $R^1=H$, $R^2=C_4H_3S$ (thienyl); d $R^1=H$, $R^2=4\text{-}CH_3OC_6H_4$; e $R^1=NO_2$, $R^2=CH_3$; f $R^1=Cl$, $R^2=4\text{-}ClC_6H_4$

This reaction pathway is explained by conjugation between the electron-acceptor carbonyl group and the electron-donor furan ring. In this case the carbon atom in the 2 position has the maximum π-electron density, and reaction intermediate A is therefore formed. Splitting out of nitrous acid from A also leads to the formation of nitro compounds IIa-f.

When the amount of nitrogen tetroxide is increased above the stoichiometric value, furylpropenone Id forms, in addition to nitro ketone IId, 1-(5-nitro-2-furyl)-2-nitro-3-(4-methoxyphenyl)propen-3-one (III), which becomes the only product in the case of a considerable ex-

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*Deceased.

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