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NEW REACTION FOR THE PREPARATION OF LOWER OXODIHYDROFURANS

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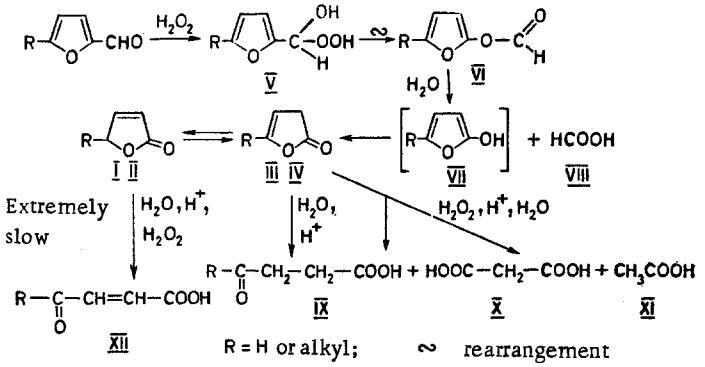
A reaction for the preparation of lower oxodihydrofurans by oxidation of formylfurans with hydrogen peroxide is proposed. The mechanisms of their formation and transformations are discussed.

Oxodihydrofurans are widely used in organic synthesis [1, 2] and to obtain polymers for special purposes [3, 4] and have high and diversified physiological activity [1, 2, 5].

Of the lower lactones, 2-oxo-5-methyl-2,3-dihydrofuran III (β,γ-angelica lactone) is the most readily available compound and has been the subject of the greatest study. It is obtained by dehydration of levulinic acid [6, 7]. The more simply constructed 2-oxo-2,5-dihydrofuran has been obtained from β,γ-dihalo- and hydroxyhalobutyric acids [8], from butyrolactone through bromobutyrolactone [9], by pyrolysis [10] of 2,5-diacetoxy-2,5-dihydrofuran, or by acid hydrolysis of 2-acetoxyfuran [11]; however, all of these methods are based on the use of a starting compound that is difficult to obtain and are laborious and give the products in low yields.

During an investigation of the oxidation of furfural with hydrogen peroxide we detected oxodihydrofurans I and IV in the intermediate reaction products; in the case of oxidation of 5-methylfurfural we detected 5-methyl-2-oxodihydrofurans II and III (see the scheme below, Figs. 1 and 2, and Table 1). The formation of I-IV during the oxidation of formylfurans with hydrogen peroxide occurs during the hydrolysis of ester VI [12], which is the product of rearrangement of hydroxyhydroperoxyfurfural V [13]. It is known [11] that acetoxyfuran is also hydrolyzed to give lactones I and IV. The immediate hydrolysis product — hydroxyfuran VII — could not be detected in the reaction mixture because of its instability [14, 15]. Methods for the preparation of the hydroxyfuran are indicated in the literature [16, 17], but other researchers have found that they could not reproduce them. It has been assumed that α-hydroxyfuran is formed in the radiative oxidation of the furan—water system (1:1000) [18]. The oxidation of formylfurans with hydrogen peroxide gives, in addition to VII, formic acid (VIII), which probably catalyzes the conversions of hydroxyfuran and its homologs of isomeric forms of oxodihydrofurans I-IV [13].



Thus hydroxyfurans of the VII type are present in the oxo form in the reaction mixture. This constitutes one of the differences between the peroxide oxidation of formylfurans and the oxidation of aromatic aldehydes. In the latter case the resulting phenols are stable

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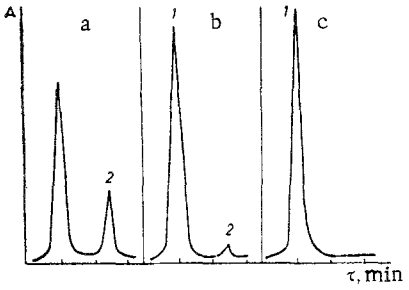

Fig. 1

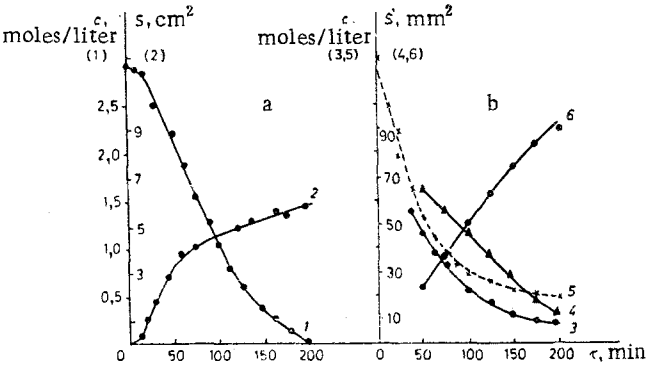

Fig. 2

Fig. 1. Gas—liquid chromatogram of 2-oxodihydrofuran: a) starting compound, synthesized by oxidation of furfural with H_2O_2 without additional treatment; b) after heating the starting compound at 130°C for 2 h or after maintenance at 5°C for 2 months; c) after heating the starting compound with triethylamine, diethylamine, piperidine, or cobalt oxide; 1) 2-oxo-2,5-dihydrofuran; 2) 2-oxo-2,3-dihydrofuran (the A scale pertains to the recorder readings).

Fig. 2. Transformations of formylfurans and oxodihydrofurans: a) in the oxidation of furfural (F) with 28% H_2O_2; b) in the oxidation of 5-methylfurfural (MF) with H_2O_2 (continuous lines) and in the hydrolysis of this oxide of 2-oxo-5-methyl-2,3-dihydrofuran (dash line 5) [F(MF) to H_2O_2 ratio of 1:2.2 at 60 ± 2°C]; 1) furfural; 2) 2-oxo-2,5-dihydrofuran; 3) methylfurfural; 4) and 5) 2-oxo-5-methyl-2,3-dihydrofuran; 6) levulinic acid (S is the area of the spot on the thin-layer chromatogram, and S' is the area of the peak on the gas—liquid chromatogram).

TABLE 1. Characteristics of the Lower Oxodihydrofurans

Compound	Elementary comp.[a]		bp, °C (mm)	n_D^{20}	IR spectrum[b]		GLC, exit time, min
	C	H			C=O	C=C	
2-Oxo-2,5-dihydrofuran	57,38 (57,14)	4,92 (4,79)	90—92 (12)	1,4650	1782, 1744 d	1605	1,6
2-Oxo-2,3-dihydrofuran	was not isolated in individual form						0,6
2-Oxo-5-methyl-2,5-dihydrofuran	61,43 (61,21)	6,25 (6,17)	85—86 (10)	1,4545	1731, 1765 d	1600	1,3
	61,30 (61,21)	6,26 (6,17)	73 (7); 44 (3)	1,4472	1800	—	0,8

[a]The calculated values are given in parentheses. [b]The IR spectrum contains several bands of the C—O—C bond (1050-1200 cm^{-1}).

oxidation products [19]. The instability of VII also explains the ease and irreversibility of the hydrolysis of VI, which, in turn, is responsible for the rapid rearrangement of peroxide V [12, 13].

We have previously carried out the oxidation of furfural and 5-methylfurfural under conditions that ensure complete oxidation of oxo and dibasic acids [20]. A comparison of the calculated energies of formation of the substances and the heat effects of the individual steps of the reaction shows that oxodihydrofurans are the most stable reaction products. Their subsequent transformations during hydrolysis or oxidation require considerable expenditures of energy [13] (41-45 kcal/mole). To determine the optimum conditions for the preparation of I-IV we investigated their hydrolysis and oxidation under the conditions of the reaction of formylfurans with hydrogen peroxide: at 60 ± 0.2°C in the presence of formic acid, which is formed during the oxidation. 2-Oxo-5-methyl-2,3-dihydrofuran undergoes 100% hydrolysis to levulinic acid after 6 h at 60°C and after 1 h at 100°C (Table 2). It was not possible to obtain 2-oxo-2,3-dihydrofuran (IV) in individual form. However, re-

TABLE 2. Formation of Levulinic Acid in the Hydrolysis of 2-Oxo-5-methyl-2,3-dihydrofuran at 60°C and of Succinaldehyde in the Hydrolysis of a Mixture of 2-Oxo-2,5-dihydrofuran and 2-Oxo-2,3-dihydrofuran (Fig. 1a) at 100°C

Time, min	Levulinic acid		Succinaldehyde	
	mole/liter	%	mole/liter · 10^3	%
0	—	—	—	—
70	0,8	23,8	4,7	0,11
120	1,2	38,0	11,2	0,28
180	1,9	58,0	18,8	0,47
240	2,3	69,7	18,6	0,46
290	2,5	77,5	—	—
345	3,2	98,5	14,7	0,37
540	—	—	9,8	0,24

action product I contains 5-20% of β,γ isomer IV. Peak 2 on the gas–liquid chromatogram corresponds to it; a product, the chromatogram of which contains only peak 1, corresponding to isomer I (Fig. 1, curves a and c), was isolated when IV was heated with triethylamine. During acid hydrolysis peak 2 vanishes, and up to 0.5% (based on the sum of I and IV) succinaldehyde accumulates after 6 h (Table 2). It is known that succinaldehyde is the product of hydrolysis of β,γ-crotonolactone [10-12]. Up to 13-15% succinaldehyde is formed during distillation of the hydrolyzate. The possible product of hydrolysis of I — hydroxycrotonic acid — is not formed under the adopted conditions.

In the acid hydrolysis of II, 2% levulinic acid was formed after 6 h, evidently as a result of partial isomerization of II to III, after which III undergoes hydrolysis.

Appreciable changes are not observed in the oxidation of the α,β isomers of 2-oxodihydorfurans I and II with hydrogen peroxide after 6 h. Very small amounts of β-formylacrylic acid are detected in the oxidates from I, whereas β-acetylacrylic and levulinic acids are detected in the oxidates from II. The degree of formation of these acids reaches 13-15% of the theoretical value only after prolonged standing of the oxidates (up to 3 months).

In the case of the oxidation of β,γ isomer III it undergoes 40% conversion to levulinic acid as a result of the accompanying hydrolysis, and the remaining III is converted to malonic acid (40%) and unsaturated oxo acids with unestablished structures. Acetic acid was also detected in the oxidate.

It is apparent that, in contrast to the β,γ isomers, which are readily hydrolyzed and oxidized via the scheme presented above, the α,β isomers of 2-oxodihydrofurans do not undergo changes under the conditions adopted for the oxidation of formylfurans with H_2O_2. This made it possible to use the oxidation of furfural and 5-methylfurfural with H_2O_2 for the preparation of the corresponding α,β-oxodihydrofurans. Oxidation of formylfurans at 60-70°C with 15-30% aqueous H_2O_2 at a formylfuran to H_2O_2 ratio of 1:2.2-3.0 is the optimum procedure for the preparation of I and II [21, 22]. Under these conditions the accumulation of 2-oxo-2,5-dihydrofuran predominates over its transformations (Fig. 2a). At the same time, the β,γ isomers undergo profound changes dudring the oxidation of formylfurans with H_2O_2. This is shown graphically by the curves (4 and 5) of the change in the percentage of 2-oxo-5-methyl-2,3-dihydrofuran during the oxidation of methylfurfural with H_2O_2 and hydrolysis of III by the oxidate (Fig. 2b). Its masimum concentration in the oxidate 50 min after the start of the reaction is only 20% based on the methylfurfural. In conformity with the scheme, III is subsequently converted to levulinic acid IX (Fig. 2b, curve 6). It is apparent that III is hydrolyzed at a rate close to the rate of oxidation of 5-methylfurfural.

The individuality of the synthesized I and II was proved by gas–liquid chromatography (GLC), and the absence of unsaturated acid and oxo acid impurities was proved by polarography.

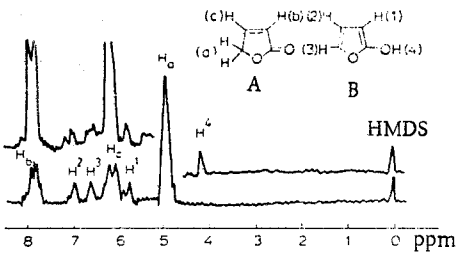

Fig. 3. High-resolution NMR spectrum relative to hexamethyldisiloxane: H_a, H_b, and H_c are the signals of compound A, and H^1, H^2, H^3, and H^4 are the signals of compound B.

The structures of I and II are confirmed by the IR and PMR spectra. The IR spectrum (Table 1) contains bands characteristic for α,β-unsaturated lactones [1]. The PMR spectrum (Fig. 3) of structure A contains a singlet (δ_a = 4.95 ppm) and two doublets (δ_b = 7.85, and δ_c = 6.15 ppm). The ratio of the integral intensities of the signals is $S_a:S_b:S_c$ = 2:1:1. The spin-spin coupling constants are $J_a = J_b$ = 6 Hz (the cis protons for the olefin bond). In addition, there are also signals at δ 4.17, 5.80, 6.58, and 6.95 ppm with relatively weak intensities, which may be characteristic for structure B. This can be evaluated as the presence in 2-oxo-2,5-dihydrofuran of a small amount of its tautomeric enol form — hydroxyfuran VII (see the above scheme). The presence in the IR spectrum of a band of weak intensity at 3500 cm^{-1}, which, in analogy with phenols, is characteristic for the OH group of enols [24], also constituted evidence for this.

The yields of I and II are 35-40% of the theoretical values, and one observes the simultaneous liberation of, in addition to I, succinic acid, and, in addition to II, levulinic acid. On the basis of the proposed methods, the production of I is limited to a pilot-plant apparatus with the use of nonstandard-grade furfural and still residues from its production [23].

EXPERIMENTAL

Gas—liquid chromatography of the lactones and 5-methylfurfuran was carried out with a Khrom-4 chromatograph with a 2.5-m long glass column with a diameter of 4 mm; the support was Chromaton N-AW (0.250-0.315 mm) impregnated with polymethylphenylsiloxane oil (15% of the mass of the support), the carrier gas was nitrogen, the flow rate was 50 ml/min, and the column temperature was 160°C. The IR spectra of thin films of the compounds were recorded with a UR-20 spectrometer at 800-4000 cm^{-1}. The PMR spectrum was recorded without a solvent at 18°C with a JNM-3H-60 spectrometer with hexamethyldisiloxane as the internal standard. The polarograms were recorded with an LP-60 polarograph with a phosphate inert electrolyte at pH 7.25 with the addition of hydrazine hydrochloride (for the oxo acids) and with a phosphate inert electrolyte at pH 7.25 and simultaneously in 0.1 N HCl (for the unsaturated acids). Thin-layer chromatography (TLC) of the lactones was carried out on Silufol plates in a benzene—ether system (20:1). Paper chromatography of the acids and oxo acids was carried out on M-16 paper in a HCOOH—butanol—H_2O system (1:9:4). The consumption of the formylfurans was monitored with an SF-4 spectrophotometer at the absorption maxima of aqueous solutions of furfural (278 nm) and methylfurfural (292 nm).

2-Oxo-2,5-dihydrofuran. A thermostatted reactor equipped with a stirrer and reflux condenser was charged with 1920 g (20 mole) of furfural, and 5000 ml (43.8 mole) of 27% hydrogen peroxide was added. The reaction was carried out with vigorous stirring and thermostatting at 60 ± 1°C. After 3 h, the mixture was cooled to 35°C or lower, 35 g of cobalt oxide was added to decompose the peroxides and bring about isomerization of IV to I, and the mixture was stirred for another hour. The cobalt oxide was separated, and the oxidate was vacuum evaporated at 20-30 mm. The water was removed by distillation, and the residual mixture of crystals and a dark-yellow syrupy mass was separated by centrifugation. A product with bp 88-92°C (12 mm) was distilled from the oil at a bath temperature of 150-160°C. 2-Oxodihydrofuran containing 5-15% unsaturated acids (maleic and formylacrylic) was obtained. To remove these impurities the product was treated with freshly distilled cyclopentadiene (CPD): it was stirred with an equal of CPD with cooling (with ice water). At

the end of the vigorous reaction, the mixture was cooled, the precipitated adducts were separated, and the oil was vacuum distilled at 90-92°C (12 mm) to give 622 g (37%) of a substance that was identified as 2-oxo-2,5-dihydrofuran (Table 1 and Fig. 1). When the oxidate was not treated with cobalt oxide, the product was 2-oxo-2,5-dihydrofuran containing 2-oxo-2,3-dihydrofuran (5-20%) (Fig. 1a). The impurity content was reduced to 0.5-2% when the mixture was heated at 130°C for 2 h or allowed to stand in a refrigerator for 2 months (Fig. 1b). The following procedure was used to completely remove the β,γ isomer. The product was treated with 5% triethylamine, and the mixture was heated at 100°C on a glycerol bath for 1 h, after which it was vacuum distilled (Fig. 1c). Heating the oxodihydrofurans with equal volumes of acetic anhydride, 20% H_2SO_4, or ethanol under these conditions had no effect on the isomer ratio.

2-Oxo-5-methyl-2,5-dihydrofuran. An 11-g (0.1 mole) sample of crude 5-methylfurfural was mixed with 31.5 ml (0.25 mole) of 27% H_2O_2, and the mixture was treated as described above with vigorous stirring and thermostattting (60 ± 1°C). After 2 h, the oxidate was cooled and treated with 0.11 g of thiourea, and the mixture was heated at 40-60°C for 30 min. It was then subjected to vacuum evaporation, and the crystals were separated. The concentrated oil was vacuum distilled on an oil bath at 120-140°C. The product, with bp 85-86°C (10 mm), was identified as 2-oxo-5-methyl-2,5-dihydrofuran (Table 1). Where necessary, purification was carried out by the method used to purify I. The yield was 30%.

Hydrolysis of 2-Oxo-5-methyl-2,3-hydrofuran and 2-Oxo-5-methyl-2,5-dihydrofuran (II and III). The hydrolysis was carried out with a molar ratio of [II or III]:[HCOOH]:[H_2O] = 1:1:10. A mixture of 3 ml (0.0322 mole) of II or III, 1.24 ml (0.0322 mole) of formic acid, and 6 ml of water was heated with stirring in a flask equipped with a reflux condenser with thermostatting at 60° for 6 h and at 100°C for 2 h.

Hydrolysis of a Mixture of 2-Oxo-2,5-dihydrofuran and 2-Oxo-2,3-dihydrofuran (I and IV). (Fig. 1a). The hydrolysis was carried out with vigorous stirring on a boiling-water bath in a flask equipped with a reflux condenser. A mixture of 11.1 g of I and IV, 20 ml of water, and 2 ml of concentrated HCl was subjected to hydrolysis for 9 h, after which the hydrolyzate was evaporated in vacuo at 40-50°C (12 mm). The residue was then subjected to fractional distillation in vacuo to give a product with bp 80-90°C (12 mm).

The oxidation of a mixture of I-IV was carried out with 27-30% aqueous H_2O_2 in the presence of formic acid at 60°C with vigorous stirring for 6 h. The molar ratio of the components in the oxidate was [I-IV]:[H_2O_2]:[HCOOH] = 1:2.2:1. After analysis of their compositions, the oxidates were allowed to stand at room temperature for 3 months.

The consumption of the formylfurans and oxodihydrofurans and the accumulation of the acids were monitored during the preparation of I-IV and during their hydrolysis and oxidation by means of known polarographic and chromatographic methods. Samples were selected at the instant the media became homogeneous.

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SYNTHESIS OF γ-PYRONES, FLAVONES, AND ISOCOUMARINS BY DESTRUCTIVE OXIDATION OF PYRANYLIDENES AND THEIR BENZO ANALOGS

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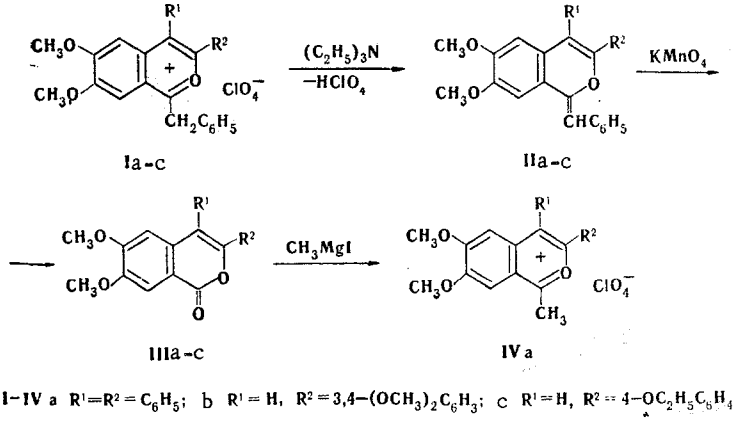
Preparative methods for the synthesis of isocoumarins, γ-pyrones, and flavones by destructive oxidation of methylenepyrans with potassium permanganate in acetone were developed.

A method for the conversion of carbonyl-containing pyran derivatives to pyrylium salts has been worked out [1] and is widely used in synthetic practice. There is virtually no method for the reverse transition from pyrylium salts or their derivatives. Thus various attempts to accomplish this conversion by nucleophilic reaction of pyrylium salts with hydroxide ion have been unsuccessful because of the instability of the resulting pyranols [2].

In the present communication we describe the synthesis of some pyrones and their benzo analogs by oxidative destruction of pyranylidenes, which are readily obtained from pyrylium salts.



I–IV a $R^1=R^2=C_6H_5$; b $R^1=H$, $R^2=3,4-(OCH_3)_2C_6H_3$; c $R^1=H$, $R^2=4-OC_2H_5C_6H_4$

Thus $HClO_4$ is split out when 1-benzyl-2-benzopyrylium salts (I) are treated with triethylamine in an anhydrous medium to give stable bases — benzylideneisochromenes II. The

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