Chemistry of Heterocyclic Compounds, Vol. 40, No. 8, 2004

INVESTIGATION IN THE AREA OF FURAN ACETAL COMPOUNDS. 13*. SYNTHESIS AND STRUCTURE OF 1,3-DIOXACYCLANES BASED ON FURFURAL AND GLYCEROL

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The optimum conditions were found for the condensation of glycerol with furfural. It was shown that the reaction of glycerol with furfural gives a mixture of the cis and trans isomers of five- and six-membered furan 1,3-dioxacyclanes. The cis- and trans-5-hydroxy-2-furyl-1,3-dioxanes were isolated by column chromatography, and their stereochemical structure was established by IR and NMR spectroscopy.

Keywords: glycerol, 1,3-dioxane, 1,3-dioxolane, stereoisomers, conformation.

Owing to the wide range of useful characteristics found among the numerous derivatives of furan one of the most promising and vigorously developing branches of the chemistry of heterocycles is the chemistry of furan compounds. Intensive study of cyclic furan acetals has made a substantial contribution to the development of stereochemistry and has opened up new wide-ranging possibilities for the production of practically valuable substances. The high biological activity of furan 1,3-dioxacyclanes is well known [2-5].

Acetalization of furan aldehydes by various diols is usually employed for the production of cyclic furan acetals [6-10]. By kinetic investigation of this process it was possible to formulate theories concerning the mechanism of the reaction and to perfect a synthesis procedure ensuring minimal resin formation [1, 11-13].

The use of glycerol in this reaction is interesting in respect of both the development of the chemistry of heterocyclic compounds and the production of substances that are structurally similar to natural compounds. It is known [14-26] that glycerol enters into condensation with carbonyl compounds under the conditions of acid catalysis in an inert medium, forming 1,3-dioxacyclanes. The condensation of glycerol with ketones leads to 2,2-disubstituted 4-hydroxymethyl-1,3-dioxolanes [14, 17-21], while condensation with aldehydes leads to the formation of a complex mixture of isomers, i.e., the *cis* and *trans* forms of 2-substituted 4-hydroxymethyl-1,3-dioxolanes and 5-hydroxy-1,3-dioxanes [22, 23, 26-29]. There are data on the separation of the isomers, i.e., the products from the reaction of benzaldehyde and acetaldehyde with glycerol, and their identification by spectral methods [22, 26-32]. There are few publications on the synthesis of 1,3-dioxacyclanes by the reaction of furan aldehydes with glycerol [33, 34], and they do not report on the isomeric composition, the fine structure, or the characteristics of the compounds that are formed.

We realized the reaction of glycerol with furfural [35] and as a result obtained a product in the form of a thick viscous liquid (Table 1), which will subsequently be called furfurylideneglycerol.

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* For Communication 12, see [1].

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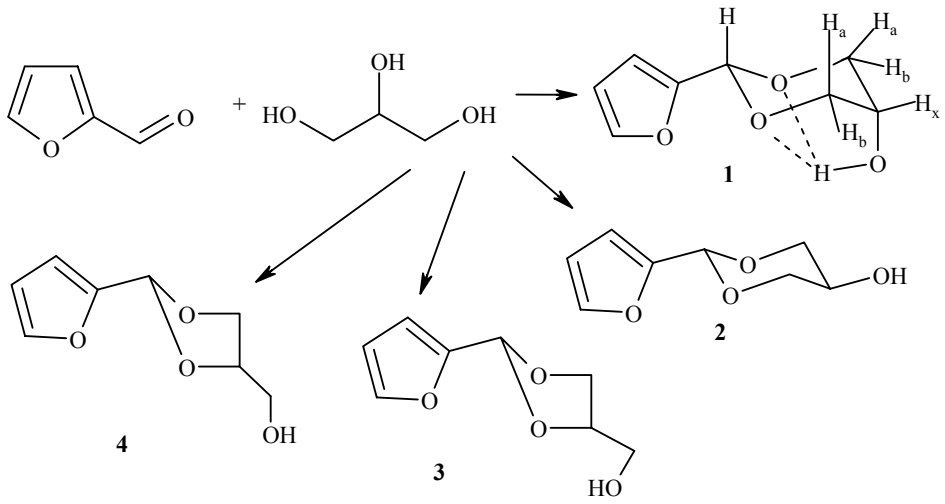
The ^{1}H NMR spectrum of furfurylideneglycerol contains signals for the protons of the furan ring, the respective multiplet bands of the methylene and methine protons of the dioxacycle and the hydroxyl proton in the region of 4.3-3.4 ppm, and four singlet signals at 5.9, 5.8, 5.6, and 5.4 ppm, which we assigned to the H-2 proton of the 1,3-dioxacyclane (Table 2). A spectrum of such a type makes it possible to suppose that the product from the reaction of furfural and glycerol represents a mixture of four isomers of five- and six-membered 1,3-dioxacyclanes having two substituents. By column chromatography of the condensation product we isolated three fractions, i.e., two crystalline fractions and one liquid.



In the region of 5.4-5.6 ppm the ^{1}H NMR spectra of the substances contain a single singlet, which corresponds to the resonance of the H-2 proton and demonstrates the individuality of the compounds. Analysis of the ^{1}H NMR spectra of the crystalline compounds makes it possible to assign them the structure of 1,3-dioxane derivatives **1** and **2**; the presence of a multiplet with intensity of 1H at 3.2 and 3.6 ppm, corresponding to the H-5 proton of the dioxane ring, and the splitting of the signal for the proton of the OH group into a doublet with J = 7.7 Hz indicate a vicinal arrangement for the H_x proton and the OH group [36].

In the ^{1}H NMR spectrum of the isomer **1** the two multiplets at 3.9 and 4.1 ppm correspond to the H-4 and H-6 protons. The axial and equatorial protons are not equivalent. The difference in the chemical shifts of their signals ($\Delta\delta$ = 0.2 ppm) confirms the chair conformation of the 1,3-dioxane ring in compound **1** [37]. The spin–spin coupling constant of the H_a, H_b, and H_x protons, forming an ABX system, is J = 3.5 Hz. According to the Karplus rule [36] this indicates that they have a mutually skewed orientation, which is only possible with the equatorial arrangement of the H-5 proton and, consequently, the axial arrangement of the OH group. In the light of the foregoing and of the fact that the furan fragment as a "heavy substituent" occupies the equatorial position [38] it can be assumed that the 1,3-dioxane **1** has the *cis* configuration.

The ^{1}H NMR spectrum of the isomer **2** contains multiplet bands at 3.5 and 4.0 ppm, corresponding to the axial (H_a) and equatorial (H_b) protons at the C(4) and C(6) atoms and indicates that the isomer has the chair conformation. The bands at 4.4 ppm were assigned to the hydroxyl proton and that at 3.2 ppm to the H_x proton at the C(5) atom. On the basis of the ^{1}H NMR spectrum and data in [27] it is possible to give the isomer **2** the structure of *trans*-2-(2-furyl)-5-hydroxy-1,3-dioxane in the *chair* conformation with an axial H_x proton and the *trans* arrangement of the furan ring and the hydroxyl group.

In the ^{1}H NMR spectrum of the liquid fraction there are two signals of almost equal intensity at 5.9 and 5.8 ppm, belonging to the protons at the C(2) atom of the five-membered heterocycle [27]. Consequently, the liquid fraction represents a mixture of isomers, i.e., *cis*- and *trans*-2-(2-furyl)-4-hydroxymethyl-1,3-dioxolanes **3** and **4** in approximately equal proportions. Multiplet bands at 3.9-4.4 ppm correspond to the resonance of the protons at the C(4) and C(6) atoms of the 1,3-dioxolane ring and the protons of the hydroxymethyl group.

TABLE 1. The Physicochemical and Spectral Characteristics of 2-Furyl-1,3-dioxacyclanes

Compound	bp, °C/mm, mp, °C	Density d_{17}	Refractive index n_D^{17}	R_f (hexane–ether 1:1)	IR spectrum (vaseline oil), ν, cm^{-1}			UV spectrum (water), λ_{max} (log ε), nm
					OH	C=CH ar	O–C–O	
Furfurylidene-glycerol	150–157/9	1.2673	1.5037	—	3400 (3645 3604)*	3140, 3110, 1600, 1570	1150, 1080, 1010	212.8 (3.93)
1	63–64	—	—	0.16	3230 (3604)*	3140, 3110, 1600, 1570	1150, 1080, 1000	214.6 (3.89)
2	57–58	—	—	0.26	3250	3140, 3110, 1610, 1380	1140, 1090, 1025	
3, 4	—	1.2484	1.5013	0.22	3400	3140, 3110, 1600	1150, 1100, 1080, 1020	

* In CCl_4.

TABLE 2. The ^{1}H NMR Spectra of 2-Furyl-1,3-dioxacyclanes

Compound*	Chemical shifts, δ, ppm (*J*, Hz)					
	Furan protons		H-2	H-4, H-6 ($2CH_2$)	H-5	OH
	H-5	H-3, H-4				
Furfurylidene-glycerol	7.5 (1H, m)	6.3 (2H, m)	5.9, 5.8, 5.6, 5.4 (1H, s, s, s, s)	4.3-3.4 (6H, m)		
1	7.5 (1H, dd, J_{35} = 0.8, J_{45} = 1.8)	6.4 (2H, m)	5.6 (1H, s)	3.9 (2H,dddd, H_a-4, H_a-6); 4.1 (2H,dddd, H_b-4, H_b-6, $^{2}J_{4A4B} = {}^{2}J_{6A6B}$ = 11.5, $^{3}J_{AX} = {}^{3}J_{BX}$ = 3.5, $^{4}J_{HH}$ = 1.5, $^{4}J_{HH}$ =0.75)	3.6 (1H, ddd, $^{3}J_{XOH}$=7.7, $^{3}J_{AX} = {}^{3}J_{BX}$ = 3.5)	4.2 (1H, d, $^{3}J_{XOH}$=7.7)
2	7.4 (1H, t, J_{35} = 0.8, J_{45} = 1.8)	6.3 (2H, m)	5.4 (1H, s)	3.5 (2H, m, H_a-4, H_a-6); 4.1 (2H, m, H_b-4, H_b-6)	3.2 (1H, m)	4.4 (1H, br. s)
3, **4**	7.4 (1H, m)	6.4 (2H, m)	5.9, 5.8, (1H, s, s)	3.9-4.4 (5H, m)		2.8 (1H, br. s)

* The spectra of furfurylideneglycerol, of the compounds **1** and **2** were recorded in $(CD_3)_2CO$, of the compounds **3** and **4** in CD_2Cl_2. The spectrum of compound **1** was obtained on a Bruker AC-200P instrument.

The furan protons of the isomers **1**-**4** resonate in the usual regions for these protons [39].

Thus, the product from the acid-catalyzed reaction of furfural and glycerol contains all four isomers **1**-**4**. The ratios of the various isomeric forms **1**:**2**:**3**:**4** in the reaction product, determined by means of the ^{1}H NMR spectrum by integration of the bands in the region of 5.3-5.9 ppm corresponding to the resonance of the H-2 protons of each of the four isomers, amount to 15:10:40:35.

In the IR spectra of furfurylideneglycerol and compounds **1**-**4** there is a series of bands characteristic of the absorption of the O–C–O fragment in the region of 1110-1150 cm^{-1}, the furan ring at 1570-1600 cm^{-1}, and the stretching vibrations of the hydroxyl group at 3110-3140 cm^{-1}.

In the IR spectra of dilute solutions of furfurylidene in carbon tetrachloride there are two absorption bands at 3645 and 3604 cm^{-1}, while for compound **1** there is one band at 3604 cm^{-1} (Table 1). The higher-frequency absorption band was assigned to the vibrations of the free hydroxyl group [40, 41], while the absorption at 3604 cm^{-1} was assigned to an intramolecular hydrogen bond [41, 42]. The high stability of the configuration of this isomer **1** can be explained by the presence in the molecules of the isomer **1** of an intramolecular hydrogen bond between the hydrogen atoms of the hydroxyl group and the oxygen atoms of the heterocycle.

The electronic spectra of furfurylideneglycerol and the 1,3-dioxane **1** contain one absorption maximum in the ultraviolet region at 213 and 215 nm respectively.

The synthesis of furan acetals is traditionally conducted in benzene solution in the presence of acidic catalysts KU-2 in the H^+ form [34] and *p*-toluene(benzene)sulfonic acid [34] with the reagents in various ratios [34, 35]. We determined the optimum conditions for the synthesis, making it possible to realize the condensation of furfural with glycerol with yields of 70-75%: Equimolar proportions of the reagents, catalyst *p*-toluenesulfonic acid (0.03% on the total mass of the initial reagents), solvent benzene. The reaction is conducted in the boiling solvent for 3-3.5 h with azeotropic distillation of the water that forms. The ratios of the products **1**:**2**:**3**:**4** in the product obtained under the above-mentioned conditions amounted to 15:10:40:35 (here and subsequently determined from the ^{1}H NMR spectra).

Furfurylideneglycerol, which is a mixture of isomers **1**-**4** with the composition indicated above, is stable at room temperature for three months, in contrast to the unstable analog benzylideneglycerol [27]. After three months the composition of furfurylideneglycerol changes; the five-membered rings isomerize to the more stable six-membered rings, and the acetals subsequently decompose (furfural appears as impurity). If the temperature is reduced (~2-3°C) the furfurylideneglycerol remains for ~6 months.

It was established that the various temperature and time factors for the realization of the reaction lead to change in the ratio of the isomers, and this agrees with the theories put forward in [24, 29-31]. If the temperature of the reaction medium is increased to 110°C (solvent boiling toluene) and the reaction rate in increased, the five-membered isomers **3** and **4**, which are kinetically controlled products [the ratios of the acetals **1**:**2**:**3**:**4** amount to 10:5:45:40], predominate in the reaction product. With decrease in the rate of the process at room temperature (the reaction time amounts to several days) the dioxolane **3** and **4** and dioxane **1** and **2** derivatives are formed in approximately identical amounts. (The ratios of the acetals **1**:**2**:**3**:**4** amount to 30:18:27:25.) Here, however, the overall yield of the product decreases appreciably – in the first case as a result of resin formation and in the second as a result of the low reaction rate.

EXPERIMENTAL

The IR spectra were recorded on a Specord-71 instrument at room temperature. The ^{1}H NMR spectra were recorded on Tesla BS-467 (60 MHz, internal standard HMDS) and Bruker AC-200-P (200 MHz, internal standard TMS) instruments. The ^{13}C NMR spectrum was recorded on a Bruker AM-300 instrument (75 MHz) in deuterochloroform with TMS as internal standard. The electronic spectra were recorded in ethanol on a Specord UV-Vis spectrophotometer.

Conditions for the Reaction of Furfural with Glycerol. In a three-neck flask fitted with a stirrer, a reflux condenser, and a Dean–Stark tube we placed furfural (19.2 g, 200 mmol), glycerol (18.4 g, 200 mmol), benzene (80 ml), and *p*-toluenesulfonic acid (0.011 g). The mixture was boiled for 3 h with stirring. The end of the reaction was determined by the cessation of the deposition of water in the trap. After distillation of the solvent the product was isolated by vacuum distillation. We obtained 25.5 g (75%) of the condensation product. Found %: C 56.8; H 5.40. $C_8H_{10}O_4$. Calculated %: C 56.5; H 5.90.

Distribution of the Isomers of 2-Furyl-1,3-dioxacyclanes. The mixture of isomers weighing 1.2 g was separated on a column (3.5 × 18 cm) of silica gel L 40/100 with mixtures of hexane and ether in ratios of 7:3 (450 ml) and 1:1 (350 ml) or ether (300 ml) as eluant. With the first mixture of solvents we eluted 0.05 g of the oily compound **2**, which gradually crystallized. With the second mixture we eluted 0.75 g of a liquid fraction containing the acetals **3** and **4**. With ether we eluted the crystalline compound **1**. The separation of the isomers was monitored by TLC on Silufol UV-254 plates with a 1:1 mixture of hexane and ether as eluant. A 2N solution of 2,4-dinitrophenylhydrazine was used as developer.

***cis*-Hydroxy-2-(2-furyl)-1,3-dioxane (1).** ^{13}C NMR spectrum, δ, ppm: 63.2, 67.7, 77.5, 98.5 (C(5), C(4), C(6), C(2) (1,3-dioxacycle), 109.6, 113.4, 143.9, 152.0 (C(3), C(4), C(2), C(5) (furan ring).

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