

THE STABILITY OF ISOMERS AND THE CLEAVAGE
OF THE SEMIACETAL BOND
IN 2,3-DIALKOXY-2,3-DIHYDROBENZOFURANS

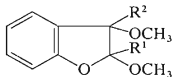
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The effect of alcoholic solutions of mineral acids on the ratio of isomers in 2,3-dimethoxy-2,3-dihydrobenzofuran (*I*), 3-methyl-2,3-dimethoxy-2,3-dihydrobenzofuran (*II*) and ethyl 3-methyl-2,3-dimethoxy-2,3-dihydrobenzo-2-furoate (*III*) was investigated. From acetal *I* pure *trans*-isomer is formed under acid conditions, from acetal *II* methyl 2-(hydroxyphenyl)propionate (*IV*) is formed, and acetal *III* remains unchanged under the reaction conditions. The reaction was studied with perdeuterated reagents, using various alcohols as medium and applying physico-chemical methods. The effect of the investigated reactions on the distribution of the products in electrochemical oxidation of benzofuran was demonstrated.

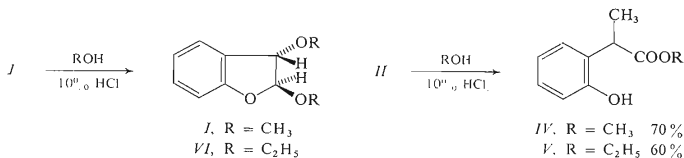
2,3-Dialkoxy-2,3-dihydrobenzofurans are formed by chemical and electrochemical alkoxylation of benzofuran derivatives¹. In fact they are analogues of 2,5-dialkoxy-2,5-dihydrofurans which are formed by the same reaction from furan compounds. The last mentioned compounds are useful in organic synthesis and their preparation is well elaborated²⁻⁵. During a study of electrochemical alkoxylation of benzofuran we observed¹ that the ratio of the *cis* and *trans* isomers of acetal *I* formed varies in a broad range even when the conditions of the electrochemical reaction were equal. In view of the fact that the basic criterion for the utilisability of acetals in synthesis is the stability of the semiacetal grouping, and for reasons of the mentioned unclarity in electrochemical synthesis, we considered that it would be useful to study in this paper the stability of the semiacetal grouping in these substances in greater detail.



- I*, $R^1 = R^2 = H$
II, $R^1 = H$; $R^2 = CH_3$
III, $R^1 = COOC_2H_5$; $R = CH_3$

For the study proper the earlier described¹ acetals *I*–*III* were used which enabled the study of the effect of substitution on carbons 2 and 3 of the heterocyclic ring on the stability of each compound.

The reactions were first carried out with 10% HCl solution in dry methanol and ethanol. Acetals *I* and *II* were used as substrates. The products, and thus also the reaction course, were different in both cases. From the mixture of the isomers *I* pure *trans-I* was always isolated, irrespective of the starting mixture. Acetal *II* (both pure *trans* isomer and a mixture of *cis* and *trans* isomers in a 1 : 9 ratio was used) afforded substances which were identified on the basis of physical and chemical data as esters *IV* or *V*, according to whether methanol or ethanol was used as medium. The course of both reactions is represented in Scheme 1.



SCHEME 1

Acetal *III* was submitted to the reaction in ethanol only, because possible reesterification reactions could possibly take place. It was shown by a repeated experiment that the starting ratio of the isomers, *trans* : *cis* = 85 : 15, remains unchanged even when the reaction time was prolonged to 4 hours. Further reactions with acetals *I* and *II* were carried out with the use of solutions of mineral acids of various concentrations. The reactions were evaluated always at a predetermined time interval by analysis of the reaction mixture by gas chromatography. The results of these experiments are summarized in Table I. On the basis of these experiments the reaction of acetals *I* and *II* could be carried out with 0.1% D₂SO₄ solution in CD₃OD, directly in the cell of the ¹H-NMR spectrometer. The cells were filled under dry nitrogen and the spectra taken in the following intervals: 0, 0.5, 3 and 48 hours. In the case of both acetals the spectra obtained were identical with the starting compound. This means that under the mentioned conditions (30°C) no exchange of the methoxyl groups took place. Therefore a reaction with 10% D₂SO₄ in CD₃OD at 40°C was carried out with the pure *trans* isomer of acetal *II*. The values for the exchange of D–H were thus determined for single groups in the molecule. The experiment was repeated under identical conditions with methanol and sulfuric acid; under these conditions no further conversion of acetal *II* took place to a measurable extent. The results of the D–H exchange (in %) are given in Table II.

From the mentioned facts it may be judged that the semiacetal bond in 2,3-dialkoxy-2,3-dihydrobenzofuran is relatively stable in acid medium, which is confirmed by the restricted exchange of hydrogen in the position 2 of the heterocyclic ring in the *trans* isomer of acetal II in 10% D₂SO₄. For this reason the recently described⁶ mechanism of equilibration of the isomers initiated by the oxonium ion on the oxygen

TABLE I

Time Dependence of the Ratio of Isomers I and II in Methanolic Solutions of Mineral Acids

Medium	Isomer	Time, min						
		0	1	5	10	20	60	360
		Acetal I						
50°C, 10% HCl	<i>cis</i>	59	15	4	3	2	2	—
	<i>trans</i>	41	85	96	97	98	98	—
20°C, 10% HCl	<i>cis</i>	59	20	17	14	12	2	—
	<i>trans</i>	41	80	83	86	88	98	—
20°C, 1% HCl	<i>cis</i>	59	49	38	32	22	17	—
	<i>trans</i>	41	51	62	68	78	83	—
20°C, 1% H ₂ SO ₄	<i>cis</i>	48	41	32	—	20	18	—
	<i>trans</i>	52	59	68	—	80	82	—
40°C, 0.1% H ₂ SO ₄	<i>cis</i>	45	44	44	—	40	36	15
	<i>trans</i>	55	56	56	—	60	64	85
		Acetal II						
20°C, 1% H ₂ SO ₄	<i>cis</i>	6	5	3	—	—	0	—
	<i>trans</i>	94	95	97	—	—	100	—

TABLE II

D—H Exchange (%) in Individual Groups of *trans* II under the Effect of 10% D₂SO₄ in CD₃OD, 40°C

Time	0.5'	1'	5'	10'	30'	60'
3-OCH ₃	35	52	92	99	100	100
2-OCH ₃	0	0	15	15	15	15
2-H	0	0	15	15	15	15

atom can be excluded. This mechanism has been proved in 2,3-dimethyl-2,3-dihydrobenzofuran. The formation of esters of 2-(2-hydroxyphenyl)-propionic acid can be explained by the splitting off of methanol, which gives rise to 2-methoxybenzofuran which is further split under formation of *IV* or *V*, in dependence on the medium used. The reason for this is the presence of the methyl group in the position 3 of acetal *II* where a very rapid exchange of the methoxy group for the trideuteriomethoxyl group has also been demonstrated, while the D—H exchange took place in all other groups either slower by an order of magnitude or not at all. In a medium with a lower concentration of acid acetal *II* undergoes a reaction giving acetal *I* exclusively. In the case of acetal *I* it has been demonstrated by exchange of the methoxyl groups for ethoxyls that an exchange of alkoxy groups does indeed take place. However, in the case of acetal *II* the reaction takes place even at a very low concentration of acid. In view of the fact that in this medium no exchange of alkoxy groups takes place (the reaction was carried out directly in the cell of the $^1\text{H-NMR}$ spectrometer) but the equilibration of the isomers does to a demonstrable extent, only one explanation is possible, *i.e.* that the dihydrobenzofuran skeleton is not planar. Within the frame of conformational equilibria of single isomers the formation of forms could possibly take place which would permit equilibration without the necessity for an exchange of alkoxy groups with the medium.

On the basis of these facts we considered it useful to reproduce our earlier experiments¹ with the alkoxylation of benzofuran by the electrochemical method. We had already found earlier¹ that the distribution of the ratio of isomers of acetal *I* changes at identical electrochemical conditions within broad limits. During the reproduction we arranged the experiment in such a manner that the working up of the reaction mixture should affect the composition of the products as little as possible. In addition to this the mixture was controlled at given time intervals during the electrochemical reaction. Under these conditions the reaction gives a reproducible ratio of isomers *I* on the carbon anode; *i.e.* 54% of the *trans* and 46% of the *cis* isomer. The discrepancies observed earlier must therefore have been caused by the differences in the working up of the reaction mixtures. In conclusion it can be stated that 2,3-dialkoxy-2,3-dihydrobenzofurans show a considerably higher stability towards acid medium than their furan analogues.

EXPERIMENTAL

Apparatus Used

The electrolyser was a glass kettle of 500 ml volume provided with a magnetic stirrer and external cooling. The carbon anode was a 130 mm long stick of 25 mm diameter and the cathode a nickel cylinder arranged concentrically. The electrolyses were carried out at a constant current. Gas-chromatographic determinations were carried out on a CHROM-31 apparatus provided with

a flame ionisation detector. Carrier gas nitrogen, column 120×0.6 cm packed with 10% butanediol succinate on Chromaton (0.2–0.25 mm). The infrared spectra were measured on a Perkin-Elmer 325 apparatus in CS_2 for the $600\text{--}1200\text{ cm}^{-1}$ range and CCl_4 for the $1200\text{--}4000\text{ cm}^{-1}$ range. The $^1\text{H-NMR}$ spectra were measured on a Varian XL-100 instrument at 100 MHz, and on a Tesla BS 477 instrument at 60 MHz, in deuteriochloroform.

Reaction of Acetals I–III with 10% Alcoholic Hydrogen Chloride

One gram of acetal was refluxed for one hour in 50 ml of alcoholic HCl. The mixture was neutralized with an alcoholic solution of sodium ethoxide (pH 8), alcohol was evaporated in a vacuum, the residue partitioned between 100 ml of ether and 20 ml of water. The ethereal layer was dried over MgSO_4 , the solvent evaporated and the product purified by distillation.

trans-2,3-Dimethoxy-2,3-dihydrobenzofuran (0.45 g, 45%), b.p. $85\text{--}87^\circ\text{C}/17$ Torr, identical with an authentic specimen¹.

trans-2,3-Diethoxy-2,3-dihydrobenzofuran (VI) was isolated using ethanol in the reaction of acetal I, (0.5 g, 46%), b.p. $65\text{--}67^\circ\text{C}/0.4$ Torr. It was identified by comparison with an authentic sample¹.

Methyl 2-(2-hydroxyphenyl)propionate (IV) was isolated when methanol was used in the reaction of acetal II, yield 0.7 g, 70%, b.p. $88\text{--}90^\circ\text{C}/0.3$ Torr. For $\text{C}_9\text{H}_{10}\text{O}_3$ (180.2) calculated: 66.65% C, 6.56% H; found: 66.51% C, 6.40% H. $^1\text{H-NMR}$ spectrum: 1.50 (d, $J = 7$ Hz, 3 H, CH_3); 3.69 (s, 3 H, OCH_3); 3.98 (q, $J = 7$ Hz, 1 H, CH); 6.75–7.20 (m, 4 H, H—Ar); 7.30 (s, 1 H, OH).

Ethyl 2-(2-hydroxyphenyl)propionate (V) was isolated when ethanol was used in the reaction of acetal II, yield 0.65 g, 60%, b.p. $95^\circ\text{C}/0.5$ Torr. For $\text{C}_{11}\text{H}_{14}\text{O}_3$ (194.2) calculated: 68.20% C, 7.28% H; found: 68.03% C, 7.04% H. $^1\text{H-NMR}$ spectrum: 1.26 (t, $J = 7$ Hz, 3 H, CH_3); 1.55 (d, $J = 7$ Hz, 3 H, CH_3); 3.81 (q, $J = 7.5$ Hz, 1 H, CH); 4.18 (q, $J = 7$ Hz, 2 H, $\text{OCH}_2\text{—}$); 6.80–7.25 (m, 4 H, H—Ar); 7.65 (s, 1 H, OH). IR spectrum: 842, 856, 865, 880, 935, 988, 1016, 1028, 1030, 1060, 1070, 1090, 1110, 1150, 1190, 1228, 1240, 1269, 1302, 1318, 1378, 1395, 1464, 1475, 1478, 1487, 1502, 1583, 1595, 1609, 1704, 1733, 1826, 2930, 2975, 3030, 3300, 3610.

Study of the Ratio of Isomers after Methoxylation of Benzofuran

A solution of 11.8 g (0.1 mol) of benzofuran in 480 ml of methanol and 10 g of H_2SO_4 was electrolysed with a 3 A current at -20°C until a total charge of 0.4 F was introduced. When 0.02, 0.04, 0.08, 0.16 and 0.4 F had passed through the solution 30 ml of the reaction mixture were withdrawn which were neutralized with methanolic sodium methoxide (pH 8), methanol was evaporated in a vacuum, the residue partitioned between ether and water, the ethereal layer dried over MgSO_4 and evaporated and the residue analysed by gas chromatography ($t = 190^\circ\text{C}$, nitrogen flow 50 ml/min).

Determination of the Ratio of Isomers of Acetals I, II in the Reaction with Methanolic Solutions of Sulfuric Acid

The studied compound (40 μl) was injected into 1 ml of the corresponding methanolic solution in a thermostat. At certain time intervals 40 μl of the solution were withdrawn which were alkalized with excess alcoholic KOH and diluted with 100 μl of ether. The solutions were analysed directly by gas chromatography.

Reaction of Acetal II with a 10% Solution of D_2SO_4 in CD_3OD

A solution of 1.4 ml (2.7 g) of D_2SO_4 in 24 g of CD_3OD was prepared under dry nitrogen; 4 g of *trans*-II were then added at 40°C in one portion and 4 ml aliquots were then withdrawn from this solution at definite time intervals. The samples were immediately neutralized with excess ammonia, perdeuteriomethanol was evaporated under reduced pressure and the residue partitioned between ether and water. The ethereal layer was dried over $MgSO_4$ and ether evaporated. The residue was distilled in a vacuum. The yield was in all experiments 0.25–0.3 g of product, b.p. 53–55°C/0.07 Torr. The samples were analysed by 1H -NMR spectrometry.

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