THERMAL TRANSFORMATIONS OF METHYL 3-(2,5-DIMETHOXY-2,5-DIHYDRO-2-FURYL)PROPIONATE

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The primary products of the pyrolysis of diastereomers of methyl 3-(2,5-dimethoxy-2,5-dihydro-2,5-dihydro-2-furyl)propionate are methyl 3-(5-methoxy-2-furyl)- - and 3-(5-methoxy-2,5-dihydro-2-furylidene)propionates. The pyrolysis products also contain methyl 3-(2-furyl)acrylate, whereas methyl 3-methoxy-3-(2-furyl)-propionate is formed when the pyrolysis is carried out in the presence of p-toluenesulfonic acid.

The extensive use of 2,5-dimethoxy-2,5-dihydrofuran derivatives in organic synthesis [1, 2], particularly for the synthesis of prostaglandins [3-5], as well as other natural compounds [1], has attracted attention in recent years. Nevertheless, an extremely small amount of data relative to their thermal stabilities is available. It is known that methanol is split out to give 2-methoxyfuran when 2,5-dimethoxy-2,5-dihydrofuran is heated in the presence of β-naphthalenesulfonic acid at 360°C [6, 7], whereas 2-methyl- and 2-methoxymethyl-5-methoxyfuran, respectively, are obtained by pyrolysis of 2-methyl- and 2-methoxymethyl-2,5-dimethoxy-2,5-dihydrofuran [7].

However, we have observed that even under the conditions of vacuum distillation [105-106°C (4.0 hPa)] of large amounts of diastereomeric methyl 3-(2,5-dimethoxy-2,5-dihydro-2-furyl)propionates (Ia, b) several products of decomposition of the principal substance are formed in 7-30% amounts. In the present research we made a detailed study of the composition of the compounds formed during thermal treatment of esters Ia, b. Starting ester I was obtained by methoxylation of methyl 3-(2-furyl)propionate (II) with bromine in methanol at −5°C (see Scheme 1). We established that the ratio of isomers Ia and Ib in the resulting mixture is close to 3:2. The isomers were separated by means of column chromatography; on the basis of an analysis of the PMR spectra, a structure with a cis orientation of the methoxy groups was assigned to less polar isomer Ia, whereas the more polar isomer Ib has a trans orientation of the methoxy groups. According to [8], in the PMR spectra of trans-2,5-dimethoxy-2,5-dihydrofuran derivatives the chemical shift of the 5-H proton is shifted 0.2-0.3 ppm to the weak-field side as compared with the cis analog. For Ia, b, δ_{5-H} is 5.43 and 5.72 ppm, respectively.

The pyrolysis of individual diastereomers Ia, b and a mixture of them was carried out at 140-180°C without a solvent for 0.5 to 3.5 h with a catalytic amount of p-toluenesulfonic acid or quinoline and also without a catalyst. The pyrolysis products were separated into individual components by means of column chromatography and were analyzed by TLC, GLC, and PMR and mass spectrometry. The characteristics of the reaction products are presented in Tables 1 and 2.

We found that the composition of the products of decomposition of diastereomers Ia, b do not differ qualitatively, but their relative amounts depend on the mutual orientation of the methoxy groups attached to the dihydrofuran ring, the nature of the catalyst, and the reaction temperature and time (see Table 2).

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TABLE 1. Characteristics of Isomeric Methyl 3-(2,5-Dimethoxy-2,5-dihydro-2-furyl)propionates (Ia, b) and Their Pyrolysis Products

Compound	GLC: relative retention vol.	R_f		Mass spectrum, m/z (relative intensity, %)	PMR spectrum, δ, ppm
		A	B		
Ia	3,35	0,39	0,15	215 (3), 185 (6), 184 (4), 167 (10), 153 (100), 129 (92), 125 (44), 121 (10), 111 (40), 101 (64), 97 (48), 71 (32), 69 (6), 59 (26), 55 (4)	6,03 (dd, J=1,0 and 5,8 Hz, 4-H); 5,85 (dd, J=1,0 and 5,8 Hz, 3-H); 5,43 (t, J=1 Hz, 5-H); 3,64 (s, $COOCH_3$); 3,47 and 3,15 (s, OCH_3); 2,5—2,0 (m, CH_2CH_2)
Ib	4,01	0,32	0,15	215 (3), 185 (6), 184 (8), 167 (8), 153 (72), 129 (100), 125 (14), 121 (12), 111 (40), 101 (37), 97 (14), 59 (8), 55 (16)	6,05 (dd, J=1,0 and 5,8 Hz, 4-H); 5,85 (dd, J=1,0 and 5,8 Hz, 3-H); 5,72 (t, J=1,0 Hz, 5-H); 3,64 (s, $COOCH_3$); 3,43 and 3,08 (s, OCH_3); 2,6—2,0 (m, CH_2CH_2)
III	2,70	0,60	0,34	184 (42), 112 (5), 111 (100), 109 (34), 83 (5)	5,83 (m, J=0,8 and 3,7 Hz, 3-H); 4,94 (d, J=3,7 Hz, 4-H); 3,76 (s, OCH_3); 3,65 (s, $COOCH_3$)
IVa	3,07	0,48	0,20	184 (48), 160 (10), 156 (7), 153 (46), 152 (10), 125 (56), 124 (10), 121 (7), 117 (10), 113 (22), 111 (57), 104 (16), 97 (64), 94 (16), 84 (20), 83 (100), 70 (46), 59 (23), 55 (56), 54 (23)	6,34 (dd, J=1,0 and 5,8 Hz, 4-H); 6,05 (dd, J=1,0 and 5,8 Hz, 3-H); 6,01 (t, J=1,0 Hz, 5-H); 4,69 (t, J=7,0 Hz, CH); 3,65 (s, $COOCH_3$); 3,38 (s, OCH_3); 3,25 (d J=7,0 Hz, CH_2)
IVb	4,14	0,40	0,13		
V	1,18	0,67	0,42	152 (38), 121 (100), 111 (13), 109 (6), 108 (5), 93 (12), 78 (12), 65 (30), 63 (8), 55 (5)	7,47 (dd, J=0,5 and 1,2 Hz, 5-H); 7,42 (d, J=15,6 Hz, α-H); 6,60 (dd, J=0,5 and 3,3 Hz, 3-H); 6,45 (dd, J=1,2 and 3,3 Hz, 4-H); 6,31 (d, J=15,6 Hz, β-H); 3,37 (s, $COOCH_3$)
VI	1,0	0,57	0,29	184 (5), 169 (16), 153 (5), 147 (4), 124 (5), 112 (6), 111 (100), 95 (10), 94 (8), 81 (3), 66 (4), 65 (5), 59 (7), 55 (7)	7,39 (dd, J=0,5 and 1,8 Hz 5-H); 6,33 (dd, J=1,8 and 3,3 Hz, 4-H); 6,31 (dd, J=0,5 and 3,3 Hz, 3-H); 4,67 (dd, J=8,7 and 5,1 Hz, CH); 3,68 (c, $COOCH_3$); 3,27 (s, OCH_3); 2,96 and 2,74 (dd, J=8,7 and 15,5 Hz; dd, J=5,1 and 15,5 Hz, CH_2)

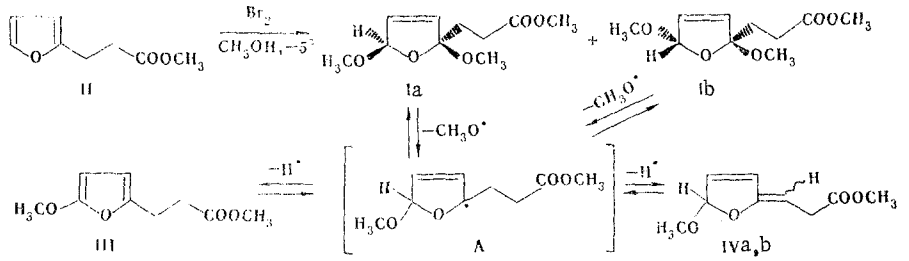
TABLE 2. Pyrolysis of Diastereomeric Methyl 3-(2,5-Dimethoxy-2,5-dihydro-2-furyl)propionates

Compound	Catalyst (2.5 mg)	Pyrolysis conditions		Composition of the pyrolysis products according to GLC data, %						
		temp., °C	time, h	Ia	Ib	III	IVa,b	V	VI	unidentified impurities
Ia	—	160	1,0	55,6	—	7,7	18,5	9,1	—	9,0
	—	140	3,5	75,7	—	3,0	18,8	2,5	—	3,3
	p-Toluenesulfonic acid	140	3,5	—	—	7,1	4,4	19,4	65,6	3,5
	Quinoline	140	3,5	67,5	—	4,3	19,7	3,6	—	5,0
Ib	—	160	1,0	—	27,6	21,8	40,5	1,8	—	8,3
	—	140	3,5	—	39,4	15,4	35,5	0,7	—	9,0
Ia (60%) + Ib (40%)	—	140	3,5	55,0	14,1	9,8	19,5	0,4	—	1,2
	p-Toluenesulfonic acid	140	3,5	0,5	0,5	6,1	7,0	8,9	29,8	47,2
	Same	180	0,5	31,0	6,4	15,0	39,6	3,9	3,1	1,0
	Quinoline	140	3,5	41,9	5,5	15,8	30,8	4,3	—	1,4

The principal pyrolysis pathways are processes involving splitting out of methanol to give methyl 3-(5-methoxy-2-furyl)- (III) and 3-(5-methoxy-2,5-dihydro-2-furylidene)propionates (IVa, b).*

Methanol is split out with greater difficulty from Ia than from isomer Ib. Thus, for example, isomer Ib under identical pyrolysis conditions forms III and IVa, b in amounts that are greater by factors of three to five and two to 2.5, respectively, than in the case of Ia (see Table 2). This is explained by initial homolytic detachment of the less shielded (as compared with isomer Ia) 2-methoxy group from the 2,5-dihydrofuran system of ester Ib with subsequent stabilization of radical A in the form of III and IVa, b. It is apparent from the data in Table 2 that IVa, b are formed in higher yield than III.

Scheme 1



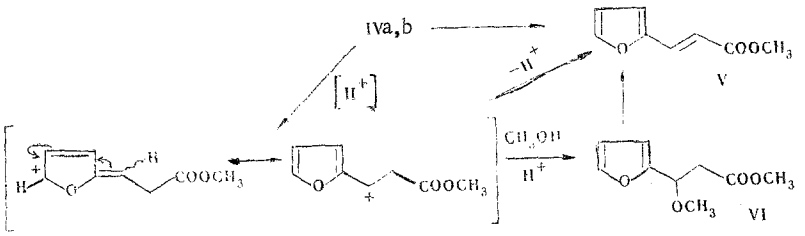
A similar pathway of elimination of methanol from methyl 2,5-dimethoxy-2,5-dihydro-2-furylacetate with the quantitative formation of methyl 5-methoxy-2,5-dihydrofurylideneacetate was noted in [9].

Catalytic amounts of quinoline do not have a substantial effect on the rate and direction of pyrolysis of esters Ia, b. p-Toluenesulfonic acid has a more substantial effect. For example, Ia at 140°C for 3.5 h forms only a small amount of esters IVa, b, but the principal decomposition products are methyl 3-(2-furyl)acrylate (V, 19%) and methyl 3-methoxy-3-(2-furyl)propionate (VI, 66%) (see Table 2).

Ester V is always present in the products of pyrolysis of Ia, b (see Table 2). By means of TLC we observed that it is the product of further thermal decomposition of esters IVa, b. In addition, this compound is readily formed by heating esters IVa, b with catalytic amounts of p-toluenesulfonic acid or an aqueous solution of sodium hydroxide in methanol. We observed that under the influence of a methanol solution of sodium hydroxide VI also readily splits out methanol to give ester V (see Scheme 2).

As noted above, ester VI is formed in the pyrolysis of Ia, b only in the presence of p-toluenesulfonic acid. In a separate experiment by TLC we proved that it is also obtained by heating a methanol solution of esters IVa, b in the presence of catalytic amounts of p-toluenesulfonic acid (see Scheme 2).

Scheme 2



Since methanol is split out in the pyrolysis of diastereomers Ia, b, and methanol, in the presence of an acidic catalyst, is capable of adding to IVa, b to give ester VI, the amount of the latter in the pyrolysis products evidently depends on the efficiency of vaporization of the methanol that is split out. Thus when the reaction is carried out at 140°C for 3.5 h, the yield of ester VI is higher than in the pyrolysis of Ia, b at 180°C for 30 min because of the rapid vaporization of methanol (see Table 2).

*The more polar unstable IVb isomer is formed in negligible amounts, and it could not be isolated in pure form.

Judging from the data obtained as a result of the present study, it is expedient to use 2,5-dimethoxy-2,5-dihydrofuran derivatives in subsequent syntheses without purification, which requires prolonged heating, since the products of decomposition of the principal substance may contaminate not only the starting compound but also its products.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in deuterochloroform were obtained with WH-90 or WM-360 spectrometers with hexamethyldisiloxane as the internal standard. The mass spectra were obtained with an MS-50 mass spectrometer with direct introduction of the samples; the samples were cooled with compressed air at room temperature, and the ionization-chamber temperature was 150°C.

Gas-chromatographic analysis was carried out with a Varian-3700 chromatograph with a flame-ionization detector with a 1.2-m long glass column with a diameter of 2.5 mm packed with 5% OV on Chromosorb 750 (60/80 mesh); the carrier gas was helium, the column temperature was 95°C, the vaporizer temperature was 200°C, and the detector temperature was 250°C. Calibration was used for quantitative analysis. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates (Czechoslovakian SSR) in the following solvent systems: A) hexane–ethyl acetate (2:1), B) hexane–ether (4:1). The plates were developed in UV light and by spraying with a reagent prepared from 2.5 g of vanillin, 100 ml of ethanol, and 1 ml of concentrated sulfuric acid, after which the plates were heated at 130°C.

Methyl 3-(2,5-Dimethoxy-2,5-dihydro-2-furyl)propionate (Ia, b). A flask equipped with a stirrer, a thermometer, and a dropping funnel was changed with 42.4 g (0.4 mole) of anhydrous sodium carbonate and 150 ml of methanol, the mixture was cooled with stirring to −10°C, and 33.5 g (0.2 mole) of ester II (containing 92% of the principal component) was added. A solution of 32 g (0.2 mole) of bromine in 100 ml of methanol was added dropwise at −5 to −10°C in the course of 1-1.5 h, and the mixture was stirred for another 15 min, after which it was allowed to warm up spontaneously to room temperature. At the end of the reaction, the liquid was decanted, and the inorganic precipitate was washed with methanol (two 30-ml portions). The solvent was evaporated with a rotary evaporator at a water-bath temperature no higher than 40°C, 125 ml of distilled water was added to the residue, the organic layer was separated, and the aqueous layer was extracted with ether (150 ml). The organic and ether layers were combined and evaporated with a rotary evaporator. Benzene was added in small portions to the residue for azeotropic drying, and the mixture was evaporated with a rotary evaporator. The residue was subjected to vacuum distillation to give 31.1 g (72%) of methyl ester I 105-106°C (4.0 hPa) and n_D^{20} 1.4520 [bp 128-130°C (12.0 hPa) and n_D^{20} 1.4537 [10]].

For the preparative separation of isomers Ia, b, a glass column with a diameter of 3 cm was filled with 150 g of L 40/100 silica gel (Chemapol, Czechoslovakian SSR), and 150 ml of hexane–ethyl acetate (2:1) to which 1.5 ml of triethylamine had been added was initially passed through the absorbent. A 1.5-g sample of a mixture of esters Ia, b was then applied to the column and eluted with hexane–ethyl acetate (2:1) to give 0.55 g of ester Ia, 0.60 g of a mixture of Ia and Ib, and 0.33 g of ester Ib.

Pyrolysis of Ester I. A 0.24-g sample of Ia, Ib, or a mixture of them was heated under the conditions indicated in Table 2. The pyrolysis products were analyzed by GLC and TLC.

For separation, 1.35 g of the mixture of products obtained by pyrolysis of esters Ia, b at 180°C for 30 min in the presence of p-toluenesulfonic acid was applied to a column filled with 70 g of Silasorb 600 (30 um) (Chemapol, Czechoslovakian SSR) sorbent and eluted with hexane–ether (4:1) to give 0.02 g of ester V, 0.14 g of ester III, 0.05 g of ester VI, 0.30 g of ester IVa, and 0.31 g of ester IVb. Fractions containing starting Ia, b were not collected.

Pyrolysis of Methyl 3-(5-Methoxy-2,5-dihydro-2-furylidene)propionate (IVa, b). A) A 10-mg sample of ester IVa was heated in a small test tube at 180°C for 10 min, after which it was cooled, 1 ml of ethyl acetate was added, and the contents were analyzed by TLC in system B. Ester IVa (R_f 0.20) and V (R_f 0.42) were detected in the reaction mixture.

B) A small crystal of p-toluenesulfonic acid was added to 10 mg of ester IVa, and the mixture was heated at 180°C for 2 min. It was then cooled and treated with 1 ml of ethyl acetate, and the mixture was analyzed by TLC in system B. Only V (R_f 0.42) was detected in the reaction mixture.

C) A 10-mg sample of ester IVb was heated in a small test tube at 180°C for 10 min, after which it was cooled, 1 ml of ethyl acetate was added, and the contents were analyzed by TLC in system B. Compound IVb (R_f 0.13), IVa (R_f 0.20), and a small amount of V (R_f 0.42) were found in the reaction mixture.

Reactions of Ester IVa in Methanol. A) An ∿10 mg sample of IVa was dissolved in 0.25 ml of methanol containing 5% sodium hydroxide, one drop of water was added, and the mixture was allowed to stand at room temperature for 24 h. It was then analyzed by TLC in system B. Ester IVa (R_f 0.20) and a small amount of V (R_f 0.42) were detected in the reaction mixture.

B) An ∿10 mg sample of ester IVa was dissolved in 0.25 ml of methanol, a small crystal of p-toluenesulfonic acid was added, and the mixture was refluxed for 5 min. It was then cooled and analyzed by TLC in system B. Only VI (R_f 0.29) was found in the reaction mixture.

Reaction of Methyl 3-Methoxy-3-(2-furyl)propionate (VI) with a Methanol Solution of Sodium Hydroxide. An ∿10 mg sample of ester VI was dissolved in 0.25 ml of methanol containing 5% sodium hydroxide, one drop of water was added, and the mixture was heated at 60°C for 5 min. It was then cooled and analyzed by TLC in system B. Only ester V (R_f 0.42) was detected in the reaction mixture.

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SYNTHESIS AND AMINOMETHYLATION OF 4,5-DIHYDROXYBENZOFURAN DERIVATIVES

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Reduction of the corresponding o-quinones of benzofuran gave 4,5-dihydroxybenzofuran derivatives, and methylation of the latter gave 4-hydroxy-5-methoxy and 4,5-dimethoxy derivatives of benzofuran. The aminomethylation of 4-hydroxy-5-methoxy derivatives of benzofuran was studied; a series of 7-aminomethyl derivatives was obtained.

In contrast to 4-hydroxy- and 5-hydroxybenzofuran derivatives, very little study has been devoted to 4,5-dihydroxybenzofuran derivatives. Moreover, they are evidently of interest as analogs of pyrocatechol derivatives.

The most convenient method for the synthesis of 4,5-dihydroxybenzofurans is the reduction of benzofuran o-quinones [1, 2]. Another recently described synthesis of 4,5-dihydroxybenzofuran derivatives is not a preparative method [3].

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