

ELECTROSYNTHESES OF 3-ACETYL- AND 3-METHOXYCARBONYL- -2,5-DIMETHOXY-2,5-DIHYDROFURANES

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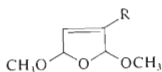
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Electrochemical methoxylation of furane derivatives has been used to synthesize 3-acetyl-2,5-dimethoxy-2,5-dihydrofurane (*I*) and methyl 2,5-dimethoxy-2,5-dihydro-3-furoate (*II*). Addition reaction of methanol with the ester *II* gave rise to methyl 2,4,5-trimethoxytetrahydro-3-furoates *IVa–IVc*, which were separated and identified by their ^1H NMR spectra. Using the same method, we identified isomeric 3-hydroxymethyl-2,4,5-trimethoxytetrahydrofuranes *Va–Vc*, formed by reduction of the ester *II* with a hydride, and methyl 2,5-dimethoxytetrahydro-3-furoates *VIa–VIc*, formed by hydrogenation of *II* on Pd.

In a connexion with the synthesis of 10-oxa-prostaglandine derivatives it was necessary to investigate the possibility of nucleophilic addition reactions with the double bond of such 2,5-dialkoxy-2,5-dihydrofuranes¹ as have this double bond conjugated with the carbonyl function. We have attempted working out a simple synthesis of suitable compounds, starting from 3-substituted derivatives of furane. The compounds selected for further study were 3-acetyl-2,5-dimethoxy-2,5-dihydrofurane (*I*) and methyl 2,5-dimethoxy-2,5-dihydro-3-furoate (*II*).



- I*, R = COCH₃
II, R = COOCH₃
III, R = CH(OH)CH₃

2,5-Dimethoxy-2,5-dihydrofuranones^{2,3} are synthesized by chemical or electrochemical alkoxylation of furane compounds. From the literature^{3,4} it is known that methoxylation of ketones is difficult to carry out. Besides, the reaction leads direct to the corresponding ketals. For these reasons, the method chosen to prepare the ketone *I* was an indirect one. We made use of the ready accessibility of 3-(1-hydroxyethyl)-2,5-dimethoxy-2,5-dihydrofurane⁵ (*III*) and studied oxidation of this alcohol to the ketone *I*. In an attempt to find the optimum oxidation method for tens of grams of the starting compound, a number of agents were used. The results of these experiments are given in Table I. In larger-scale preparations best results were obtained with pyridinium chlorochromate on alumina, the somewhat lower

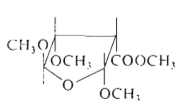
yields being outweighed by an exceptionally easy method of isolation. The remaining unreacted alcohol (1–2%) can be removed by filtration of the chloroform solution through a layer of silica gel.

To synthesize the ester *II*, the needed methyl 3-furoate was prepared by esterification of 3-furoic acid¹¹. Methoxylation of 3-furoic acid itself or its esters has not yet been described. First we tried to apply the known procedure of electrochemical methoxylation of 2-furoic acid, which also leads to esterification¹², but the ester desired was isolated in a yield of 10% only. With the method commonly used for methoxylation of alkyl 2-furoates the yields were better if the reaction was conducted in a more dilute solution. An electrolyser of simple construction was employed. In this equipment methyl 3-furoate was converted into ester *II* in a yield of 80%. The electrolyser lent itself well to anodic oxidation in a number of other cases, 1 mol of a substrate being used. In experiments aimed at optimizing this technique we discovered that methyl 2,4,5-trimethoxytetrahydro-3-furoate (*IV*) can also be obtained. This arises in solutions brought to pH > 8 by a consecutive 1,4-addition of methyl alcohol to the primarily formed ester *II*, which occurs during mere standing of the ester in the methanolic solution. The product was isolated in a yield of 82%. In the course of these experiments we obtained mixtures of products resulting from partial addition reactions. Using preparative gas chromatography we succeeded in isolation of all these components and, by analysis of their ¹H NMR spectra, even determined the relative configurations in the tetrahydrofuran ring. This analysis also cast light on the material balance of the electrochemical methoxylation and the consecutive addition. The ester *IVe* was also isolated from the products of partial addition.

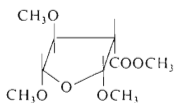
TABLE I
Results of the oxidation *III*→*I*

Agent	Yield, %	Ref.
Pyridine CrO ₃ /CH ₂ Cl ₂	83	6
K ₂ CrO ₄ /H ₂ SO ₄ /CHCl ₃ , (n-C ₄ H ₉) ₄ NHSO ₄	50 ^a	7
Active MnO ₂	70	8
CrO ₃ /(C ₂ H ₅) ₂ O, Celite/CH ₂ Cl ₂	70 ^a	9
Pyridine V ₂ O ₅ HCl/Al ₂ O ₃ /benzene	74	10

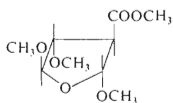
^a About 80% conversion with an excess of the agent.



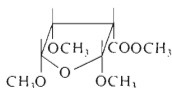
IVa, 46 %



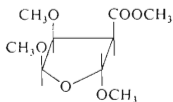
IVb, 24 %



IVc, 27 %

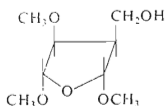


IVd, 3 %

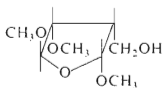


IVe

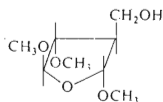
As to the ^1H NMR spectra of the systems studied, the literature gives complete analysis of the spectra of 2,5-dimethoxy-2,5-dihydrofuranes^{13,14} and 2,3,3,4,4,5-hexamethoxytetrahydrofuran¹⁵, along with their crystallographic data. The general regularities in the ^1H NMR spectra, of 2,5-dialkoxy-2,5-dihydrofuranes¹⁶⁻¹⁸ were also described. In addition, the literature presents analyses of ^1H NMR spectra of similar systems^{19,20}. These data allow of deriving rules, which enabled us to assign the individual structures. The interaction constants for the tetrahydrofuran ring have the following most probable values: J_{23} *cis* = 4.5–7 Hz, J_{23} *trans* = 0–3.5 Hz, J_{34} *cis* = 6–10 Hz, J_{34} *trans* < 6.5 Hz, interactions over several bonds < 1 Hz. The chemical shifts of the individual protons are enhanced by the methoxyl and ester groups if these are on the same side of the ring (shift to higher δ). As part of our study we also reduced the ester group with lithium aluminium hydride, and again separated the products by preparative gas chromatography. A mixture of isomeric alcohols was obtained in a yield of 92%. Three of the isomers were isolated sufficiently pure and identified as Va–Vc; these made up over 70% of the mixture. Under the conditions of the preparative gas chromatography (140°C) Va and Vb underwent spontaneous conversion into Vc. Although this isomerization cannot as yet be characterized in more detail, it appears that its driving force is the thermodynamic stability of the arising Vc. For the same reason we also investigated hydrogenation of the



Va

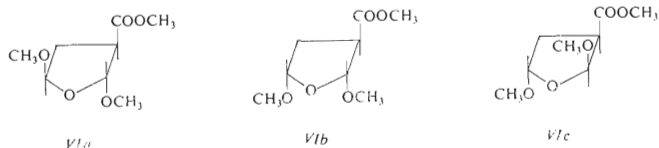


Vb



Vc

ester *II*, giving rise to a mixture of the corresponding methyl 2,5-dimethoxytetrahydro-3-furoates *VI*, which were separated by preparative gas chromatography and identified by analysis of their ^1H NMR spectra as *VIa*, *VIb* and *VIc*. The respective ^1H NMR spectra are given in Table II. Although the assignments of the individual structures on the basis of their ^1H NMR data cannot be regarded as safe, we tried to make them more reliable by interpreting the series of compounds in the order of their successive formation.



By working out simple syntheses of the compounds *I* and *II*, as representatives of five-membered cyclic unsaturated acetals with a double bond in conjugation with an ester or ketone group, and by proving that this system can react in the sense of a nucleophilic addition, we have made accessible a starting compound for syntheses of new 10-oxaprostaglandines¹.

TABLE II

Shifts (δ) and interaction constants (Hz) of the compounds studied

Compound	2	3	4	5	J_{23}	J_{34}	J_{45}	Other
<i>I</i>	5.99	6.69	—	5.67; 5.74	—	—	—	3.42; 3.54 2 . OCH ₃
<i>II</i>	5.97	6.80	—	5.68; 5.84	—	—	—	3.40; 3.81 2 . OCH ₃
<i>IVa</i>	5.52	3.28	4.00	4.97	5.0	3.8	3.3	3.36; 3.40; 3.46; 3.78 4 . OCH ₃
<i>IVb</i>	5.35	2.99	4.00	5.00	4.6	6.4	3.8	3.36; 3.40; 3.46; 3.78 4 . OCH ₃
<i>IVc</i>	5.35	3.00	3.99	5.00	3.8	2.8	2.5	3.40; 3.48; 3.50; 3.76 4 . OCH ₃
<i>IVd</i>	5.52	3.14	4.21	5.18	5.0	7.7	5.5	3.40; 3.48; 3.50; 3.76 4 . OCH ₃
<i>IVe</i>	5.16	3.15	4.43	4.95	5.5	7.8	3.0	3.40; 3.44; 3.48; 3.73 4 . OCH ₃
<i>Va</i>	5.17	2.50	3.94	5.00	4.0	7.0	—	3.42; 3.44; 3.46 3 . OCH ₃
<i>Vb</i>	5.08	2.36	3.92	4.96	6.0	7.0	3.0	3.42; 3.44; 3.46 3 . OCH ₃ 3.86 CH ₂ ; $J = 5 \text{ Hz}$
<i>Vc</i>	5.00	2.30	3.53	4.98	1.2	2.0	3.0	3.76; CH ₂ ; $J = 8 \text{ Hz}$; 3.38; 3.41; 3.44 OCH ₃
<i>VIa</i>	5.39	2.90	2.32	5.10	2.2	—	4.6	3.34; 3.40; 3.71 3 . OCH ₃
<i>VIb</i>	5.10	2.90	2.34	5.10	3.0	—	4.6	3.34; 3.40; 3.71 3 . OCH ₃
<i>VIc</i>	5.15	3.12	2.42	5.23	5.5	—	5.0	3.41; 3.50; 3.77 3 . OCH ₃

EXPERIMENTAL

The boiling points and the melting points are not corrected. The analytical samples were dried for 12 h at a pressure of 67 Pa. The ^1H NMR spectra were measured using an apparatus Varian XL100 (100 MHz) in deuteriochloroform, with tetramethylsilane as internal standard. The IR spectra were measured with an apparatus Perkin-Elmer 325 in tetrachloromethane. The mass spectra were measured in an apparatus LKB Gas Chromatograph-Mass Spectrometer 9000. Gas chromatography, preparative and analytical, was carried out in an apparatus Chrom 31 (Laboratorní přístroje, Prague), equipped with a flame-ionization detector. The analytical columns were of steel (120 . 0.6 cm) and of glass (0.3 \times 200 cm), packed with 5% of butanediolsuccinate on Chromosorb W. The preparative column, with the same packing, was of glass, 2.2 \times 120 cm. The carrier gas was nitrogen in all cases. The chromatography proceeded isothermally at 150 to 180°C.

The electrochemical oxidation was performed in an all-glass 2 l kettle, equipped with a lid with four ground-glass necks in it; these were used for a glass stirrer, a thermometer and two wire suspensions of the electrodes (copper wire, diameter 1 mm), along with pipes for work in an inert atmosphere. The copper wires and the pipes were sealed in polyethylene stoppers NZZ9 with an epoxide resin. The electrodes were two carbon plates, 13 \times 8 \times 1 cm, each with a working surface of 250 cm², held fixed in a teflon framing. The whole electrolyser was cooled by submersion in a cooling bath. The efficient stirring made it possible to work under galvanostatic conditions with a current up to 10 A.

3-Acetyl-2,5-dimethoxy-2,5-dihydrofuran (I)

A) CrO_3 , *pyridine* in CH_2Cl_2 : To 170 ml of dichloromethane (freshly distilled from P_2O_5) and 10 ml of pyridine was added, under stirring and cooling to 5°C, 6.7 g of chromium trioxide, which had been dried *in vacuo* over P_2O_5 . The stirring was continued for 20 min. To the agent thus formed was added 1.74 g (10 mmol) of the alcohol III. After 15 min the supernatant was poured off and the residue was washed with 50 ml of dichloromethane. The combined organic portions were successively shaken in the cold with ice-cold 5% NaOH (till discolouration occurred), ice-cold 5% HCl (to pH 1) and with a saturated solution of sodium hydrogen carbonate. The solution was then dried with MgSO_4 and distilled to remove the volatile components; yield 1.43 g (83%) of the ketone I, b.p. 78–83°C/67 Pa. For $\text{C}_8\text{H}_{12}\text{O}_4$ (172.2) calculated: 55.80% C, 7.27% H; found: 55.67% C, 7.12% H.

B) *Active MnO*₂. A mixture of the alcohol III (1.2 g, 6.9 mmol), tetrachloromethane (20 ml) and active manganese dioxide⁸ (12 g) was stirred for 2 h at 20°C. The solid phase was filtered off and washed with 10 ml of the pure solvent. After removal of the solvent distillation at 79 to 82°C/70 Pa gave 0.9 g (70%) of a homogeneous product I.

C) *Complex pyridine*. $\text{CrO}_3 \cdot \text{HCl}$ on *alumina*¹⁰. A mixture of the alcohol III (23 g, 0.13 mol), benzene (400 ml) and the oxidation agent (200 g, 0.21 mol) was stirred for 20 h at 25°C. The agent was filtered off and the filtrate was distilled; yield 16.9 g (74%) of I, b.p. 75–79°C/58 Pa. ^1H NMR spectrum: 2.38 (s, 3 H, CH_3CO); 3.42–3.54 (m, 6 H, OCH_3); 5.67 and 5.74 (2 \times s, 1 H, H-5 *cis*, *trans*); 5.99 (s, 1 H, H-2); 6.69 (s, 1 H, H-4). IR spectrum (cm^{-1}): 603 w, 723 o, 852 w, 893 s, 985 s, 998 s, 1 030 s, 1 068 s, 1 108 s, 1 122 s, 1 195 s, 1 233 s, 1 242 s, 1 265 m, 1 360 m, 1 383 m, 1 420 w, 1 430 w, 1 625 s, 1 695 s, 2 850 m, 2 950 m, 2 975 m, 3 015 w.

Methyl 2,5-Dimethoxy-2,5-dihydro-3-furoate (II)

A) *Methoxylation of 3-furoic acid*. A mixture of methanol (100 ml), 3-furoic acid (1 g) and concentrated sulphuric acid (2 ml) was electrolysed on the carbon electrodes at a tempera-

ture not exceeding 10°C under galvanostatic conditions until the starting compound had disappeared (TLC, silica gel, benzene-methanol-acetic acid 90 : 2.5 : 2.5). The mixture was neutralized with a solution of sodium hydrogen carbonate, the methanol was distilled off and the residue was extracted with three 100 ml portions of ether. The combined ethereal extracts were dried with MgSO₃ and the ether was removed by distillation; yield 11.4% of the ester *II*.

B) *Methoxylation of methyl 3-furoate*: A mixture of methyl 3-furoate (25 g), methanol (1 800 ml) and concentrated sulphuric acid (20 ml) was electrolysed at -10°C and a constant current of 6 A. The degree of conversion was monitored by TLC (silica gel, benzene-10% of methanol). After 10 h the cooled mixture was neutralized with aqueous sodium hydrogen carbonate, the methanol was immediately removed *in vacuo* and the residue was extracted with three 200 ml portions of ether. The combined extracts were dried and distilled; yield 32.6 g (84%) of the ester *II*, b.p. 125–133°C/1.6 kPa. For C₈H₁₂O₅ (188.3) calculated: 51.06% C, 6.43% H; found: 51.17% C, 6.51% H.

Methyl 2,4,5-Trimethoxytetrahydro-3-furoate (*IV*)

Methyl 3-furoate (70 g) in methanol (1 800 ml) and concentrated sulphuric acid (20 ml) was methoxylated at -10°C and 6–7 A. The mixture was then brought to pH > 8 by an addition of sodium methylate and left standing for 12 h at 25°C. The methanol was removed *in vacuo* and the residue was extracted with ether (4 × 200 ml). Distillation gave 80.3 g (82%) of a mixture of the esters *IV*, b.p. 130–145°C/1.6 kPa. For C₈H₁₄O₅ (190.2) calculated: 49.53% C, 6.46% H; found: 49.61% C, 6.58%.

3-Hydroxymethyl-2,4,5-trimethoxytetrahydrofuran (*V*)

The ester *III* (10.6 g) was added to lithium aluminium hydride (4.2 g) in ether (300 ml) and the mixture was boiled under a reflux condenser for 1 h. To the stirred mixture were successively added water (4.2 ml), 15% aqueous NaOH (4.2 ml) and water again (13 ml). The solids were filtered off and washed with ether. The organic portions were dried with MgSO₄. Distillation afforded 16.3 g (92%) of the alcohol *V*, b.p. 115–135°C/1.7 kPa. For C₈H₁₆O₅ (192.2) calculated: 49.98% C, 8.39% H; found: 50.03% C, 8.36% H. IR spectrum (cm⁻¹): 880 m, 960 s, 1 010 s, 1 040 s, 1 100 s, 1 195 s, 1 330 m, 1 385 s, 1 460 s, 1 470 s, 2 870 s, 2 940 s, 3 450 s,

Methyl 2,5-Dimethoxytetrahydro-3-furoate (*VI*)

The ester *II* (32.5 g) in methanol (400 ml) with 10% Pd on active carbon (2 g), was hydrogenated for 10 h at 14–15 MPa and 25°C. The catalyst was filtered off and washed with methanol. After removal of methanol distillation gave 29.9 g (91%) of the ester *VI*, b.p. 110–128°C/1.6 kPa. For C₈H₁₄O₅ (190.2) calculated: 50.52% C, 7.41% H; found: 50.47% C, 7.31% H.

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