STEREOSELECTIVE PHOTOCHEMICAL ADDITION OF ACETALDEHYDE TO THE PRODUCTS OF CLAUSON–KAAS REACTION

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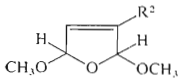
Photochemical addition of acetaldehyde to 2,5-dimethoxy-2,5-dihydrofuran (*I*) (and the pure stereoisomers *Ia* and *Ib*), methyl 2,5-dimethoxy-2,5-dihydrofuran-2-carboxylate (*II*), methyl 2,5-dimethoxy-2,5-dihydrofuran-3-carboxylate (*III*) and *cis*-2-hydroxymethyl-2,5-dimethoxy--2,5-dihydrofuran (*IV*) was studied. The acetyl group enters into the position 4 of the arising tetrahydrofuran system, *trans* relative to the ester or hydroxymethyl group in the position 2.

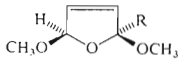
The addition of acetaldehyde to 2,5-dimethoxy-2,5-dihydrofuran, described by us previously[1], has now become important since it could be utilized in the synthesis of prostaglandine analogues[2–7]. For this reason, we investigated this reaction in more detail, particularly as concerns its applicability and stereochemical course in the cases of substituted derivatives. The results are summarized in the present paper.

As starting compounds we chose the cyclic acetals *I*–*IV*. Compounds *I*, *Ia*, *Ib*, *II* and *IV* were prepared by published procedures[8–10], compound *III* was obtained in 17% yield by electrochemical methoxylation of methyl furan-3-carboxylate. Structure of the acetal *IV* was proved by its synthesis from the benzoate *V* whose X-ray structure is known[11]. The photochemical addition of acetaldehyde to acetals, prepared by Clauson–Kaas reaction, generally proceeds smoothly and affords isomerically pure products in good yields.

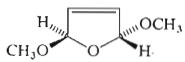
In order to study the stereochemical course of the reaction, the addition was carried out also with the pure isolated acetals *Ia* and *Ib*. In both cases a mixture of the both possible products *VIa* and *VIb* was formed. The ^{1}H-NMR spectra distinguished the geometric relationship between both methoxy groups but not the configuration of the substituent at $C_{(3)}$. This fact agrees with the data published for analogous substituted tetrahydrofuran derivatives[8,12,13]. The stereochemical situation changes substantially by introduction of a substituent into the position 2. The reaction with a mixture of both stereoisomers of *II* afforded again only two compounds instead of the expected eight. Analysis of ^{1}H-NMR spectra and comparison with data for similar systems[14] unequivocally assigned structures *VIIa* and *VIIb* to these products.



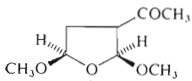
I, $R^1 = R^2 = H$
II, $R^1 = COOCH_3$, $R^2 = H$
III, $R^1 = H$, $R^2 = COOCH_3$



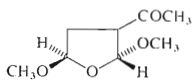
Ia, R = H
II, $R = CH_2OH$
V, $R = CH_2OCOC_6H_5$



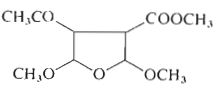
Ib



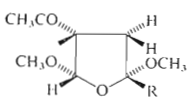
VIa



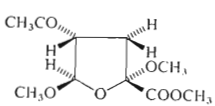
VIb



X



VIIa, $R = COOCH_3$
VIII, $R = CH_2OH$
IX, $R = CH_2OCOCH_3$



VIIb,

The acetyl group thus enters exclusively into the position 4 of the tetrahydrofuran system and *trans* relative to the ester function in the position 2. The structural assignment was made on the basis of the coupling constant J_{34} (less than 1·5 Hz for *cis*-arrangement of the protons and about 4 Hz for the *trans*-arrangement). In order to verify the value of the coupling constant J_{34} using a closely similar compound with known configuration, we performed the same reaction with the stereoisomerically pure acetal *IV*. The reaction indeed afforded the pure hydroxy ketone *VIII* which was accompanied only by its acetate *IX* whose structure was confirmed by acetylation of *VIII*. In both cases we found the corresponding value of the coupling constant J_{34}.

Photoaddition using 3-substituted acetals (reaction of *III*) proceeds more slowly and requires greater excess of acetaldehyde and longer irradiation. Also the yield is lower. Because of the complicated ^{1}H-NMR spectrum of the arising keto acetal *X* we were not able to follow the stereochemical outcome of this reaction. In conclusion, we can say that the photoaddition of acetaldehyde to unsaturated acetals of the 2,5-dialkoxy--2,5-dihydrofuran type represents a suitable synthetic method which, moreover, in the case of 2-substituted derivatives, proceeds selectively.

EXPERIMENTAL

N either melting nor boiling points are corrected. The IR spectra were measured on a Perkin–Elmer 325 spectrometer, mass spectra on a LKB 8500 instrument, ^{1}H-NMR spectra on a Varian XL-100 spectrometer (deuteriochloroform, δ-scale, tetramethylsilane as internal standard). The electrochemical oxidation was performed in an all-glass electrolyzer with concentric cylindrical electrodes made of platinum net; the mixture was stirred magnetically. Gas–liquid chromatography was carried out on a Chrom 31 instrument (Laboratorní přístroje, Prague; flame-ionization detector, carrier gas nitrogen, 240 × 0·6 cm column with 15% CWX-20M on Chromosorb W). The photochemical additions were performed in a glass reactor with a cooled mercury lamp placed in a quartz mantle; the reaction mixture was stirred by introduction of dry nitrogen.

3-Acetyl-2,5-dimethoxytetrahydrofuran (*VI*)

A mixture of the acetal *I* (65 g; 0·5 mol) and distilled acetaldehyde (700 ml) was irradiated at 10—14°C for 24 h. Acetaldehyde was evaporated and the residue fractionated, affording 75 g (86%) of *VI*, boiling at 110°C/2·4 kPa; purity higher than 97% (gas–liquid chromatography). IR spectrum, cm^{-1}: 982, 1035, 1108, 1376, 1452, 1730, 2835, 2932, 2955, 2997. Mass spectrum m/e, %: 43 (100%), 71 (60%), 114 (24%), 41 (24%), 69 (21%), 116 (17%), 58 (16%), 99 (10%), M—1 $^+$173 (2%). For $C_8H_{14}O_4$) 174·2) calculated: 55·18% C, 8·10%H, 24·14% OCH_3; found: 55·21% C, 8·44% H, 25·01%OCH_3, ^{1}H-NMR spectrum *VIa*: 2·21 (s, 3 H, CH_3CO), 2·04—2·40 (m, 2 H, H—4), 3·36 (s, 3 H, OCH_3), 3·43 (s, 3 H, OCH_3), 3·40 (m, 1 H, H—3), 5·10 (m, 2 H, H—2, H—5). *VIb*: 2·23 (s, 3 H, CH_3CO), 2·04—2·40 (m, 2 H, H—4), 3·31 (s, 3 H, OCH_3), 3·45 (s, 3 H, OCH_3), 3·40 (m, 1 H, H—3), 5·10 (m, 1 H, H—5), 5·32 (d, 1 H, H—2, J = 3·8 Hz).

Methyl 3-Acetyl-2,5-dimethoxytetrahydrofuran-2-carboxylate (*VII*)

Irradiation of *II* (94·1 g; 0·5 ml) in acetaldehyde (700 ml) for 40 h, followed by fractionation, afforded 35 g of the starting compound *II* and 65 g of *VII* (91%, based on the consumed *II*), b.p. 109—115°3/0·13 kPa. The products *VIIa* (*b.p.* 114—115°C/0·13 kPa) and *VIIb* (b.p. 114 to 115°C/0·13 kPa) were obtained by fractionation. For $C_{10}H_{16}O_6$ (232·2) calculated: 51·78% C, 6·95% H, 40·07% OCH_3; found: 52·07% C, 7·10% H, 38·99% OCH_3. ^{1}H-NMR spectrum: *VIIa*: 2·22 (s, 3 H, $COCH_3$), 3·20—3·60 (m, 2 H, H—3), 3·33 (s, 3 H, OCH_3), 3·52 (s, 3 H, OCH_3), 3·40 (m, 1 H, H—4), 3·80 (s, 3 H, $COOCH_3$), 5·29 (d, 1 H, H—5, J = 4 Hz). *VIIb*: 2·22 (s, 3 H, $COCH_3$), 3·20—3·60 (m, 2 H, H—3), 3·22 (s, 3 H, OCH_3), 3·44 (s, 3 H, OCH_3), 3·40 (m, 1 H, H—4), 3·80 (s, 3 H, $COOCH_3$), 5·45 (d, 1 H, H—3, J = 1·8 Hz).

4-Acetyl-2-hydroxymethyl-2,5-dimethoxytetrahydrofuran (*VIII*)
and 4-Acetyl-2-acetoxymethyl-2,5-dimethoxytetrahydrofuran (*IX*)

Irradiation of the alcohol *IV* (50 g; 0·378 mol) in acetaldehyde (700 ml) for 48 h, followed by fractionation afforded 45 g of *VIII*, b.p. 123°C/0·13 kPa, and 3 g of a fraction b.p. 132—137°C/0·13 kPa, containing 92% *VIII* and 8% *IX* (according to gas–liquid chromatography). Total yield 72% (8 g of *IV* recovered). Alcohol *VIII*. For $C_9H_{16}O_5$ (204·2) calculated: 52·93% C, 7·90% H, 30·39% OCH_3; found: 52·82% C, 7·91% H, 29·45% OCH_3. ^{1}H-NMR spectrum: 2·19 (s, 3 H, CH_3CO), 2·30 (m, 2 H, H—3), 3·31 (s, 3 H, OCH_3), 3·40 (m, 1 H, H—4), 3·46 (s, 3 H, OCH_3), 3·60 (bs, 2 H, CH_2), 5·19 (d, J = 3·8 Hz, 1 H, H—5), one exchangeable proton.

4-Acetyl-2-acetoxymethyl-2,5-dimethoxytetrahydrofuran (*IX*)

The alcohol *VIII* (10·2 g; 0·05 mol) in pyridine (100 ml) was mixed at 0°C with acetic anhydride (10·2 g; 0·1 mol) and set aside at room temperature for 24 h. The mixture was poured on ice and water (1 000 ml) and extracted with ether (3 × 200 ml). The combined ethereal extracts were thoroughly washed with 5% hydrochloric acid, then with saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, taken down and distilled, affording 9·3 g (75%) of *IX*, b.p. 135°C/0·13 kPa. For $C_{11}H_{18}O_6$ (246·26) calculated: 53·65% C, 7·37% H, 25·20% OCH_3; found: 53·87% C, 7·41% H, 24·23% OCH_3. ^{1}H-NMR spectrum: 2·10 (s, 3 H, CH_3COO), 2·24 (s, 3 H, CH_3CO), 2·30 (m, 2 H, H—3), 3·33 (s, 3 H, OCH_3), 3·43 (m, 1 H, H—4), 3·50 (s, 3 H, OCH_3), 4·00, 4·12, 4·24, 4·36 (AB-system, 2 H, CH_2). 5·19 (d, $J = 4$ Hz, 1 H, H—5).

Methyl 4-Acetyl-2,5-dimethoxytetrahydrofuran-3-carboxylate (*X*)

The acetal *III* (2 g; 0·01 mol) in acetaldehyde (70 ml) was irradiated for 36 h. Distillation afforded 1·3 g of *X*, b.p. 125°C/0·13 kPa (53%). For $C_{10}H_{16}O_6$ (232·2) calculated: 51·78% C, 6·95% H, 40·07% OCH_3; found: 52·03% C, 7·01% H, 41·01% OCH_3. ^{1}H-NMR spectrum: 2·28 (m, 3 H, CH_3CO), 3·48 (m, 8 H, 2 × OCH_3, H—3, H—4), 3·75 (m, 3 H, $COOCH_3$), 5·28 (m, 2 H, H—2, H—5).

Methyl 2,5-Dimethoxy-2,5-dihydrofuran-3-carboxylate (*III*)

A mixture of methyl 3-furoate (12·6 g; 0·1 mol), methanol (300 ml) and sulfuric acid (5 ml) was electrolyzed at —40°C till the total amount of electricity amounted to 4·5 F mol^{-1}. The mixture was neutralized with sodium methoxide, taken down *in vacuo* and shaken between ether (200 ml) and water (200 ml). The ethereal layer was dried over magnesium sulfate, taken down and the product distilled, affording 2·5 g (13%) of *III*, b.p. 109°C/44 kPa. For $C_8H_{12}O_5$ (188·1) calculated: 51·09% C, 6·38% H; found: 51·17% C, 6·52% H. ^{1}H-NMR spectrum: 3·45 (m, 6 H, 2 × OCH_3); 3·76 (s, 3 H, $COOCH_3$); 5·63 (d, $J = 2$ Hz, H—5 *trans*; 5·69 (s, H—5 *cis*) total 1 H; 5·94 (s, 1 H, H—4); 6·76 (bs, 1 H, H—2).

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