ELECTROCHEMICAL OXIDATION OF 2-FURYLACETIC ACID DERIVATIVES

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Received May 10th, 1979

Depending on reaction conditions, the electrochemical methoxylation of 2-furylacetonitrile (*I*) afforded either (2,5-dimethoxy-2,5-dihydro-2-furyl)acetonitrile (*V*) or (5-methoxy-2,5-dihydro-2-furfurylidene)acetonitrile (*VIII*). Analogous reaction of methyl 2-furylacetate (*II*) gave either methyl (2,5-dimethoxy-2,5-dihydro-2-furyl)acetate (*VI*) or methyl (5-methoxy-2,5-dihydro-2-furfurylidene)acetate (*IX*). The electrochemical ethoxylation of ethyl 2-furylacetate afforded — among other products — also γ-lactone of ethyl 3-hydroxy-2,4-hexadienedioate (*X*).

Experiments aiming at the preparation of prostadienoic acid derivatives have shown the possible use of 2-furylacetic acid derivatives[1] as starting compounds. The first step consists of the electrochemical oxidation of these derivatives in an alcoholic medium (Clauson–Kaas alkoxylation). The present work concerns alkoxylation of 2-furylacetonitrile (*I*), methyl 2-furylacetate (*II*) and ethyl 2-furylacetate (*III*). The electrochemical behaviour of 2-furylacetic acid (*IV*) derivatives has not been studied as yet[2].

Preparation of these compounds started from 2-furfuryl chloride[3] which was transformed by reaction with alkali metal cyanide in dimethylformamide[4] into the nitrile *I* in 78% yield without any perceptible rearrangement[5], the isomer purity of the product being 98% (gas–liquid chromatography). The acid *IV*, prepared in 78% yield by alkaline hydrolysis of the nitrile *I*, was transformed in practically quantitative yield into the esters *II* and *III* by treatment with diazomethane and diazoethane, respectively[6].

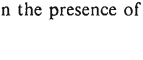
Already the electrochemical oxidation of the nitrile *I* and the methyl ester *II* under the common conditions of Clauson–Kaas reaction (methanol, NH_4Br, −30°C) has shown that this reaction affords various products according to the chosen conditions of electrolysis and work-up of the reaction mixture.

The "normal,, products *V* and *VI* were formed only when a neutral, or better alkaline, medium was maintained throughout the whole process. Otherwise, mixtures of both the possible products *V* and *VIII* (or *VI* and *IX*) were formed. The electrolysis of the ester *II* was to a certain extent accompanied by elimination of methanol

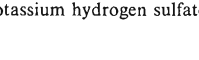
under formation of *IX*. In the case of the nitrile *I*, this elimination occurred only at higher temperatures during the work-up of the reaction mixture.

The conditions and results of the selected electrochemical oxidations are summarized in Table I. It is evident that the reaction can be conducted so that it gives the pure "normal" product *V* or *VI*, or the elimination product *VIII* or *IX*. In both cases the reaction afforded a mixture of both possible positional isomers which were isolated in the pure state.

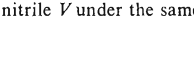
The dimethoxy derivatives *V* and *VI* differ in stability. Whereas the ester *VI* lost quantitatively methanol under formation of *IX* by heating to 100°C for 1 h *in vacuo* in the presence of trace of potassium hydrogen sulfate, the nitrile *V* under the same



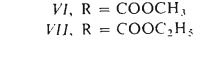
I, R = CN
II, R = $COOCH_3$
III, R = $COOC_2H_5$
IV, R = COOH



V, R = CN
VI, R = $COOCH_3$
VII, R = $COOC_2H_5$



VIII, R = CN
IX, R = $COOCH_3$



X

TABLE I

Electrochemical Methoxylation of 2-Furylacetonitrile (*I*) and Methyl 2-Furylacetate (*II*)

Starting compounds	Auxiliary electrolyte	Anode : : Cathode	*t*, °C *I*, A	Composition of the mixture	F, mol^{-1}	Yield, %
I	$NaClO_4$	C/Ni	—50°/1·5	*I* (56%), *V* (44%)	18	52
I	$NaClO_4$	Pt/Pt	—50°/1·5	*V* (98%)[a]	5	91
I	H_2SO_4	Pt/Pt	—50°/1·5	polymers	5	—
I	NH_4Br	Pt/Pt	0°/1·5	*V* (2%), *VIII* (98%)[b]	4·5	88
II	NH_4Br	Pt/Pt	—20°/1·0	*VI*, *IX etc.*	6	40
II	$NaClO_4$	Pt/Pt	—20°/1·0	*VI* and *IX* 3 : 1[c]	6	90
II	$NaClO_4$	Pt/Pt	—50°/1·5	*VI* (98%)[d]	4	65
II	$NaClO_4$	C/Ni	—30°/1·5	*VI*, *IX* 4 : 1	6	54

[a] Isomer ratio 2 : 1; [b] isomer ratio 3 : 2; [c] transformed to pure *IX*; [d] made alkaline with CH_3ONa at —40°C.

conditions did not change (according to gas–liquid chromatography) even after 6 h. The transformation of *V* to *VIII* took place in the presence of traces of bromine, which was either generated by oxidation of an auxiliar electrolyte ($2\,Br^- - 2\,e^- = Br_2$) or directly added into the methanolic solution of the compound *V*. The use of only trace amounts of bromine is essential because it reacts with the oxidation products under formation of complex mixtures. The electrochemical oxidation of ethyl 2-furylacetate (*III*) afforded a mixture of products in which we detected "normal" alkoxylation products *VII* as well as products of their reaction with bromine. Crystallisation afforded a product which was identified as *X* on the basis of spectral data and comparison with an authentic specimen[7,8].

EXPERIMENTAL

The melting and boiling points are uncorrected. Analytical samples were dried for 12 h at 70 Pa. ^{1}H-NMR spectra were measured on a Varian XL-100 instrument in $CDCl_3$ with tetramethylsilane as internal standard; chemical shifts are given in δ units. IR spectra were taken on a Perkin–Elmer 325 spectrophotometer in CCl_4 and CS_2. Gas–liquid chromatographic analyses were performed on a CHROM-31 (Laboratorní přístroje, Prague) chromatograph (flame ionisation detector, carrier gas nitrogen, 120 × 0·6 cm column filled with 10% butanediol succinate on Chromaton N-AW). Mass spectra were measured on an LKB 8500 spectrometer.

The electrochemical oxidations were carried out in an all-glass electrolyzer (200 ml) with an electromagnetic stirrer and exchangeable platinum (concentric cylinders of Pt-net), graphite (rod) or nickel (cylinders of Ni-sheet) electrodes. The area of the electrodes was about 40 cm^2; the electrolyzer was cooled with a dry ice–ethanol mixture, unless stated otherwise.

2-Furylacetonitrile[4] (*I*)

Furfuryl chloride[3] (14·1 g; 0·121 mol) was added dropwise to a stirred suspension of sodium cyanide (9·3 g; 0·19 mol) in dimethylformamide (50 ml) and the mixture was stirred at 100°C for 1 h. After cooling, the mixture was diluted with ether and water in order to dissolve the inorganic salts. The aqueous layer was extracted twice with ether, the combined extracts washed several times with saturated sodium chloride solution, dried over magnesium sulfate and taken down. Distillation of the residue afforded 9·1 g (78) of *I*, b.p. 75—78°C/2 kPa, which, according to gas–liquid chromatography, contained only 2% of 5-methyl-2-furonitrile.

2-Furylacetic Acid (*IV*)

A mixture of *I* (32 g; 0·3 mol) and 20% aqueous sodium hydroxide solution (200 ml) was made homogeneous by addition of ethanol. The solution was refluxed till the evolution of ammonia ceased (4 h), the ethanol evaporated *in vacuo* and the acid isolated by acidification of the residue with conc. hydrochloric acid. Crystallisation from hexane afforded 29·4 g (78%) of the acid *IV*, m.p. 57—59°C (reported[5] m.p. 67—68°C).

2,5-Dimethoxy-2,5-dihydro-2-furylacetonitrile (*V*)

A solution of *I* (5·35 g; 50 mmol) and $NaClO_4$ (2 g) in methanol (150 ml) was electrolysed at —50° (cooling bath) on Pt-electrodes at a constant current (1·5 A) until the total amount of electricity

5 F mol^{-1} was achieved (disappearance of the starting compound). Sodium hydrogen carbonate (0·5 g) and ether (150 + 150 ml) were added to the mixture. The aqueous layer was extracted with ether (2 . 50 ml), the combined ethereal extracts dried over magnesium sulfate, taken down and the residue distilled, affording 7·2 g (91%) of the product *V*, b.p. 125°C/1·5 kPa. For $C_8H_{11}NO_3$ (169·2) calculated: 56·79% C, 6·55% H, 18·28% N, 36·68% OCH_3; found: 56·49% C, 6·64% H, 18·16% N, 37·16% OCH_3. IR spectrum, cm^{-1}: 834, 867, 969, 1027, 1040, 1104, 1139, 1162, 1197, 1301, 1336, 1347, 1481, 1443, 1453, 1468, 1635, 2270, 2855, 2956, 3015. ^{1}H-NMR spectrum: 2·86 (s, 2 H, CH_2); 3·18 and 3·22 (s, 3 H, OCH_3 *cis* + *trans*); 3·48 and 3·53 (s, 3 H, OCH_3 *cis*, *trans*); 5·57 and 5·75 (s, 1 H, H—5 *cis*, *trans*) 6·00 (m, 1 H, H—4) 6·20 (m, 1 H, H—3). Mass spectrum (10 eV), *m/e*, (%): 138 (100); 129 (50); 109 (12·5); 112 (10); 139 (9), 178 (9).

cis and *trans*-5-Methoxy-2,5-dihydro-2-furfurylideneacetonitrile (*VIII*)

A) A solution of *I* (5·4 g; 50·5 mmol) and ammonium bromide (2 g) in methanol (130 ml) was electrolysed at 5—7°C (bath) on Pt-electrodes at a constant current (1·5 A; total amount of electricity 4·5 F mol^{-1}). According to gas–liquid chromatography, the reaction mixture contained less than 1% of *I*. After evaporation of methanol, the residue was shaken with ether, the extract dried over magnesium sulfate and taken down. Distillation of the residue (column) afforded a mixture of the isomers *VIII* (6·1 g), b.p. 105—115°C/0·2 kPa. The isomer *VIIIa* (shorter g.l.c. retention time), m.p. 35—37°C, was isolated in 98% purity by crystallisation of the lower-boiling distillation fractions. The isomer *VIIIb* (longer g.l.c. retention time), m.p. 47—50°C, crystallised from the crude electrolysis product on standing. For $C_7H_7NO_2$ (137·1) calculated: 61·31% C, 5·15% H, 10·22% N, 22·62% OCH_2; found: 61·59% C, 5·29% H, 9·99% N, 21·90% OCH_3. IR spectrum (mixture of isomers), cm^{-1}: 917, 934, 952, 986, 1023, 1092, 1125, 1168, 1205, 1335, 1380, 1593, 1657, 2225, 2845, 2895, 2940, 2970, 3010, 3090. ^{1}H-NMR spectrum: *VIIIa* 3·44 (s, 3 H, OCH_3); 4·70 (s, 1 H, $=C<^{CN}_{H}$); 6·05 (s, 1 H, H—5); 6·50 (d, J = 7 Hz, 1 H, H—4); 6·75 (*d*, J = 7 Hz, 1 H, H—3). *VIIIb* 3·56 (s, 3 H, OCH_3); 4·48 (s, 1 H, CH—CN); 6·12 (s, 1 H, H—5), 6·38; 6·44; 6·49; 6·54 (AB syst., 2 H, H—3, H—4). Mass spectrum, *m/e* (%): 106 (100); 137 (40); 122 (30); 51 (30); 79 (26); 52 (20); 38 (18); 66 (16); 50 (16).

B) Compound *V* (1 g; 6 mmol) was dissolved in a solution of bromine (0·1 ml) in methanol (100 ml) and kept at 20°C for 1 h. Methanol was evaporated *in vacuo*, the residue taken between water and ether (50 + 50 ml), the ethereal layer washed with a saturated sodium hydrogen carbonate solution, dried over magnesium sulfate and taken down. Distillation afforded 0·43 g of a mixture of both isomers (6 : 4) of *VIII*.

Methyl 2,5-Dimethoxy-2,5-dihydro-2-furylacetate (*VI*)

A solution of *II* (14·1 g; 0·1 mol) and $NaClO_4$ (4 g) in methanol (100 ml) was electrolysed at —45° (bath) on Pt-electrodes at a constant current of 3 A (total amount of electricity 4 F mol^{-1}). The mixture was made alkaline (pH 8) by addition of sodium methoxide in methanol at —40°C, methanol was evaporated *in vacuo* and the residue partitioned between ether and a 2% solution of sodium hydrogen carbonate. The ethereal layer was dried over magnesium sulfate, taken down and the residue distilled, affording 8·4 g of *VI*, b.p. 117—119°C/1 kPa. (Yield 65%; 5 g of *II* were recovered.) For $C_9H_{14}O_5$ (202·2) calculated: 53·46% C, 6·98% H; found: 52·85% C, 6·96% H. IR spectrum, cm^{-1}: 628, 832, 982, 1025, 1045, 1100, 1120, 1168, 1194, 1267, 1330, 1342, 1373, 1439, 1467, 1633, 1746, 2845, 2915, 2945, 2960, 3005. ^{1}H-NMR spectrum: 2·85 (m, 2 H, CH_2); 3·15 and 3·22 (s, OCH_3 *cis* and *trans*); 3·45 and 3·53 (s, 3 H, OCH_3 *cis* and *trans*); 3·69

(s, 3 H, $COOCH_3$); 5·49 and 5·75 (s, 1 H, H—5 *cis* and *trans*); 6·15 (m, 2 H, H—3, H—4). Mass spectrum, *m/e* (%): 111 (100); 171 (69); 129 (58); 101 (46); 139 (40); 59 (38); 170 (29); 41 (21); 39 (19); 55 (18); 53 (17); 81 (15); 83 (15); 155 (11).

Methyl 5-Methoxy-2,5-dihydrofurfurylideneacetate (*IX*)

A solution of *II* (2·8 g; 19·8 mmol) and $NaClO_4$ (4 g) in methanol (100 ml) was electrolysed at —20°C (bath) on Pt-electrodes at a constant current of 1·5 A (total amount of electricity 6 F mol^{-1}). The solvent was evaporated *in vacuo*, the residue taken between ether (100 ml) and saturated sodium hydrogen carbonate solution (100 ml), the aqueous layer extracted with ether (2 × 50 ml), the combined ethereal extracts dried over magnesium sulfate and taken down. The residue (3·2—3·9 g), containing *VI* and *IX* (3 : 1) was heated with a small crystal of $KHSO_4$ to 100°C at 1—2 kPa for 30 min and then distilled, affording 2·8 g (83%) of *IX*, b.p. 78—82°C/ /0·1 kPa; purity 98% (g.l.c.). The product solidified on standing; m.p. 32—35°C. For $C_8H_{10}O_4$ (170·2) calculated: 56·47% C, 5·92% H; found: 57·02% C, 6·08% H. IR spectrum, cm^{-1}: 812, 827, 892, 953, 983, 1003, 1038, 1076, 1105, 1134, 1296, 1368, 1380, 1436, 1583, 1648, 1705, 2845, 2900, 2960, 3020. ^{1}H-NMR spectrum: 3·49 (s, 3 H, OCH_3); 3·74 (s, 3 H, $COOCH_3$); 5·40 (s, 1 H, =CH—); 6·03 (s, 1 H, H—5); 6·49 (bd, J = 6 Hz, 1 H, H—4); 7·50 (d, J = 6 Hz, 1 H, H-3). Mass spectrum, *m/e* (%): 111 (100); 140 (37); 40 (30); 69 (28); 170 (26); 59 (26); 52 (24); 51 (22); 42 (22); 124 (21); 55 (20); 53 (18); 156 (13); 83 (13); 79 (13); 43 (13).

Ethyl 3-Hydroxy-2,4-hexadienedioate γ-Lactone (*X*)

A solution of *III* (2 g; 12·9 mmol) and ammonium bromide (4 g) in ethanol (100 ml) was electrolysed at —20°C (bath) (Pt-electrodes, constant current 1·5 A, total amount of electricity 5 F . . mol^{-1}). After evaporation of the solvent, the residue was extracted with ether, the ethereal layer washed with sodium hydrogen carbonate solution, dried over magnesium sulfate and taken down, leaving 2·4 g (18%) of product from which 0·4 g of *X* crystallised; m.p. 75—77°C. For $C_8H_8O_4$ (168·2) calculated: 57·15% C, 4·79% H; found: 56·97% C, 4·83% H. IR spectrum, cm^{-1}: 830, 867, 884, 1040, 1063, 1093, 1112, 1152, 1263, 1300, 1360, 1380, 1396, 1565, 1660, 1722, 1805, 1824, 3000. ^{1}H-NMR spectrum: 1·33 (t, 3 H, CH_3—CH_2—O); 4·18 (q, 2 H, CH_3CH_2O); 5·94 (d, J = 2 Hz, 1 H, =CH—); 6·47 (dd, J = 2 Hz, 1 H, H—3); 8·37 (d, J = = 6 Hz, 1 H, H—2).

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Translated by M. Tichý.