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HYDROGENATION OF 4-(2-FURYL)-2-OXOBUTENOIC ACID SODIUM SALT ON RANEY NICKEL

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The hydrogenation of 4-(2-furyl)-2-oxobutenoic acid sodium salt on a nickel catalyst has been studied. Using Raney nickel catalyst, the corresponding salts of 4-(2-furyl)-2-oxobutanoic acid, 4-(2-furyl)-2-hydroxybutanoic acid, and aliphatic hydrogenolysis products of the initial compound were obtained. The sodium salt of 2-hydroxy-4-(2-tetrahydrofuryl) butanoic acid and the condensation product 4-(2-furylethyl)-3-(2-furylmethyl)-2-oxo-3,4-didehydroglutaric acid were detected in the hydrogenolysate. A method has been developed for obtaining the sodium salts of 4-(2-furyl)-2-oxobutanoic and 4-(2-furyl)-2-hydroxybutanoic acids.

The hydrogenation of 2-oxo-4-phenylbutenoic acid sodium salt and its esters on Raney nickel and on palladium black has been studied [2, 3] in order to obtain 4-substituted 2-oxo-butanoic acids and their esters, which are valuable intermediates in the synthesis of antihypertensive and analgesic preparations [1]. The corresponding salt of 2-hydroxy-4-phenylbutanoic acid was formed selectively on hydrogenating the sodium salt of 2-oxo-4-phenylbutenoic acid on nickel catalysts [3]. The use of palladium catalysts (Pd or 10% Pd/C) enabled the process to be directed towards the preparation of the corresponding derivatives of 2-oxo-4-phenylbutanoic acid, the selectivity of formation of which on hydrogenating the sodium salt was significantly greater than on hydrogenating esters of 2-oxo-4-phenylbutenoic acid.

It was shown by us that on reducing the sodium salt of 4-(2-furyl)-2-oxobutenoic acid with sodium borohydride, the sodium salt of 4-(2-furyl)-2-hydroxybutenoic acid was formed, isomerization of which to the corresponding keto compound was unsuccessful [4]. Resinification occurred under the isomerization conditions. The properties and preparation of 4-(2-furyl)-2-oxobutanoic acid and its derivatives have not been described in the literature.

When hydrogenating the sodium salt of 4-(2-furyl)-2-oxobutenoic acid on palladium black in the presence of a hydrogen donor (cyclohexene, ammonium formate) under conditions comparable with the hydrogenation of the corresponding benzene derivative (up to 80°C), hydrogenolysis of the furan ring was observed and a mixture of unidentified aliphatic products was formed [5].

The sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid was isolated from the reaction products on hydrogenating the sodium salt of 4-(2-furyl)-2-oxobutenoic acid on Raney nickel with molecular hydrogen at 50°C and an initial concentration of starting material of 0.07 M [5]. Hydrogenolysis of the furan ring was also observed in this case.

Results are given in the present report of the hydrogenation of the sodium salt of 4-(2-furyl)-2-oxobutenoic acid on Raney nickel at 20-95°C and initial concentration of starting material 0.17-0.24 M. The ratio of the mass of starting material and catalyst was 1:0.55-0.86 (Table 1). The sodium salts of 4-(2-furyl)-2-oxo-butanoic, 4-(2-furyl)-2-hydroxybutanoic, and 2-hydroxy-4-(2-tetrahydrofuryl)butanoic acids were identified in the reaction products. Analysis by HPLC indicated that at incomplete conversion of the starting material an intermediate substance was formed which was probably the sodium salt of 4-(2-furyl)-2-hydroxybutenoic acid, the amount of which was lower with increased reaction time and temperature. The best yields (50-66%) of the sodium salt of 4-(2-furyl)-2-oxobutanoic were obtained at a reaction time providing a high conversion (94-99%) of raw material. The yield of oxo compound was sharply reduced when the starting material was absent from the reaction mixture. It may be suggested that hydrogenation of the initial molecule to the sodium salt of 4-(2-furyl)-2-oxobutanoic

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TABLE 1. Hydrogenation of the Sodium Salt of 4-(2-Furyl)-2-oxobutenoic Acid on Raney Nickel Catalyst*

Initial concentration of starting material, M	Reaction temperature, °C	Reaction time, h	Yield, %		Unreacted starting material
			4-(2-furyl)-2-oxobutanoic acid sodium salt	4-(2-furyl)-2-hydroxybutanoic acid sodium sallt	
0,24	20	1,0	35,7	4,4	29,0
		2,5	58,2	14,8	2,6
		3,0	47,2	36,1	—
		3,66	10,6	58,2	—
		4,5	—	74,2	—
		5,0	—	76,2	—
0,17	60	0,5	27,1	4,1	23,0
		1,17	52,2	7,4	21,0
		1,83	66,0	16,8	1,3
		2,33	34,3	54,7	—
		3,0	6,9	82,3	—
		4,0	—	87,9	—
		5,0	—	88,4	—
		6,0	—	89,0	—
0,24†	90...95	3,0	24,4	52,3	—
		5,0	—	68,8	—

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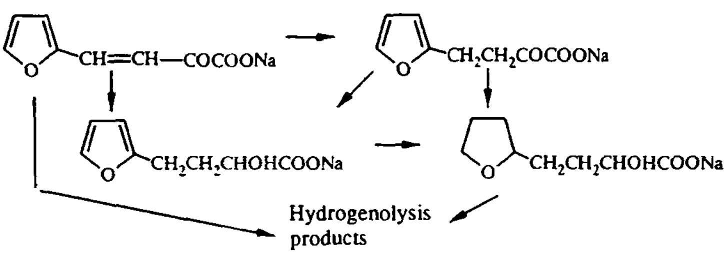
*Solvent ethanol–water, 1:1.7, starting material:catalyst, 1:0.86.
†Starting material:catalyst, 1:0.55.

acid and then to the corresponding hydroxy compound occurs at the same active center on the catalyst. When unreacted raw material was absent from the hydrogenation mixture, the yield of the sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid was sharply increased, reaching 89% at 60°C.

The hydrogenation of 4-(2-furyl)-2-oxobutenoic acid sodium salt on Raney nickel catalyst may therefore be used to obtain 4-(2-furyl)-2-oxobutanoic acid sodium salt at a reaction time (2 h, 60°C) providing incomplete conversion of the starting material (the reaction mixture was yellow). The same reaction may also be used to obtain 4-(2-furyl)-2-hydroxybutanoic acid sodium salt at a reaction time (5-6 h, 60°C) providing complete conversion of 4-(2-furyl)-2-oxobutenoic acid sodium salt to the corresponding hydroxy compound (under these conditions the reaction mixture was colorless). The sodium salt of 4-(2-furyl)-2-oxobutanoic acid was isolated from the reaction mixture using its lower solubility in ethyl alcohol compared with the sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid. The conversions are represented in the following scheme:



Similarly to the hydrogenation of the sodium salt of 2-oxo-4-phenylbutenoic acid in [3], the shape of the kinetic curves for product accumulation indicates a parallel–sequential reaction mechanism (Fig. 1). At small reaction times and little conversion of starting material, the sodium salt of 4-(2-furyl)-2-oxobutanoic acid is formed as well as the corresponding hydroxy acid derivative, which indicates the parallel reaction course. With increasing reaction time, the yield of keto derivative falls and the yield of hydroxy acid derivative increases (sequential reaction course). At complete conversion of the starting material the corresponding tetrahydrofuran derivative is detected in the reaction mixture. This is probably formed by sequential conversions of the keto and hydroxy acids.

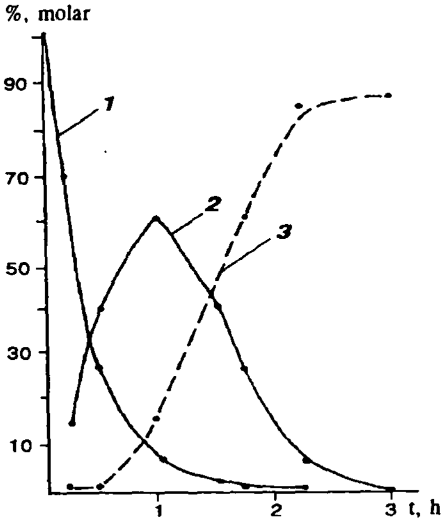


Fig. 1

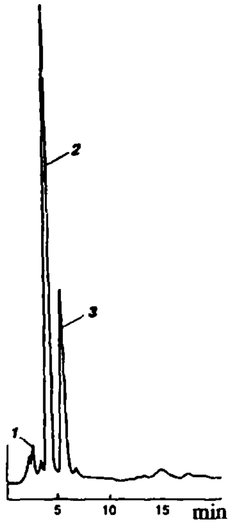


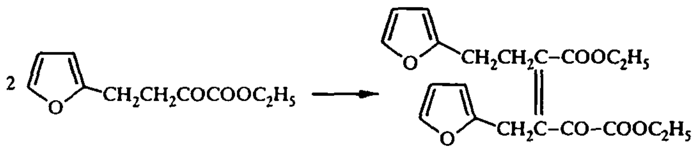
Fig. 2

Fig. 1. Dependence on reaction time of the conversion of starting material and accumulation of products (75-85°C; starting material:catalyst 1:0.86, initial concentration of raw material 0.19 M): 1) unreacted starting material; 2) sodium salt of 4-(2-furyl)-2-oxobutanoic acid; 3) sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid.

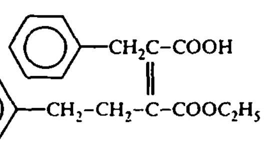
Fig. 2. Chromatogram of the hydrogenation products of the sodium salt of 4-(2-furyl)-2-oxobutenoic acid: 1) sodium salt of 4-(2-furyl)-2-oxobutenoic acid; 2) sodium salt of 4-(2-furyl)-2-oxobutanoic acid; 3) sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid.

The hydrogenolysis products are also seemingly formed by a parallel–sequential scheme.

On comparing the results of hydrogenating derivatives of the furan and benzene series it may be concluded that the sodium salt of 4-(2-furyl)-2-oxobutanoic acid possesses a lower reactivity on hydrogenation to the corresponding hydroxy compound than the sodium salt of 2-oxo-4-phenylbutanoic acid. Under hydrogenation conditions, the furan compound probably forms a complex with the nickel, and the carbonyl group of the keto acid participates in complex formation, thus stabilizing this compound. When hydrogenating furan compounds, side processes of furan hydrogenolysis and condensation reactions play a greater role. A condensation product, the ethyl ester (after esterification) of 4-(2-furylethyl)-3-(2-furylmethyl)-2-oxo-3,4-didehydroglutaric acid, was detected in the hydrogenated mixture.



On hydrogenating and esterifying the corresponding benzene analog, an oxidative decarboxylation product was formed, viz. monoethyl 2-benzyl-3-(β-phenylethyl)maleate.



Such differences in structure of the condensation products of the corresponding furan and benzene compounds indicate the high stability of the furan derivative, possibly due to complex formation with nickel with carbonyl group participation.

EXPERIMENTAL

The PMR spectra were taken on a WH 90 DS (Bruker) instrument in D_2O solution with DSS as internal standard. Mass spectra were taken on a Kratos MS 25 chromato-mass spectrometer with an ionizing voltage of 70 eV.

The sodium salt of 4-(2-furyl)-2-oxobutenoic acid was obtained by the reaction of ethyl pyruvate and furfural in alkaline medium [5]. Product purity was 98%.

The starting material and reaction products, viz. the sodium salts of 4-(2-furyl)-2-oxobutanoic and 4-(2-furyl)-2-hydroxybutanoic acids, were investigated by HPLC on a Dupont 850 chromatograph, detector was a UV spectrometer, column 4.6 × 250 mm packed with Zorbax Pro-10 C8 sorbent. The eluent was 20% acetonitrile and 80% 0.1 M phosphate buffer pH 2.5, λ 220 nm.

Purification of the sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid for analytical purposes was carried out with a Buchi preparative chromatograph, column 26 × 470 mm packed with Silasorb C_{18} sorbent. Eluent was 30% acetonitrile and 70% 0.1 M ammonium acetate.

Sodium Salt of 4-(2-Furyl)-2-oxobutanoic Acid. 4-(2-Furyl)-2-oxobutenoic acid sodium salt (0.7 g, 3.72 mmole), moist Raney nickel catalyst (0.6 g) (the freshly prepared catalyst was stored under water), ethanol (8 ml), and water (14 ml) were placed in a two-necked flask fitted with a magnetic stirrer, a reflux condenser, and a tube for introducing hydrogen. Hydrogenation with molecular hydrogen was carried out for 1 h 50 min at 60°C (the color of the reaction mixture changed from intense to pale yellow). At the end of the reaction the catalyst was filtered off, washed with water (3 × 20 ml), and the solution evaporated. A substance (0.65 g) was obtained which contained the sodium salt of 4-(2-furyl)-2-oxobutanoic acid (0.47 g, 66% yield), 4-(2-furyl)-2-hydroxybutanoic acid sodium salt (0.12 g, 16.8% yield), and starting material (0.01 g). A chromatogram of the hydrogenation products by HPLC is shown in Fig. 2. The sodium salt of 4-(2-furyl)-2-oxobutanoic acid was recrystallized from ethanol. A substance (0.39 g) was obtained with a content of the main product of 97.2%. The yield was 54.5% calculated on starting material. PMR spectrum (D_2O): 7.42 (1H, α-Fu); 6.13 and 6.38 (2H, β-Fu); 2.87-3.18 ppm (4H, CH_2-CH_2).

Sodium Salt of 4-(2-Furyl)-2-hydroxybutanoic Acid. The sodium salt of 4-(2-furyl)-2-oxobutenoic acid (0.7 g, 3.72 mmole) was dissolved in a mixture of ethanol (8 ml) and water (14 ml). Moist Raney nickel catalyst (0.6 g) was added and the mixture hydrogenated for 5 h under the conditions described above until disappearance of the color. The catalyst was filtered off, washed with water (3 × 20 ml), and the solution evaporated. A substance (0.65 g) was obtained which contained the sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid (0.63 g, 88.5% yield). For analytical purposes the product was purified on the preparative chromatograph. PMR spectrum (D_2O): 7.44 (1H, α-Fu); 6.19 and 6.42 (2H, β-Fu); 4.10 ppm (1H, CHOH).

Other Products from the Hydrogenation of 4-(2-Furyl)-2-oxobutenoic Acid. The sodium salt of 4-(2-furyl)-2-oxobutenoic acid (1.0 g, 5.32 mmole) was dissolved in a mixture of ethanol (8 ml) and water (14 ml), moist Raney nickel catalyst (0.9 g) was added, and the mixture was hydrogenated for 5 h as described above. At the end of the reaction the catalyst was filtered off and washed with water (3 × 30 ml). The filtrate was evaporated and the dry residue dissolved in a 1:1 mixture of ethanol and ether. The main bulk of the sodium salt of 4-(2-furyl)-2-hydroxybutanoic acid is dissolved by this and the insoluble portion was filtered off. The bright solid was air-dried. The substance obtained (0.0885 g) was dissolved in 2.3 ml DMF. Ethyl iodide (0.1 ml) was added and the mixture stirred at room temperature in the dark for 24 h. At the end of the reaction the solution was evaporated. The residue was dissolved in water and extracted with a 1:1 mixture of hexane and ethyl acetate. The solution obtained was dried over anhydrous Na_2SO_4, evaporated, and a dark oil (0.0744 g) obtained. It was determined by chromato-mass spectrometry that the oil contained ethyl 4-(2-furylethyl)-3-(2-furylmethyl)-2-oxo-3,4-didehydroglutarate, mass spectrum, m/z (%): 374 (20) M^+; 301 (18) $[M-COOC_2H_5]^+$; 227 (38); 199 (38); 173 (100); 151 (16); 131 (16); 107 (20); 94 (80); 81 (50); 65 (19); 29 (49); ethyl 2-hydroxy-4-(2-tetrahydrofuryl)-butanoate, mass spectrum, m/z (%): 184 (0.5) $[M-H_2O]^+$; 129 (20) $[M-COOC_2H_5]^+$; 71 (100) $[M-CH_2CH_2-CHOH-COOC_2H_5]^+$; 84 (10); 55 (12); 43 (28); ethyl 4-(2-furyl)-2-hydroxybutanoate, mass spectrum, m/z (%): 198 (27) M^+; 125 (10); 104 (55); 95 (28) $[M-CHOH-COOC_2H_5]^+$; 81 (100) $[M-CH_2CHOH-COOC_2H_5]^+$; 76 (74); 68 (22); 53 (28); 29 (12).

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