SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF O-AROYLPYRUVOYL- AND O-AROYLACETYLOXIMES OF ALDEHYDES OF THE FURAN SERIES

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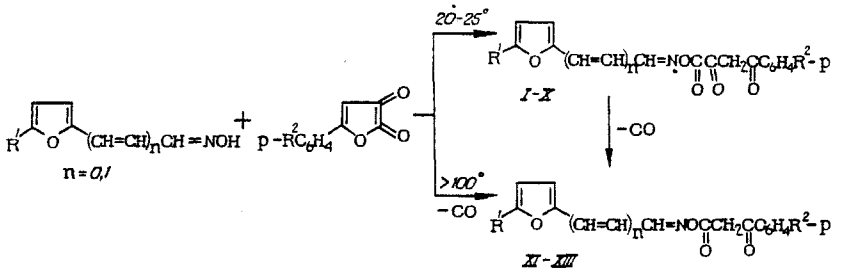
Derivatives of 5-nitrofuran are widely used in medical practice as antimicrobial agents [6]. In this respect oximes of 5-nitrofurfurals are promising [4]. In connection with the fact that the radicals of aroylpyruvic and aroylacetic acids are split off in the organism with formation of natural products and thus, obviously, contribute to the participation of the pharmacological groups connected with them in metabolic conversions, it was of interest to synthesize O-aroylpyruvoyl- and O-aroylacetyloximes of aldehydes of the furan series and to study their antimicrobial activities.

On reaction of 5-nitrofurfural oxime, 3-(2-furyl)propenal oxime, and 3-(5-nitrofuryl)-propenal oxime with 5-aryl-2,3-dihydrofuran-2,3-diones in water-free dioxane at room temperature, the coresponding O-aroylpyruvoyl derivatives I-X were obtained.



It seems that the formation of oximes I-X proceeds by a scheme that is similar to that of the formation of esters of aroylpyruvic acids from alcohols and 5-aryl-2,3-dihydrofuran-2,3-diones [1, 3]. The oxime hydroxyl, as do other BH nucleophilic groups, attacks the carbon atom of the lactone carbonyl of 5-aryl-2,3-dihydrofuran-2,3-diones with subsequent opening of the furan ring, which leads to final products I-X. When the reaction is carried out at 100-110°C for 50-60 min the products are O-aroylacetyloximes of 5-nitrofurfural and 3-furylpropenal XI-XIII. The formation of products of aroylacetylation in the reaction of weak BH nucleophiles with 5-aryl-2,3-dihydrofuran-2,3-diones was also observed earlier [2]. It is caused by hydrolysis of the latter at temperatures above 80°C, which proceeds with generation of unstable aroylketenes. Addition of the BH nucleophile to the carbonyl group of the cumulated system of the aroylketene leads to formation of products of aroylacetylation. However, in the case of oximes of aldehydes of the furan series, as was shown above, there proceeds, at a much higher rate in comparison with the decarbonylation reaction of the 5-aryl-2,3-dihydrofuran-2,3-diones, a ring-opening reaction of the latter with formation of compounds I-X. Therefore, the only cause of the formation of aroylacetyl derivatives XI-XIII is the decarbonylation of compounds I-X under the reaction conditions. Indeed, it was found that compounds I-X at a temperature of 100-110°C undergo thermolysis and give compounds XI-XIII in high yields. The thermal instability of compounds I-X is unexpected because other derivatives of aroylpyruvic acids are subject to decarbonylation only above 180-200°C [7] and is obviously connected with a decrease in strength of the single O–C(=O) bond owing to transfer of the electron-accepting influence of the nitrofuran ring through the C=N bond.

Oximes I-X, just as the majority of compounds containing an aroylpyruvoyl moiety, are completely enolized in solution. Judging by PMR spectral data, oximes that contain an aroylacetyl fragment are enolized for 15-20%.

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TABLE 1. O-Aroylpyruvoyl- and O-Aroylacetyloximes of Furfurals and 3-(2'-Furyl)propenals

Compound	R¹	R²	n	mp, °C	Yield %	Empirical formula	IR-spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm	Antimicrobial activity	
									E. coli	St. aureus
I	H	H	1	118—9	85	$C_{17}H_{13}NO_5$	1735 3115	6,28 (1H, s, CH), 6,45 (1H, s, CH), 6,65 (1H, s, CH), 6,85 (1H, s, CH), 6,95—8,35 (8H, m, CH arom), 11,05 (1H, s, OH)	500	250
II	NO_2	H	1	130—1	88	$C_{17}H_{12}N_2C_7$	1748 3140	6,86 (1H, s., CH), 6,93 (1H, s, CH), 7,00 (1H, s, CH), 7,06 (1H, s, CH), 7,33—8,10 (7H, m, CH arom.), 11,60 (1H, s, OH)	62,5	3,9
III	NO_2	Me	1	127—8	80	$C_{18}H_{14}N_2O_7$	1730 3150	2,33 (3H, s, CH_3), 6,80—7,06 (4H, q, 4CH), 7,1—8,06 (6H, CH, CH arom.), 11,46 (1H, s, OH)	62,5	3,9
IV	NO_2	Me	0	124—5	83	$C_{16}H_{12}N_2O_7$	1748 3120— 3140	2,78 (3H, s, CH_3), 6,85 (1H, s, CH), 7,05—8,13 (7H, m., CH arom.+aliph.), 12,53 (1H, s, OH)		
V	H	Me	1	116—7	78	$C_{18}H_{10}NO_5$	1738 3140	2,35 (3H, s, CH_3), 6,30—6,65 (3H, t, 3CH), 6,84 (1H, s, CH), 7,05—8,10 (7H, m, CH arom.), 11,30 (1H, s, OH)	1000	500
VI	H	Et	1	114—5	93	$C_{19}H_{17}NO_6$	1745 3125	1,30 (3H, t, OCH_2CH_3), 4,06 (2H, q, OCH_2CH_3), 6,33—8,16 (11H, m, CH), 11,0 (1H, s, OH)	1000	250
VII	NO_2	Et	1	128—9	94	$C_{19}H_{16}N_2O_8$	1740 3140	1,30 (3H, t, OCH_2CH_3), 4,06 (2H, q, OCH_2CH_3), 6,66—8,06 (10H, m, CH), 11,53 (1H, s, OH)	62,5	1,9
VIII	NO_2	Et	0	129—30	91	$C_{17}H_{14}N_2O_8$	1750 3140	1,30 (3H, t, OCH_2CH_3), 4,06 (2H, q, OCH_2CH_3), 6,73—8,16 (8H, m, CH), 12,06 (1H, s, OH)	62,5	3,9
IX	NO_2	Cl	1	150—1	89	$C_{17}H_{12}CN_2O_7$	1744 3150	6,73 (1H, s, CH), 6,83 (1H, s, CH), 6,93 (1H, s, CH), 7,06—8,06 (6H, m, CH arom.), 11,40 (1H, broad signal, OH)	62,5	3,9
X	H	Cl	1	127—8	94	$C_{17}H_{12}CNO_5$	1740 3130	6,65 (1H, s, CH), 6,75 (1H, s, CH), 6,84 (1H, s, CH), 6,93 (1H, s, CH), 7,10—8,15 (7H, m, CH arom.), 11,15 (1H, s, OH)	1000	1000
XI	NO_2	Cl	0	165—6	71*	$C_{14}H_9CN_2O_5$	1665 1741 3140	3,46 (2H, s, CH_2), 6,83 (1H, s, CH), 6,93 (1H, s, CH), 7,23—8,03 (6H, m, CH arom.), 13,66 (1H, s, OH)	inact.	1000
XII	NO_2	H	1	155—6	70*	$C_{16}H_{12}N_2O_6$	1660 1740 3150	3,44 (2H, s, CH_2), 6,68—8,00 (12H, m, CH), 13,15 (1H, s, OH)	500	1,9
XIII	NO_2	H	0	160—2	69*	$C_{14}H_{10}N_2O_5$	1663 1740 3145	3,45 (2H, s, CH_2), 6,77 (1H, s, CH), 6,80 (1H, s, CH), 6,88—8,15 (7H, m, CH arom.), 12,55 (1H, s, OH)	62,5	3,9

*Method A.

EXPERIMENTAL (CHEMICAL)

IR spectra were taken in paraffin oil on a UR-20 spectrometer (GDR). PMR spectra were recorded on a PC-60 spectrometer (60 MHz) using HMDS as internal standard. Characteristics of the prepared compounds are listed in Table 1. Found and calculated values of elemental analyses were in agreement.

Oximes of O-aroylpyruvoylfurfurals and 3-(2-furyl)-propenals (I-X). To a solution of 0.01 mole of 5-aryl-2,3-dihydrofuran-2,3-dione in 15-20 ml of water-free dioxane is added 0.01 mole of the appropriate oxime. The mixture is stirred at room temperature for 30-60 min, the precipitate is filtered off, and washed with a small amount of ether.

Oximes of O-Aroylacetylfurfurals and 3-(2-Furyl)propenals (XI-XIII). Method A. To a solution of 0.01 mole of 5-aryl-2,3-dihydrofuran-2,3-dione in 15-20 ml of water-free toluene is added 0.01 mole of the appropriate oxime and the mixture is refluxed for 50-60 min. The precipitate formed on cooling the solution is filtered off and crystallized from toluene.

Method B. A mixture of 0.01 mole of compound II of IX and 10 ml of dioxane or toluene is refluxed for 40-60 min. The solvent is evaporated and the residue is crystallized from toluene.

EXPERIMENTAL (BIOLOGICAL)

The acute toxicity was determined in white mice on intraperitoneal administration according to the method of G. N. Pershin [5].

The antimicrobial activity of the compounds was studied by the method of twofold serial dilutions in beef-extract bouillon with respect to Escherichia coli and Staphylococcus aureus. As active dose we took the lowest concentration (MIC) of the compound that inhibited the growth of the bacteria. Depending on the solubility, the weighed portion of the compound was dissolved in ethanol (95%) or dimethyl sulfoxide, which did not show a suppressive effect on the growth of the microorganisms.

Investigations of the antimicrobial activity showed that the greatest activity is found in compounds with a nitro group at the furan ring. Their MIC (mg/ml) is 62.5 for E. coli and 1.9-3.9 for S. aureus. Compounds without a nitro group possess weak activity. The number of methylene and carbonyl groups and also variation of the substituent at the aryl ring has practically no influence on the activity. Thus, introduction of an aroylpyruvoyl and aroylacetyl fragment in the oxime molecules practically does not change the activity against S. aureus and leads to a sharp fall in the activity against E. coli [4].

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