Furan derivatives. LXXXII. Effect of alkyl and aryl on physical and biological properties of alkyl 2-(5-nitrofuryl) and aryl 2-(5-nitrofuryl) ketones

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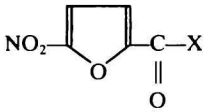
Synthesis of alkyl 2-(5-nitrofuryl) ketones (alkyl = methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl) and aryl 2-(5-nitrofuryl) ketones (aryl = phenyl, 2-thienyl, 5-nitro-2-pyrrolyl) by nitration of the corresponding alkyl and aryl 2-furyl ketones with acetyl nitrate is described. The wavenumber values of stretching vibration of the carbonyl group of alkyl 2-(5-nitrofuryl) ketones correlated with the Taft's constants σ^*. The synthesized compounds were tested for antibacterial and antifungal activities.

В работе описывается синтез 2-(5-нитрофурил)-алкилкетонов, где алкильными группами являются метил-, этил-, *н*-пропил-, изопропил-, *н*-бутил-, изобутил-, *трет*-бутил-, а также 2-(5-нитрофурил)-арилкетонов, где арильными группами являются фенил-, 2-тиенил-, 5-нитро-2-пиролил-, при помощи нитрования соответствующих алкил- и арил-2-фурилкетонов ацетилнитратом. Значения частот поглощения валентных колебаний карбонильной группы 2-(5-нитрофурил)-алкилкетонов находятся в корреляции с константами Тафта, σ^*. Были исследованы антибактериальные и антифунгальные активности синтезированных соединений.

Alkyl and aryl 2-furyl ketones are fairly well known in the literature [1—6]. In this work, methyl, ethyl, and *n*-propyl 2-furyl ketones were prepared by acylation of furan with the corresponding acyl anhydrides under the catalytic action of phosphoric acid [1]. Isopropyl, *n*-butyl, isobutyl, *tert*-butyl, and 4-nitrophenyl 2-furyl ketones were prepared by acylation of furan with the corresponding acyl chlorides [2]. Aryl 2-furyl ketones were synthesized by acylation of benzene and thiophene with 2-furoyl chloride. 2-Pyrrolyl 2-furyl ketone was prepared by the reaction of 1-pyrrolyl magnesium bromide with 2-furoyl chloride [6].

Alkyl 2-(5-nitrofuryl) ketones were prepared by nitration of the corresponding

Table 1. Characterization of the prepared compounds



Compound	X	Formula	*M*	Calculated/found			Yield %	M.p. °C	ν(C=O) cm^{-1}	λ_{max}, nm log ε
				% C	% H	% N				
I	CH_3	$C_6H_5NO_4$	155.11	—	—	—	62	76—77[a]	1701	304 4.07
II	C_2H_5	$C_7H_7NO_4$	169.14	—	—	—	45	69—70[b]	1698	306 4.04
III	*n*-C_3H_7	$C_8H_9NO_4$	183.16	52.46 52.30	4.91 4.83	7.64 7.56	65	58—59	1696	305 4.10
IV	i-C_3H_7	$C_8H_9NO_4$	183.16	52.46 52.40	4.91 4.82	7.64 7.52	56	54	1695	405 4.12
V	*n*-C_4H_9	$C_9H_{11}NO_4$	197.19	—	—	—	49	47—48[b]	1695	307 4.07
VI	i-C_4H_9	$C_9H_{11}NO_4$	197.19	54.81 55.02	5.61 5.65	7.10 7.27	54	55—57	1694	306 4.14
VII	*tert*-C_4H_9	$C_9H_{11}NO_4$	197.19	54.81 54.69	5.61 5.55	7.10 7.15	45	96—97	1689	307 4.07
VIII	Phenyl	$C_{11}H_7NO_4$	217.18	—	—	—	55	111[c]	1665	306 3.90
IX	2-Thienyl	$C_9H_5NO_4S$	223.21	—	—	—	59	160—161[c]	1655	318 4.15
X	*d*	$C_9H_5N_3O_6$	251.16	43.02 43.16	1.99 2.04	16.73 16.72	48	210 decomp.	1645	347 4.28
XI	*f*	$C_{11}H_7NO_4$	217.18	—	—	—	58	182—183[c]	1720	260 4.14

a) Ref. [13]; *b*) [14]; *c*) [5]; *d*) 2-(5-nitropyrrolyl); *e*) [4]; *f*) 4-nitrophenyl 2-furyl ketone.

ketones with a nitration mixture in acetic anhydride. After pouring the reaction mixture onto ice, the precipitated oily intermediate was not isolated but decomposed with pyridine, urea or alkali phosphate solution directly to the final alkyl 2-(5-nitrofuryl) ketone. The addition intermediates in each case were decomposed by all three bases but only the base affording the highest yield is mentioned in Experimental. Nitration of aryl 2-furyl ketones resulted in aryl 2-(5-nitrofuryl) ketones when aryl was phenyl and 2-thienyl. When aryl was 2-pyrrolyl, dinitro derivative was obtained. Mass spectrometry and ^{1}H-NMR proved that the second nitro derivative was in the position 5 of the pyrrole ring. Thus the pyrrole ring underwent nitration with acetyl nitrate on 2-pyrrolyl 2-furyl ketone contrary to phenyl and thiophene rings which were not nitrated under the described conditions. The physical constants of the synthesized derivatives are presented in Table 1. The compounds *III*, *IV*, *VI*, *VII*, and *X* have not been described so far.

The infrared spectra revealed that the position of the absorption band belonging to carbonyl group was different with the compounds *I*—*VII*. The wavenumber values ν(C=O) of these compounds correlated with the *Taft*'s σ^* constants [7]; the correlation coefficient $r = 0.95$ and the slope $\varrho = 38.28$ (Fig. 1). The different solvents (chloroform, carbon tetrachloride) did not influence the position and the shape of this band contrary to some furan derivatives where this band was split due to conformational equilibrium [8]. Under the applied experimental conditions, the synthesized 2-(5-nitrofuryl) ketones appeared only in one more stable conformation. The wavenumber values of $\nu_{as}(NO_2)$ and $\nu_s(NO_2)$ varied only slightly in the range 1350—1545 cm^{-1}.

The substituents effected only slight changes of the values of λ_{max} and log ε of alkyl and aryl 2-(5-nitrofuryl) ketones (Table 1).

With regard to the so far obtained knowledge on biological activity of nitrofuran derivatives and on their ability to induce hereditary aplastidia on *Euglenas* — bleaching activity [9], the antibacterial and antifungal activities of the synthesized

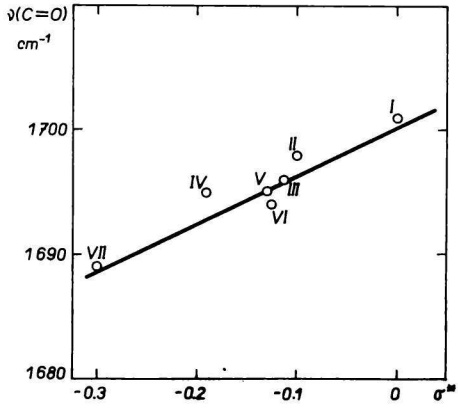


Fig. 1. Dependence of ν(C=O) values on Taft's constants σ^* for alkyl 2-(5-nitrofuryl) ketones [7]; $\varrho = 38.28$, $r = 0.95$.

Table 2

Biological activity of the prepared compounds

Compound	Effects on *Euglena gracilis*		Minimal inhibition conc.[b] against[c]				
	Lethal conc. μg/ml	Minimal bleaching conc.[a] μg/ml	*1*	*2*	*3*	*4*	
I	10	—	12.5	12.5	12.5	12.5	200
II	40	—	12.5	12.5	12.5	50	200
III	40	—	12.5	12.5	50	50	200
IV	60	—	50	50	50	200	200
V	20	—	12.5	3.125	50	50	200
VI	40	—	12.5	3.125	12.5	50	>200
VII	200	—	200	200	200	>200	>200
VIII	20	10	3.125	3.125	3.125	50	200
IX	50	10	3.125	3.125	12.5	50	200
X	200	25	3.125	3.125	3.125	50	200
XI	600	—	>200	>200	>200	200	>200

a) Concentration inducing the highest possible frequency of heterotrophic mutants.

b) The tested concentrations were 200, 50, 12.5, 3.125, 0.78 μg/ml.

c) The microorganisms followed: *1. Staphylococcus aureus; 2. Bacillus subtilis; 3. Escherichia coli; 4. Candida pseudotropicalis; 5. Aspergillus fumigatus.*

derivatives were studied. The activity was tested on chosen bacterial, yeast, and mould strains using diffusion plate method adjusted to individual microorganisms. The bleaching activity was followed on *Euglena gracilis* strain Z [10—12]. The results of these tests are presented in Table 2. Bleaching activity was found with the compounds *VIII*, *IX*, and *X*; the compounds *VIII* and *IX* displayed 100% bleaching activity at relatively low concentrations and were the most effective also with other organisms tested. It is to be stated that for a favourable biological activity the presence of NO_2 in the position 5 of the furan ring (*VIII*) is required. When the NO_2 group was in the position 4 of the benzene ring (*XI*), no bleaching activity was observed and the compound was less active also against other microorganisms. From the results summarized in Table 2 it is evident that with branching of the alkyl the biological activity of the compounds *I*—*VII* decreased. These compounds did not display bleaching activity.

Experimental

Infrared spectra of the synthesized compounds (saturated chloroform solutions) were taken on a double-beam UR-20 spectrophotometer (Zeiss, Jena) using NaCl cells (0.4 mm). The apparatus was calibrated with a polystyrene foil.

The electronic absorption spectra were measured using a recording Specord UV VIS spectrophotometer (Zeiss, Jena) in the region 200—480 nm using 1 cm cells at 25°C; concentration 5×10^{-5} M in dioxan.

Mass spectra were taken on an MS 902 apparatus with a direct inlet system at the energy of electrons 70 eV and trap current of 100 μA. The temperature of the ionization chamber was 110°C.

The ^{1}H-NMR spectra were measured with a Tesla BS-487 C instrument in 15% solution of DMSO at 25°C using TMS as internal standard.

Isopropyl 2-(5-nitrofuryl) ketone (IV)

To a mixture of acetyl nitrate prepared from acetic anhydride (102 g; 1 mole) and fuming nitric acid (38.5 g; 0.6 mole) at −5°C, isopropyl 2-furyl ketone (20.7 g; 0.15 mole) in acetic anhydride (40 ml) was added during 30 min at −10°C. The mixture was stirred for 2 hrs at −15°C and poured onto crashed ice (0.5 kg) under stirring. The precipitated oily addition intermediate was separated and the residue was neutralized with 10% solution of sodium hydroxide and extracted with ether. To the ether solution combined with the separated oil, pyridine (15.4 g; 0.2 mole) was added. Ether was distilled off *in vacuo* and the residue was poured onto ice (0.5 kg). After cooling, isopropyl 2-(5-nitrofuryl) ketone (15.3 g; 56.1%) was isolated and crystallized from the mixture ethanol—water; m.p. 54°C.

The compounds *V*—*IX* were prepared similarly.

n-Propyl 2-(5-nitrofuryl) ketone (III)

A mixture of acetic anhydride (41 g; 0.4 mole) and concentrated sulfuric acid (2 drops) was cooled to 8°C under stirring and nitric acid (9.6 g; 0.15 mole) and a solution of *n*-propyl 2-furyl ketone (13.8 g; 0.1 mole) in acetic anhydride (30 ml) were added simultaneously from separating funnels during 30 min so that the temperature varied in the range 8—10°C. Then the mixture was stirred for 1 hr and powdered sodium acetate (8.1 g; 0.1 mole) was added slowly so that the temperature did not rise above 25°C. The stirring was continued for further 45 min and the mixture was slowly poured into the solution (30°C) of urea (60 g; 1 mole) in water (90 ml). The mixture was kept for 24 hrs at room temperature and extracted with chloroform (600 ml). Afterwards, chloroform was distilled off and the residue was crystallized from the mixture ethanol—water. *n*-Propyl 2-(5-nitrofuryl) ketone (35.6 g; 65%) with m.p. 58—59°C was obtained.

The compounds *I* and *II* were prepared similarly.

2-(5-Nitrofuryl) 2-(5-nitropyrrolyl) ketone (X)

To acetic anhydride (71.4 g; 0.7 mole), fuming nitric acid (25.2 g; 0.3 mole) and concentrated sulfuric acid (0.4 ml) were added at 25—30°C. The mixture was cooled to 0°C and 2-pyrrolyl 2-furyl ketone (16.1 g; 0.1 mole) in acetic anhydride (50 ml) was added under stirring during 20 min. The mixture was stirred for 30 min and $Na_3PO_4 \cdot 12H_2O$ (114 g; 0.3 mole) in water (60 ml) was added so that the temperature did not rise above 50°C. The reaction mixture was then stirred for 1 hr at 50°C, cooled to 0°C and was allowed to stay overnight. The precipitated 2-(5-nitrofuryl) 2-(5-nitropyrrolyl) ketone (12 g; 48%) after recrystallization from ethanol, had m.p. 210°C with decomposition.

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