SYNTHESIS AND FUNGICIDAL ACTIVITY OF SEVERAL ALKYL 2-(5-NITROFURYL) KETONES AND THEIR DERIVATIVES

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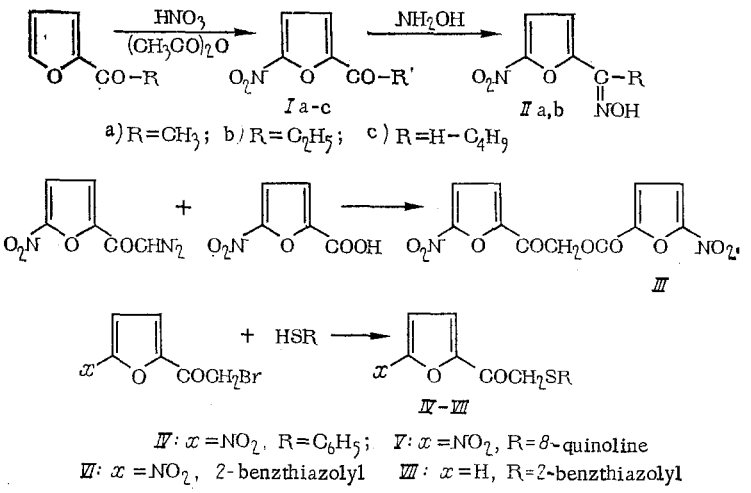
It is well known that several 5-nitrofuran derivatives have pronounced fungicidal action. Among them, in addition to a number of nitrofuryl- and nitrofurylvinyl heterocyclic compounds, are simpler (in structure) compounds such as methyl 5-nitro-2-furfuryl ether (furaspore of nitrofuryl ether) [1], 5-nitro-2-furfuraldoxime (nifuroxime) [2, 3], and 5-nitro-2-(β-nitrovinyl) furan (nitrofurylene) [4, 6], which is used in Soviet medicine. 2-Acetyl-5-nitrofuran [7, 8] and 2-chloroacetyl-5-nitrofuran [9] have the same form of antimicrobial action. It was therefore of interest to study the fungicidal action of other ketones of the nitrofuran series and their derivatives.

Some of the investigated compounds were previously synthesized. In this paper we describe the synthesis of previously unknown ketones and their derivatives or new methods for their preparation, for example, ketones Ia and Ib.



2-Acetyl-, 2-propionyl-, and 2-valeryl-5-nitrofurans (Ia-Ic) were prepared by us by nitration of the appropriate alkyl furyl ketones with fuming nitric acid in acetic anhydride with subsequent treatment of the intermediate product with sodium acetate and urea in analogy with the preparation of 5-nitrofuryl-2-methanediol diacetate [10].

2-[ω-(5-Nitrofuryl-2-carboxy) acetyl]-5-nitrofuran (III) was obtained by reaction of 2-diazoacetyl-5-nitrofuran with 5-nitrofuran-2-carboxylic acid.

The S-substituted 2-mercaptoacetyl-5-nitrofurans (IV-VI) were obtained by reaction of 2-bromoacetyl-5-nitrofuran (1 g) with the appropriate thiols. 2-[2-(Furyl-2)-2-oxoethylmercapto] benzthiazole (VII) was similarly prepared from 2-bromoacetylfuran (Id).

The fungicidal activity was determined by a previously described method [1]. The results are presented in Tables 1 and 2.

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TABLE 1. Minimum Concentration of Ketones of the Nitrofuran Series and Their Derivatives (in μg/ml) Which Retards the Growth of Pathogenic Fungi

Compound	Method of synthesis	Pathogenic fungus strain		
		Candida albicans 67/846	Epidermophyton Kaufmann—Wolf 41	Trichophyton dypseum 4/3
Ia	*	50	50	33,3
IIa	*	133	33,3	33,3
5-Nitro-2-furylglyoxal dihydrate	[11]	>200	>200	>200
Aldoxime of 5-nitro-2-furylglyoxal	[12]	133	66,7	66,7
Ib	*	133	133	133
IIb	*	133	33,3	33,3
Ic	*	100	66,7	66,7
Id	[13, 14]	66,7	66,7	66,7
2-Chloroacetyl-5-nitrofuran	[14]	16,7	16,7	16,7
2-(ω-Isonitroso-ω-chloroacetyl)-5-nitrofuran		>200	133	133
2-Acetoxyacetyl-5-nitrofuran	[14]	25	12,5	12,5
III	*	>200	>200	>200
IV	*	133	66,7	66,7
VI	*	133	133	133
VII	*	>200	33,3	33,3
Griseofulvin		No activity	2,6	3,5
Nistatin		3,5	6,9	7,8

*See experimental section.

TABLE 2. Minimum Concentration of Substance (in, μg/ml) Which Retards the Growth of Pathogenic Fungi

Pathogenic fungus strain	Compound					
	Ia	2-chloroacetyl-5-nitrofuran	2-acetoxyacetyl-5-nitrofuran	Griseofulvin	Nistatin	Nitrofurylene
Candida albicans 67/846	50	16,7	25	No activity	3,5	3,5
S	100	33,3	33,3		8,3	4,9
380	50	16,7	25	" "	3,5	4,9
Candida kruzei	66,7	16,7	25	" "	4,3	3,5
" tropicalis	66,7	16,7	25	" "	3,5	2,3
Epidermophyton rubrum	133	50	33,3	3,5	8,4	1,7
" inguinale	50	16,7	25	1,7	6,9	2,8
Wolf 41						
" Kaufmann—	50	16,7	12,5	2,6	6,9	1,6
Microsporum lanosum	33,3	16,7	12,5	3,5	6,9	0,9
" ferrugineum	100	33,3	50	1,7	3,5	1,5
Achorion schönleini	133	33,3	50	10,4	6,9	0,9
Trichophyton crateriforme	50	12,5	12,5	3,5	6,9	2,3
" faviforme	33,3	25	12,5	3,5	6,9	0,9
" violaceum	66,7	12,5	12,5	1,7	6,9	1,6
" gypseum 4/3	33,3	33,3	12,5	3,5	7,8	1,6

The most active compounds were 2-acetoxyacetyl-5-nitrofuran and 2-chloroacetyl-5-nitrofuran; however, their activity was less than that of nitrofurylene, nistatin, and griseofulvin. It is interesting to note that compound VII was ~ 4 times more active than its 5-nitro analog (VI) with respect to Epidermophyton Kaufmann-Wolf 41 and Trichophyton gypseum 4/3.

EXPERIMENTAL

2-Acetyl-5-nitrofuran (Ia). Concentrated sulfuric acid (0.2 ml) was added with stirring to 178 g of acetic anhydride, and 48 g of 98% nitric acid and a solution of 55 g of 2-acetylfuran in 51 g of acetic anhydride were added simultaneously at 8 to 10° for 30 min from different dropping funnels. After this the mixture was stirred for 1 h at 10°, 34 g of anhydrous sodium acetate was added, and the mixture was stirred for 45 min. The mixture was then poured into a heated (30°) solution of 100 g of urea in 150 ml of water and the mixture was heated to 75°. After standing for 18 h at room temperature the product was extracted

with 600 ml of chloroform. After removal of solvent the residue was crystallized from 240 ml of aqueous alcohol (1 :1) to give 24 g of a product with mp 78-79° (literature mp 77-78° [15]). An additional 3.1 g of Ia with mp 76-78° was obtained from the mother liquor by extraction with 80 ml of chloroform and crystallization from 45 ml of aqueous alcohol. The overall yield of purified Ia was 35%. Found %: C 46.55; H 3.25; N 8.98. $C_6H_5NO_4$. Calc. %: C 46.45; H 3.23; N 9.03.

2-Propionyl-5-nitrofuran (Ib). This was prepared in the same way as Ia in 45% yield with mp 68-70°, which corresponds to the literature data [16]. Found %: C 49.53; H 3.97. $C_7H_7NO_4$. Calc. %: C 49.79; H 4.17.

2-Valeryl-5-nitrofuran (Ic). This compound was obtained in the same way as Ia and had mp 48°. Found %: C 54.60; H 5.90; N 7.20. $C_9H_{11}NO_4$. Calc. %: C 54.82; H 5.62; N 7.10. λ_{max} 295 nm, log ε 4.13 (in alcohol).

2-Acetyl-5-nitrofuran Oxime (IIa). This compound was obtained by addition of an alcoholic solution of Ia to an aqueous solution of equivalent amounts of hydroxylamine hydrochloride and sodium acetate and had mp 166-168° (from aqueous alcohol). Found %: N 16.41. $C_6H_6N_2O_4$. Calc. %: N 16.43.

2-Propionyl-5-nitrofuran Oxime (IIb). This compound was obtained in the same way as IIa and had mp 162-163° (from aqueous alcohol). Found %: C 45.95; H 4.38; N 15.16. $C_7H_8N_2O_4$. Calc. %: C 46.25; H 4.27; N 15.21.

2-[ω-(5-Nitrofuryl-2-carboxy)acetyl]-5-nitrofuran (III). A mixture of 2.75 g of 2-diazoacetyl-5-nitrofuran, 5.9 g of 5-nitrofuran-2-carboxylic acid, and 100 ml of dry acetone was refluxed for 20 h. After removal of the solvent the residue was dissolved in 200 ml of ether. The ether solution was washed with aqueous sodium carbonate and water and dried with sodium sulfate. The ether was evaporated to give 3.5 g (75%) of III with mp 145-146° (from alcohol). Found %: C 42.28; H 1.81; N 9.19. $C_{11}H_6N_2O_9$. Calc. %: C 42.59; H 1.91; N 9.03. λ_{max} 295 nm, log ε 4.30 (in alcohol).

S-Substituted 2-Mercaptoacetyl-5-nitrofuran (IV-VI). A mixture of 20 mmole of Id, 20 mmole of aryl- or heteroarylmercaptan, and 50 ml of alcohol was refluxed for 1 h, and the precipitate which formed on cooling was filtered to give crystalline yellow substances.

2-ω-(Phenylmercapto)acetyl[-5-nitrofuran (IV)]. This compound was obtained in 76% yield and had mp 70-71° (from alcohol). Found %: C 54.56; H 3.56; N 5.41. $C_{12}H_9NO_4S$. Calc. %: C 54.74; H 3.45; N 5. 32. λ_{max} 245, 295 nm, log ε 4.03, 4.17 (in alcohol).

8-[2-(5-Nitrofuryl-2)-2-oxoethylmercapto] quinoline (V). This compound was obtained in 53% yield and had mp 145-147° (from aqueous dimethylformamide). Found %: C 57.36; H 3.57; S 10.37. $C_{15}H_{10}N_2O_4S$. Calc %: C 57.32; H 3.21; S 10.20.

2-[2-(5-Nitrofuryl-2)-2-oxoethylmercapto] benzthiazole (VI). This compound was obtained in 90% yield and mp 120° (from aqueous dimethylformamide). Found %: C 48.83; H 2.33; S 19.92. $C_{13}H_8O_4S_2$. Calc. %: C 48.74; H 2.52; S 20.20. λ_{max} 294 nm, log ε 4.35.

2-[2-(Furyl-2)-2-oxoethylmercapto]benthiazole (VII). This compound was prepared in the same way as VI from Id to give 90% of product with mp 105-107° (from alcohol). Found %: C 56.98; H 2.90; N 4.90. $C_{13}H_9NO_2S_2$. Calc. %: C 56.71; H 3.29; N 5.09. λ_{max} 241, 275 nm, log ε 4.19, 4.53.

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