Syntheses of Phenylthio- and Phenyl-5-Nitro-2-Furoates, and Their Antibacterial Activities

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The establishment of 5-nitro-2-furfural semicarbazone as a drug of the synthetic type has introduced mass-researches finding new derivatives of this type, in which typical examples are known as 5-nitro-2-furan-acrylamide and more recently as 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide, and these have been used in medical and other field.

However, as well known, these are rather labile as a food preservatives; for example, the heating at 85°C for sixty minutes in manufacturing of fish sausage causes break down of one-half of them into ineffective substance to micro-organisms.¹⁾

So, it is desirable to prepare a new effective and more stable derivative from chemotherapeutic as well as other practical standpoint.

On the other hand, in the course of synthetic study of furan compounds, found one of the authors that phenylthio-2-furoates showed strong inhibitive action on *Trichophyton asteroides*.²⁾

Now, the series of derivatives, phenylthio-5-nitro-2-furoates analogous to phenylthio-2-furoates mentioned above and phenyl-5-nitro-2-furoates, were prepared for the study of antibacterial activities.

The latters were synthesized with the view to comparative study as to biological activities to the formers.

Experimental

Preparation of phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V).

The phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V) were prepared as shown in schematic diagram, Fig. 1.

Fig. 1. Schematic diagram of phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V).

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5-Nitro-2-furoic acid (II); (II) is obtained by oxidation of 5-nitro-2-furfural (I) with hydrogen peroxide in pyridine.³⁾

5-Nitro-2-furoyl chloride (III); To a suspension of 10 g (II) of 20 ml phosphorous oxychloride in a 200 ml round bottomed flask fitted with reflux condenser, is added slowly 15 g phosphorous pentachloride under gently boiling. A tube from the top of the condenser conducts hydrogen chloride to cold water.

The addition of the phosphorous pentachloride occupies about one hour, and then heating is continued for two hours. The mixture is distilled under reduced pressure. The crude product boiling at 112–5°C/15 mmHg is collected. To this distillate is added 100 ml of ice-water, then white precipitate is collected by suction and dried.

The crude product thus obtained is sufficient for following purposes. Yield 6.0 g (53.6%).

Phenylthio- and phenyl-5-nitro-2-furoates, (IV and V); In a 50 ml round bottomed flask fitted with a reflux condenser, is placed a suspension of 0.9 g (III) and 10 ml of 2% sodium hydroxide solution of corresponding thiophenol or phenol (0.5 m mole) which is shown in Table 1. The mixture is then heated and kept boiling. After one-half hour it is cooled and transferred to a separatory funnel and extracted two to three times with 50 ml of chloroform. The combined chloroform extract is washed with 50 ml of 5% sodium hydroxide solution, then distilled water.

Chloroform layer is dried with anhydrous sodium sulfate and chloroform is evaporated. The residue is crystallized from methanol/water.

Thioesters (IV-a, b, c, d, e and f) and esters (V-a, b, c, d, e and f) thus prepared are shown in Table 1.

Table 1. Phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V).

No	Compounds	Starting materials	M.p. °C	Yield %	Formula	Elementary analysis			
						Calculated		Found	
						C	H	C	H
IV-a	X=SC ₆ H ₅	C ₆ H ₅ SH	148	26	C ₁₁ H ₇ NO ₄ S	53.01	2.83	53.51	3.10
IV-b	S(p-CH ₃ C ₆ H ₄)	p-CH ₃ C ₆ H ₄ SH	92	50	C ₁₂ H ₉ NO ₄ S	54.75	3.45	55.52	3.54
IV-c	S(p-ClC ₆ H ₄)	p-ClC ₆ H ₄ SH	118	52	C ₁₁ H ₆ NO ₄ ClS	46.57	2.13	47.17	2.42
IV-d	S(p-BrC ₆ H ₄)	p-BrC ₆ H ₄ SH	115	28	C ₁₁ H ₆ NO ₄ BrS	40.26	1.84	40.90	2.48
IV-e	S(p-NO ₂ C ₆ H ₄)	p-NO ₂ C ₆ H ₄ SH	180	15	C ₁₁ H ₆ N ₂ O ₆ S	44.90	2.05	44.86	2.43
IV-f	SCH ₂ C ₆ H ₅	C ₆ H ₅ CH ₂ SH	97	40	C ₁₂ H ₉ NO ₄ S	54.75	3.45	55.42	3.54
V-a	OC ₆ H ₅	C ₆ H ₅ OH	114	28	C ₁₁ H ₇ NO ₅	56.66	3.02	57.10	2.63
V-b	O(p-CH ₃ C ₆ H ₄)	p-CH ₃ C ₆ H ₄ OH	113	61	C ₁₂ H ₉ NO ₅	58.30	3.67	58.34	3.49
V-c	O(o-ClC ₆ H ₄)	o-ClC ₆ H ₄ OH	112	23	C ₁₁ H ₆ NO ₅ Cl	49.37	2.26	49.84	2.71
V-d	O(p-ClC ₆ H ₄)	p-ClC ₆ H ₄ OH	137	45	"	"	"	50.12	2.53
V-e	O(p-BrC ₆ H ₄)	p-BrC ₆ H ₄ OH	138	40	C ₁₁ H ₆ NO ₅ Br	42.33	1.94	43.12	2.36
V-f	O(p-NO ₂ C ₆ H ₄)	p-NO ₂ C ₆ H ₄ OH	197	17	C ₁₁ H ₆ N ₂ O ₇	47.49	2.17	48.30	2.35

Determination of minimum inhibitory concentration of phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V).

A usual serial dilution method was employed to establish the minimum inhibitive concentration. A range of concentrations of the test compound was incorporated into nutrient broth which was then inoculated with an enterotoxigenic strain of *Staphylococcus aureus* 209p, a strain of *Bacillus subtilis* and a strain of *Escherichia coli*. Incubation was at 37°C for 2 and 4 days.

Results

The relative effectiveness of phenylthio- and phenyl-5-nitro-2-furoates against *Staph. aureus* 209p is shown in Table 2. p-Bromo-phenylthio-5-nitro-2-furoate (IV-d) is superior to control, 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide against the test organism used. This tendency was observed not only at 2 days after incubation but also 4 days, at which time 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide had lost more of its effectiveness. Also, p-chlorophenylthio-5-nitro-2-furoate (IV-c) and benzylthio-5-nitro-2-furoate (IV-f) were effective.

Generally, phenylthio-5-nitro-2-furoates (IV) were more effective than phenyl-5-nitro-2-furoates (V) in the bacteriostatic point, and similar tendency was observed also in the action of phenylthio-2-furoates and phenyl-2-furoates against *Trichophyton asteroides*.²¹

The data of bacteriostatic action against other strains tested were abbreviated for the less effectiveness.

Table 2. Minimum inhibitive concentration of phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V) for *Staphylococcus aureus* 209p determined at 2 and 4 days incubation at 37°C in nutrient broth.

No		Minimum inhibitive Concentration (γ)	
		2 Days	4 Days
IV-a	X = SC ₆ H ₅	5	5
IV-b	S(p-CH ₃ C ₆ H ₄)	0.5	10
IV-c	S(p-ClC ₆ H ₄)	0.5	0.5
IV-d	S(p-BrC ₆ H ₄)	0.1	1
IV-e	S(p-NO ₂ C ₆ H ₄)	10	—
IV-f	SCH ₂ C ₆ H ₄	0.5	5
V-a	OC ₆ H ₄	10	—
V-b	O(p-CH ₃ C ₆ H ₄)	10	—
V-c	O(o-ClC ₆ H ₄)	10	—
V-d	O(p-ClC ₆ H ₄)	10	—
V-e	O(p-BrC ₆ H ₄)	10	—
V-f	O(p-NO ₂ C ₆ H ₄)	10	—
Control; 2-(2-furyl)-3-(5-nitro-2-furyl)-acryl-amide		0.5	5

Summary

1. Two type of 5-nitro-2-furoates, phenylthio-5-nitro-2-furoates (IV) and phenyl-5-nitro-2-furoates (V), of which benzen ring was substituted with methyl, halogen or nitro group, were prepared for the study of bacteriostatic activities.

2. Some of (IV), p-chlorophenylthio-5-nitro-2-furoate, p-bromo-phenylthio-5-nitro-2-furoate and benzylthio-5-nitro-2-furoate, showed strong inhibitive action on *Staphylococcus aureus* 209p in vitro.

3. Phenylthio-5-nitro-2-furoates (IV) were more effective than phenyl-5-nitro-2-furoates (V).

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