ANTIMICROBIAL ACTIVITY OF 2-ARYLFURAN DERIVATIVES AND THEIR STRUCTURAL ANALOGS

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We have already shown that a large number of derivatives of 2-arylfurans with hydroxymethyl, amide and other groupings as substituents at the 5-position of the furan ring exhibit a high tuberculostatic activity [2, 3]. The benzene ring in these compounds has a halogen, methyl, or methoxyl group as a substituent.

The present work deals with the synthesis of a series of new arylfuran derivatives with different substituents in the benzene and furan rings in order to study their antimicrobial activity.

2-Hydroxymethyl-5-(p-carbethoxyphenyl)furan (II) was synthesized by the reduction of 5-(p-carbethoxyphenyl)furfural (I) by $NaBH_4$.

5-(p-Aminophenyl)pyromucamide (IV) was obtained by the reduction of 5-(p-nitrophenyl)-pyromucamide (III) by N_2H_4 over Raney nickel.

5-(p-Methoxyphenyl)pyromucamide (V) was obtained by a modified procedure [7] in a 76% yield.

5-(p-Hydroxyphenyl)-2-methylfuran (VI) was obtained by alkaline hydrolysis of 5-(p-methoxyphenyl)-2-methylfuran.

To examine the dependence of the biological activity of the arylfuran derivatives that we studied on their structure, we synthesized the structural analogs of these compounds. We prepared derivatives of 2-arylthiophene and also of 2-aryltetrahydrofuran with a structure analogous to that of the corresponding 2-arylfuran derivatives, which, as already found [3], exhibit a marked tuberculostatic activity.

2-Hydroxymethyl-5-(p-bromophenyl)thiophene (VII) was obtained by the reduction of 5-p-bromophenyl)thiophene-2-carboxaldehyde by $NaBH_4$; compound VII was further converted into its acetate (VIII).

2-Hydroxymethyl-5-phenyltetrahydrofuran (IX) was obtained by the hydrogenation of 2-hydroxymethyl-5-phenylfuran over Raney nickel and then converted into the corresponding ethyl ether (X).

EXPERIMENTAL CHEMISTRY

The IR spectra were run on the UR-10 spectrophotometer (GDR) in a thin layer.

5-(p-Carbethoxyphenyl)furfural (I). This is obtained by the method in [6] in yield of 23%, mp 124.5-126°C (from ethyl acetate). Literature data: yield 15%, mp 115-116°C. Thiosemicarbazone, mp 226°C. Found, %: C 56.9; H 5.1; N 13.0. $C_{15}H_{15}N_3O_3$. Calculated, %: C 56.8; N 4.8; N 13.2.

2-Hydroxyphenyl-5-(p-carbethoxyphenyl)furan (II). A solution of 0.5 g (13 mmoles) of $NaBH_4$ in 10 ml of water is added dropwise to 6 g (25 mmoles) of I in 25 ml of dioxane. The reaction mixture is boiled for 1 h, then cooled and 15 ml of 10% H_2SO_4 are added. The mixture is poured into 100 ml of water and the precipitate is filtered. Yield, 3.9 g (65%) of II, mp 83.5-84°C (from hexane). Found, %: C 68.4; H 5.7. $C_{14}H_{14}O_4$. Calculated, %: C 68.3; H 5.7.

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TABLE 1. Minimal Inhibiting Concentration (in μg/ml) of Compounds II-VI and VIII

Compound	$H_{37}R_V$		ATCC-607
	without blood serum	with addition of 10% blood serum	
II	32,0	...	>1000
III	0,5	16,0	>1000
IV	2,0	250,0	>1000
V	1,0	...	>1000
VI	4,0	...	32,0
VIII	4,0	16,0	250

5-(p-Nitrophenyl)pyromucamide (III). This is obtained by the method in [7] in a yield of 75%, mp 208-210°C (from benzene). Literature data yield 65%, mp 200-202°C [7].

5-(p-Aminophenyl)pyromucamide (IV). A 1.2 g portion of Raney nickel in 20 ml of ethanol is added to a mixture of 6.6 g (28 mmoles) of III and 20 ml of $N_2H_4 \cdot H_2O$ in 200 ml of ethanol. At the end of the evolution of H , the reaction mixture is boiled for 1 h, then cooled to 5°C, and the catalyst is filtered. The precipitate formed on cooling the solution is filtered. Yield, 4.6 g (80%) of IV, mp 233-235°C (from alcohol). Found, %: C 65.1; H 5.1; N 13.7. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.3; H 5.0; N 13.9.

5-(p-Methoxyphenyl)pyromucamide (V). To a suspension of 2.7 g of 5-(p-methoxyphenyl)-mucyl chloride [2] in ether, 25 ml of 25% aqueous NH_3 solution are added in portions. The reaction mixture was stirred at room temperature for 1 h, and the precipitate is filtered. Yield, 1.9 g (76%) of V, mp 182-183°C (from alcohol). Literature data: yield 58%, mp 182-183°C [2].

2-Methyl-5-(p-hydroxyphenyl)furan (VI). A mixture of 1.9 g (10 mmoles) of 2-methyl-5-(p-methoxyphenyl) furan [1], 4 g (72 mmoles) of powdered KOH and 45 ml of diethylene glycol is stirred for 10 h at 180-185°C. The mixture is then cooled, poured into 50 ml of water, and neutralized by HCl to neutral reaction. The precipitate is filtered. Yield, 1 g (55%) of VI, mp 91-93°C (from hexane). Found, %: C 75.8; H 5.7. $C_{11}H_{10}O_2$. Calculated, %: C 75.8; H 5.8.

2-Hydroxymethyl-5-(p-bromophenyl)thiophene (VII). A solution of 0.05 g (1 mmole) of $NaBH_4$ in 4 ml of water is added dropwise to 0.5 g (2 mmoles) of 5-(p-bromophenyl)thiophene-2-carboxaldehyde [5] in 9 ml of dioxane. The precipitate is filtered. Yield, 0.44 g (88%) of VII, mp 135-137°C (from petroleum ether). Found, %: C 49.3; H 3.3; Br 29.8. $C_{11}H_9BrOS$. Calculated, %: C 49.1; H 3.3; Br 29.7.

2-Hydroxyphenyl-5-(p-bromophenyl)thiophene Acetate (VIII). A mixture of 3.3 g of VII, 3 g of NaOAc and 2 ml of Ac_2O in 20 ml of absolute benzene is heated, with stirring, at 100°C for 4 h. After cooling 100 ml of water are added to the reaction mixture. The organic layer is separated, washed with 5% sodium carbonate solution, then with water, and dried over Na_2SO_4. The solution is evaporated to yield 2.9 g (76%) of VIII, mp 74.5-75.5°C (from benzene). Found, %: C 50.2; H 3.5. $C_{13}H_{11}BrO_2S$. Calculated, %: C 50.2; H 3.5.

5-(p-Chlorophenyl)thiophene-2-carboxaldehyde Thiosemicarbazone, mp 111-113°C (from alcohol). Found, %: 48.9; H 3.3; Cl 12.3; N 14.1; S 21.6. $C_{12}H_{10}ClN_3S_2$. Calculated, %: C 48.7; H 3.4; Cl 12.0; N 14.2; S 21.7.

5-(p-Bromophenyl)thiophene-2-carboxaldehyde Semicarbazone, mp 206-208°C (from benzene). Found, %: 42.2; H 2.8; Br 18.8; N 12.4. $C_{12}H_{10}BrN_3S_2$. Calculated, %: C 42.3; H 2.9; Br 18.8; N 12.3.

2-Hydroxyphenyl-5-phenyltetrahydrofuran (IX). A solution of 2 g of 2-hydroxymethyl-5-phenylfuran [1] in 10 ml of anhydrous alcohol is hydrogenated for 7 h in a rotating autoclave at 50°C at an initial pressure of 55 atm. At the end of H_2 absorption, the reaction mixture is filtered, evaporated, and the residue distilled *in vacuo*. Yield, 1.8 g of IX, bp 246°C (1 mm), n_D^{20} 1.5382. IR spectrum, ν_{max}: 3380-3440 cm^{-1} (OH). Found, %: C 74.0; H 8.0. $C_{11}H_{14}O_2$. Calculated, %: C 74.1; H 7.9.

2-Ethoxy-5-phenyltetrahydrofuran (X). A mixture of 0.5 g (3 mmoles) of IX, 0.4 g (7 mmoles) of KOH and 2 ml (25 mmoles) of EtI is boiled, with stirring, for 2.5 h. It is then

cooled and poured into 50 ml of water, and extracted with ether. The extract is dried over $MgSO_4$ and evaporated. Yield, 0.3 g (52%) of X, bp 97-98°C (1 mm), n_D^{20} 1.4918, %: C 75.8; H 9.0. $C_{13}H_{16}O_2$. Calculated, %: C 75.7; H 8.8.

EXPERIMENTAL BIOLOGY

The antimicrobial activity of the compounds synthesized was studied in experiments *in vitro* by methods described in [4] with respect to 9 types of bacteria and 5 types of pathogenic fungi. Almost all the compounds studied were found to be practically inactive, and did not inhibit the growth of these microorganisms at a concentration of 250-500 μg/ml. Only compound VI has a marked activity with respect to gram-positive and gram-negative bacteria and pathogenic fungi (its minimal inhibiting concentration varies from 31.5 to 250 μg/ml).

We studied the tuberculostatic activity *in vitro* of compounds II-VI, VIII (see Table 1). The activity of the compounds was determined by double serial dilutions on Soton medium, beginning from 1:1000. M. tuberculosis ($H_{37}R_V$) and saprophytic mycobacteria of the ATCC-607 strain were used as test cultures. The minimal inhibiting concentration varied from 32 to 0.5 μg/ml. When a 10% horse blood serum was added, the activity of the compounds decreased. The characteristic feature of the compounds is the absence of activity against ATCC-607.

Comparison of the antibacterial activity of compounds VII-X with the activity of the previously synthesized analogous arylfuran derivatives [3] showed that the antimicrobial action of these compounds decreases when the aryl fragment is replaced by arylthienyl or arytetrahydrofuryl fragments.

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