SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 5-ARYLTHIOPHENE-2-CARBOXYLIC ACIDS

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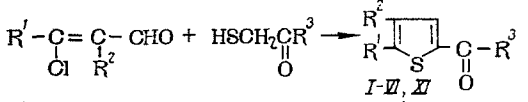
Several thiophenecarboxylic acids and their derivatives are known to display bactericidal activity, including significant antituberculosis action [1]. Biological activity in many cases can be enhanced by the introduction of an aryl substituent [2-4]. In this context we have synthesized some derivatives of 5-arylthiophene-2-carboxylic acids by condensation of a series of β-chloro-β-arylacroleins and evaluated their antimicrobial activity.



I-VI, XI

R^1 = C_6H_5, 4-$CH_3OC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$

R^2 = H, CH_3, C_6H_5; R^3 = C_2H_5O, NHC_6H_5

We used sodium methoxide as the condensing agent (2 moles per mole of β-chloro-β-arylacrolein). We were thus able to secure good yields (60-83%) of the methyl 5-arylthiophene-2-carboxylates (as a result of transesterification). For example we isolated the 5-phenylthiophene-2-carboxylate ester (I) in 75% yield, whereas in the presence of potassium hydroxide the yield was only 30% [5]. Moreover, by using a twofold excess of sodium methoxide we were able to synthesize thiophene derivatives from p- or o-nitrophenyl-substituted chloroacroleins, whereas in the presence of 1 mole of sodium ethoxide the reaction terminates with the formation of the intermediates — substituted ethyl 2-(3-oxoprop-1-enylthio)acetates [6].

Use of an equimolar quantity of sodium methoxide in the condensation of β-chloro-β-arylacroleins with ethyl thioglycolate reduced the yields of the thiophene-2-carboxylate esters.

From esters (I)-(IV) we derived the hydrazides of acids (VII)-(X). The physical constants and yields of compounds (II)-(VI) and (VIII)-(X) are summarized in Table 1.

Like ethyl thioglycolate, the anilide in a mixture with β-chloro-β-phenylacrolein and a two-fold excess of sodium methoxide was readily converted to the cyclic product, 5-phenylthiophene-2-carboxanilide (XI), though unlike ethyl thioglycolate, by using an equimolar ratio of the anilide, substituted chloroacrolein, and base we were able to isolate the intermediate in the condensation, (XII), in 80% yield. Treatment of (XII) with a second mole of sodium methoxide cyclized it to anilide (XI) (76%), while refluxing with potassium hydroxide (twofold excess) in diethylene glycol quantitatively converted it to 5-phenylthiophene-2-carboxylic acid (XIII).

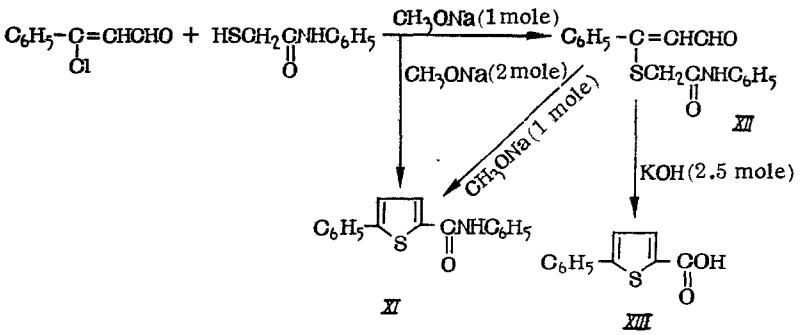


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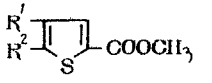
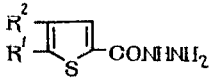
TABLE 1. Esters and Hydrazides of 5-Arylthiophene-2-carboxylic Acids



II-VII



VIII-X

Compound	R^1	R^2	Yield, %	Melting point, °C	Found, %				Formula	Calculated, %			
					C	H	N	S		C	H	N	S
II	$4\text{-}CH_3OC_6H_4$	H	72	126,5—7	62,87	4,74	—	13,23	$C_{13}H_{12}SO_3$	62,90	4,85	—	12,90
III	$3,4\text{-}(CH_3O)_2C_6H_3$	H	60	131—2	60,02	5,02	—	11,35	$C_{14}H_{14}SO_4$	60,45	5,05	—	11,50
IV	$4\text{-}NO_2C_6H_4$	H	79,5	192—3	55,24	3,52	5,68	12,20	$C_{12}H_9NO_4S$	54,75	3,40	5,33	12,12
V	$2\text{-}NO_2C_6H_4$	CH_3	83	115,5—16,5	56,52	3,98	5,06	11,33	$C_{13}H_{11}NO_4S$	56,38	3,97	5,05	11,50
VI	C_6H_5	C_6H_5	72,5	92,5—3,5	73,50	4,88	—	10,63	$C_{18}H_{14}O_2S$	73,50	4,76	—	10,87
VIII	$4\text{-}CH_3OC_6H_4$	H	88,8	203—4	—	—	11,37	13,02	$C_{12}H_{12}N_2O_2S$	—	—	11,30	12,89
IX	$4\text{-}NO_2C_6H_4$	H	78	218—20	—	—	16,58	12,70	$C_{10}H_9N_3O_3S$	—	—	16,70	12,74
X	$2\text{-}NO_2C_6H_4$	CH_3	65	210—12	—	—	15,67	11,97	$C_{11}H_{11}N_3O_3S$	—	—	15,83	12,08

From acid (XIII) via its acid chloride (XIV) we prepared the N-methylpiperazide (XV) and morpholide (XVI) of 5-phenylthiophene-2-carboxylic acid.

We examined compounds (I)-(XVI) for antimicrobial activity in the laboratory of Chemotherapy of Infectious Diseases at the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry (director, Professor G. N. Pershin). Compounds (I), (II), (V), and (VII)-(X) displayed moderate activity toward *Mycobacterium tuberculosis* $H_{37}Rv$ (minimum mycostatic concentration 4-8 μg/ml), which was attenuated by the presence of serum. Tests for antibacterial and antifungal activity revealed no highly active compounds.

EXPERIMENTAL

The IR spectra were recorded on a UR-10 spectrophotometer in Vaseline oil; mass spectra on an MX 1303 spectrometer. The purity of the synthetic compounds was verified by thin-layer chromatography (TLC) on Silufol plates in chloroform–acetone (9:1).

The substituted β-chloroacroleins were synthesized by published methods [7-10].

Methyl 5-Phenylthiophene-2-carboxylate (I). A mixture of ethyl thioglycolate (9.95 g, 0.83 mole) and sodium (1.91 g, 0.83 mole) in methanol (16.5 ml) was stirred at room temperature for 30 min. β-Chloro-β-phenylacrolein (13.8 g, 0.83 mole) was added, causing a precipitate to form. Stirring was continued for another 1 h. The reaction mixture was again treated with sodium (1.91 g, 0.83 mole) in methanol. After 1 h the precipitate was filtered off, washed with water, and dried. Crystallization gave (I) (13.2 g, 75%), mp 99-100°C (from ethanol). Found, %: C 66.29; H 4.79; S 14.70. $C_{12}H_{10}SO_2$. Calculated, %: C 66.00; H 4.60; S 14.70. IR spectrum, ν, cm^{-1}: 1700 (C=O), 1080, 1025-750 (thiophene). Mass spectrum, m/e, 218.

Esters (II)-(VI) were prepared in the same way; their physical constants and yields are summarized in Table 1.

5-Phenylthiophene-2-carbohydrazide (VII). To a warmed solution of (I) (2.18 g, 0.01 mole) in ethanol (20 ml) was added hydrazine hydrate (0.625 g, 0.0125 mole). The reaction mixture was refluxed for 5 h and then cooled. The crystalline precipitate was filtered off, washed with water, and dried. Crystallization gave (VII) (2.07 g, 92%), mp 178-180°C (from ethanol). Found, %: N 12.67. $C_{11}H_{10}N_2SO$. Calculated, %: N 12.85.

Hydrazides (VIII)-(X) were prepared like (VII) in dioxane solution; their physical constants and yields are summarized in Table 1.

5-Phenylthiophene-2-carboxanilide (XI). Thioglycolanilide (3.01 g, 0.018 mole) in methanol (40 ml) was treated with sodium (0.414 g, 0.018 mole) in methanol (3.6 ml) at room temperature with stirring. After 30 min β-chloro-β-phenylacrolein (3 g, 0.018 mole) was added. The mixture was stirred for 30 min, whereupon a second portion of sodium (0.414 g, 0.018 mole) in methanol was added. After 1 h the resulting precipitate was filtered off, washed with a small quantity of methanol and water, and dried. Crystallization gave (XI) (3.84 g, 76%), mp 212-213°C (from dioxane). Found, %: C 72.77; H 4.63; N 4.98; S 11.59. $C_{17}H_{13}N_2OS$. Calcualted, %: C 73.12; H 4.62; N 5.02; S 11.50. R_f 0.138. IR spectrum, ν, cm^{-1}: 3325 (NH), 1645 and 1545 (CONH), 1590, 1320, 1080, and 1025-750 (thiophene). Mass spectrum, m/e, 279.

2-(3-Oxoprop-1-enyl-1-phenyl-1-thio)acetanilide (XII). A mixture of thioglycolanilide (3.01 g, 0.018 mole) and β-chloro-β-phenylacrolein (3 g, 0.018 mole) in methanol (40 ml) was treated with an equimolar quantity of sodium methoxide at room temperature with stirring. After 1 h the precipitate was filtered off, washed with water, and dried. Crystallization gave (XII) (4.42 g, 82.6%), mp 154.5-155°C (from ethanol). R_f 0.538. Found, %: C 68.80; H 5.10; N 4.55; S 11.00. $C_{17}H_{15}O_2NS$. Calculated, %: C 68.73; H 5.05; N 4.62; S 10.80. IR spectrum, ν, cm^{-1}: 1700 (CO), 1640 and 1550 (CONH), 1170 and 1140 (C–C).

5-Phenylthiophene-2-carboxylic Acid (XIII). Compound (XII) (15 g, 0.0505 mole) and potassium hydroxide (7.07 g, 0.128 mole) in diethylene glycol (20% solution) was refluxed for 2 h. The solution was cooled, poured into water, and filtered. The filtrate was acidified and the resulting precipitate was filtered off, washed with water, and dried. Crystallization gave (XIII) (10.5 g, 98%), mp 185°C (from heptane); literature 184°C [11].

5-Phenylthiophene-2-carbonyl Chloride (XIV). Compound (XIII) (4 g, 0.0196 mole) and thionyl chloride (11.7 g, 0.098 mole) were refluxed for 3 h to give (XIV) (4.1 g, 94%), mp 81-82°C (from heptane); literature 80°C [11].

(N-Methyl)piperazide of 5-Phenylthiophene-2-carboxylic Acid (XV). To a solution of (XIV) (1.3 g, 0.00584 mole) in dioxane (15 ml) was slowly added N-methylpiperazine (2.33 g, 0.0233 mole), with stirring. The reaction mixture was stirred at room temperature for 30 min and then poured into water. The resulting precipitate was filtered off. The mother liquor was made alkaline and filtered. The combined precipitates were washed with water and dried. Crystallization gave (XV) (1.39 g, 83%), mp 67-68°C (from heptane). Found, %: N 9.93. $C_{16}H_{18}N_2OS$. Calculated, %: N 9.80.

Morpholide of 5-Phenylthiophene-2-carboxylic Acid (XVI). By the procedure for (XV) compounds (XIV) (1.3 g, 0.00584 mole) and morpholine (2.36 g, 0.0292 mole) gave (XVI) (1.2 g, 74.5%), mp 99-100°C (from heptane). Found, %: N 5.03. $C_{15}H_{15}NO_2S$. Calculated, %: N 5.14.

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