SYNTHESIS AND ANTIMICROBIC ACTIVITY OF 2-(2-AMINOTHIAZOLYL-4)-THIOPHENE AND ITS DERIVATIVES

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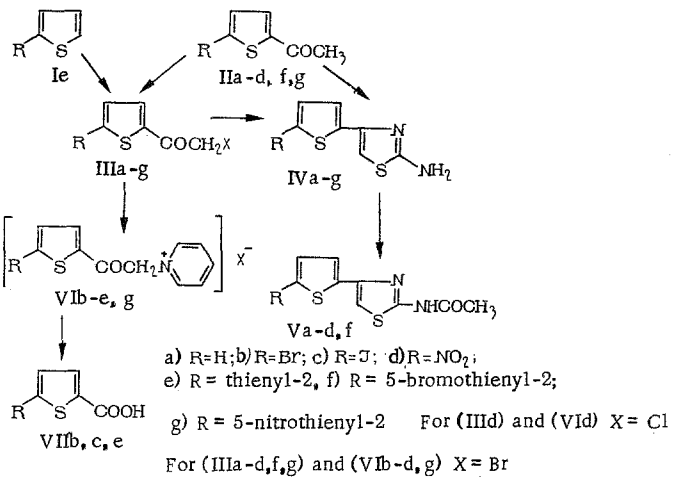
Data are present in the literature on the synthesis and antimicrobic activity of certain aminothiazolylfurans [1]. It was of interest to us to synthesize 2-(2-aminothiazolyl-4)-thiophene (IVa) and a series of its derivatives for biological investigation – all the more because a systematic study of thiazolylthiophenes has not been carried out to date, and only individual representatives of this type of compound are known [2, 3]. In this case our problem was to show to what degree introduction of various substituents into the α position of the thiophene ring of (IVa) and also salt formation and acetylation of the amino group, would affect the antibacterial activity of the preparation. For this purpose we synthesized 2-(2-aminothiazolyl-4)-5-R-thiophenes (IVa-g), their N-aceto derivatives (Va-d, f), and salts.



The 2-(ω-haloacetyl)-5-R-thiophenes (IIIa-g) necessary for the synthesis were obtained by various methods: bromination of 2-acetyl-5-R-thiophenes (IIa-d, f, g) and chloroacetylation of 2,2-dithienyl (Ie) with N, N-diethylchloroacetamide in the presence of phosphorous oxychloride. The latter method was used because a mixture of products is obtained upon bromination of 5-acetyl-2,2-dithienyl (IIe) which we could not separate. Compounds (IIIb-e, g), obtained by us for the first time, are presented in Table 1. The structure of compounds (IIIb-e, g) was confirmed by their ability to form quaternary pyridinium salts (VIb-e, g) (Table 2), cleavage of the latter in basic medium to the corresponding carboxylic acids (VIIb, c, e) [4], and also by quantitative elemental analysis data. The corresponding acids could not be isolated from the reaction mixture upon cleavage of (VId) and (VIg).

Reaction of (IIIa-g) with thiourea yielded the corresponding compounds (IVa-g) as their salts (method A). Hydrobromides of (IVd, g) are easily transformed into bases upon reaction with cold water, while hy-

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TABLE 1. 2-(ω-Haloacetyl)-5-R-thiophenes

Compound	Yield (%)	mp (deg)*	Found (wt. %)			Empirical formula	Calculated (wt. %)		
			C	H	S		C	H	S
III b	68—72	89—90	25,13	1,31	11,08	$C_6H_4Br_2OS$	25,38	1,42	11,29
III c	60—64	102	21,48	1,34	9,47	C_6H_4BrJOS	21,77	1,22	9,69
III d	60—63	102—103	28,51	1,43	12,96	$C_6H_4BrNO_3S$	28,82	1,61	12,82
III e	4,5	104—105	49,76	2,53	26,61	$C_{10}H_7ClOS_2$	49,48	2,91	26,42
III f	66—70	201—202	35,88	1,65	19,12	$C_{10}H_6BrNO_3S_2$	36,16	1,82	19,30

*Compound (IIIg) was recrystallized from chloroform; the remaining compounds were recrystallized from ethanol.

TABLE 2. Quaternary Pyridinum Salts

Compound	Yield (%)	mp (deg)*	Found (wt. %)			Empirical formula	Calculated (wt. %)		
			C	H	S		C	H	S
VI b	92	210	36,57	2,64	8,58	$C_{11}H_9Br_2NOS$	36,39	2,50	8,83
VI c	90	226—228	32,45	2,41	7,68	$C_{11}H_9BrINOS$	32,22	2,21	7,82
VI d	91	217—218 (dec.)	39,96	2,58	9,88	$C_{11}H_9BrN_2O_3S$	40,14	2,76	9,74
VI e	89	221—222	60,14	3,50	20,18	$C_{15}H_{12}ClNOS_2$	55,98	3,76	19,92
VI g	94	294—296 (dec.)	43,57	2,52	15,40	$C_{15}H_{11}BrN_2O_3S_2$	43,80	2,70	15,59

*From water

drobromides of (IVb, c, f) and hydrochloride of (IVe) are transformed into bases upon heating in alcohol or water. For this reason it was only possible to study the antimicrobic activity of hydrobromides of (IVa-c). The picrate of (IVa) and salts of (IVa) with hydrochloric, nitric, and trichloroacetic acids were synthesized for the microbiological study. Compound (IVa) was also obtained upon treatment of a mixture of (IIa) and thiourea with bromine (method B). Compounds (IVa-d, f) were characterized by their N-aceto derivatives (Va-d, f), which do not dissolve in water but are highly soluble in aqueous solutions of bases.

The obtained compounds (IV), their salts, and N-aceto derivatives (V) are presented in Table 3. The structure of (IV) and (V) was confirmed by quantitative elemental analysis data and IR spectra.

Microbiological examinations were carried out on a simple meat-peptone agar at a standard preparation concentration of 400 μg/ml. Compounds (IV), their salts, and N-aceto derivatives (V) were examined for antimicrobic effect in relation to the Gram-positive bacteria St. aureous, Bac. mesentericus, and Bac. pseudoanthracis and also the Gram-negative bacteria E. coli, S. typhi, Sh. flexneri, Sh. Sonnei, and Bact. pyocyaneum. Examination showed that (IVa) possesses to a certain degree a selective activity in relation to Gram-positive bacteria. Introduction of bromine and iodine into the α-position of the thiophene ring is accompanied by complete loss of antimicrobic properties present in (IVa), while introduction of the nitro group into the same position do not show up negatively on the appearance of selective antimicrobic properties.

Going from thiazole derivatives of thiophene (compounds (IVa, b, d) to the analogous thiazole derivatives of 2,2'-dithienyl (compounds (IVe-g) is accompanied by loss of antimicrobic properties in relation to all of the microorganisms we studied. Acetylation of the amino group leads to total loss of antimicrobic activity in all cases. With respect to salts of (IVa), their antimicrobic properties were found to be different. As a rule, transformation of (IVa) into the salt is accompanied either by a sharp decrease in antimicrobic activity, or by its total loss. An exception is the hydrochloride salt of (IVa), possessing antimicrobic activity in relation to both Gram-negative and Gram-positive test cultures.

EXPERIMENTAL

2-(ω-Bromoacetyl)thiophene (IIIa) and 5-(ω-bromoacetyl)-5'-bromo-2,2'-dithienyl (IIIf) were obtained by known methods [5, 6].

TABLE 3. Amino- and Acetaminothiazolythiophenes

Compound	Yield (%)	mp (deg)	Recrystallization solvent	Found (wt. %)			Empirical formula	Calculated (wt. %)		
				C	H	S		C	H	S
IVa	88*	130,5	Cyclohexane	45,97	3,48	35,32	$C_7H_6N_2S_2$	46,13	3,32	35,18
IVa·HB	88*	218	Ethanol	32,16	2,91	24,58	$C_7H_6N_2S_2 \cdot HBr$	31,95	2,68	24,37
IVa·HCl	92	199—200	"	38,06	2,96	29,11	$C_7H_6N_2S_2 \cdot HCl$	38,44	2,23	29,32
IVa·HNO_3	86	172—173	Water	33,92	2,50	25,84	$C_7H_6N_2S_2 \cdot HNO_3$	34,28	2,88	26,14
IVa·CCl_3CO_2H	84	151—152	Ethanol	31,05	1,72	18,31	$C_7H_6N_2S_2 \cdot C_2HCl_3O_2$	31,27	2,04	18,55
IVa, picrate	79	183—184	"	37,88	2,43	15,35	$C_7H_6N_2S_2 \cdot C_6H_3N_3O_7$	37,96	2,21	15,59
Va	98	210	"	48,42	3,76	28,35	$C_9H_8N_2OS_2$	48,19	3,60	28,59
IVb	94	148	"	31,90	1,75	24,73	$C_7H_5BrN_2S_2$	32,19	1,93	24,55
IVb HB	94	190 †	—	24,33	1,62	18,97	$C_7H_5BrN_2S_2 \cdot HBr$	24,58	1,77	18,75
Vb	96	253	Ethanol	35,82	2,12	21,02	$C_9H_7BrN_2OS_2$	35,65	2,33	21,15
IVc	96	163	"	27,47	1,42	21,04	$C_7H_5IN_2S_2$	27,28	1,64	20,81
IVc HB	96	201—202	—	21,41	1,37	16,31	$C_7H_5IN_2S_2 \cdot HBr$	21,61	1,55	16,48
Vb	97	231	Ethanol	30,59	1,84	18,54	$C_9H_7IN_2S_2$	30,87	2,01	18,31
IVd	94	267—269 (dec.)	Acetic acid	37,11	2,08	28,14	$C_7H_5N_3O_2S_2$	36,99	2,22	28,22
IVd·HBr	94	230—232‡	—	27,54	2,14	20,78	$C_7H_5N_3O_2S_2 \cdot HBr$	27,28	1,96	20,81
Vd	94	335—340 (chars)	Ethanol	40,35	2,44	23,69	$C_9H_7N_3O_2S_2$	40,14	2,62	23,81
IVe	92	202—203	Benzene	50,14	2,83	36,22	$C_{11}H_8N_2S_3$	49,97	3,05	36,38
IVf	90	185—196	Acetone	38,20	1,89	27,78	$C_{11}H_7BrN_2S_3$	38,49	2,06	28,02
IVf HBr	90	220—221‡	—	31,61	1,95	22,84	$C_{11}H_7BrN_2S_3 \cdot HBr$	31,15	1,90	22,68
Vf	99	234	Ethanol	40,47	2,20	25,17	$C_{13}H_9BrN_2OS_3$	40,52	2,35	24,96
IVg	98	>300 (chars)	Dioxane	42,25	2,05	30,86	$C_{11}H_7N_3O_2S_3$	42,70	2,28	31,09

†By method A.

‡Not recrystallized as a result of decomposition in water and alcohol.

2-(ω-Bromoacetyl)-5-R-thiophenes (IIIb-d,g)

In chloroform 25 mmoles of (IIb-d,g) were brominated with 4 g (25 mmoles) of bromine in 10 ml of chloroform. The reaction was preliminarily initiated by adding several drops of a bromine solution and heating the reaction mixture at 45-50 deg until disappearance of the bromine color. The remaining amount of bromine was added in 15-20 min at a temperature of 20 deg. The mixture was stirred an additional 30 min and then the solvent was removed in vacuum. The residue was recrystallized by treating the solution with activated carbon to give (IIIb-d,g) (see Table 1).

5-(ω-Chloroacetyl)-2,2'-dithienyl (IIIe). To a mixture of 16.63 g of (I) and 16.46 g of N,N-diethylchloroacetamide was added in drops 16.86 g of phosphorus oxychloride. The reaction mixture was held for 1 h at room temperature, then heated on a boiling water bath for 3 h. The mixture was cooled and poured into water. The mixture was extracted with ether (eight times with 50 ml), and the ether extracts were washed with water, sodium carbonate solution, and again with water. The ether extract was dried with anydrous sodium sulfate, and then the ether was distilled. The residue was treated with 700 ml of boiling petroleum ether in the presence of activated carbon. The obtained extract was evaporated to 400 ml and left for the product to crystallize. The crystals were filtered, washed with cold petroleum ether, and dried. We obtained 1.08 g of (IIIe) as pale yellow crystals. Constants of (IIIe) are presented in Table 1.

Quaternary Pyridinium Salts (VIb-e, g)

To 2 mmoles of (IIIb-e, g) was added 2 ml of dry pyridine and the mixture was heated until formation of a copious precipitate. The mixture was cooled and diluted with ether, and the precipitate was filtered, washed carefully with ether, and dried. We obtained (VIb-e, g).

Cleavage of Pyridinium Salts

We dissolved 2 mmoles of (VIb, c, e) in a mixture of 20 ml of water and 10 ml of ethanol, added 3 ml of a 10% sodium hydroxide solution, heated the mixture for 10 min on a boiling water bath, added activated carbon, and filtered the mixture. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate was filtered, washed with water, and dried. We obtained (VIIb) (VII), and (VIIe) in yields of 68, 64, and 65%, respectively; mp 141-142°, 133-134°, and 182-183°, respectively (from ethanol). Literature data: mp 141-142° [7], 133-134° [7], 183-184° [8], respectively.

2-(2-Aminothiazolyl-4)-5-R-thiophenes (IVa-g)

Method A. To a warm solution of 10 mmoles of (IIIa-g) in acetone was added all at once a warm solution of 0.76 g (10 mmoles) of thiourea in 40 ml of acetone. The mixture was boiled for 30 min and cooled; the precipitate was filtered, washed with acetone, and dried. Compounds (IVa-g) are obtained as their salts. The salt was suspended in a small amount of water and treated with aqueous ammonia. Bases (IVa-g) were filtered, washed with water, and dried.

The IR spectra of (IVa-g) contain bands corresponding to stretching vibrations of NH_2 in the 3432-3439, 3374-3288 cm^{-1} region; deformation vibrations of NH_2 in the 1622-1631 cm^{-1} region; vibrations of the thiazole ring in the 1484-1500, 1417-1427 cm^{-1} region; vibrations of the thiophene ring in the 1514-1530, 1343-1380, 1223-1266 cm^{-1} region [9-10].

Method B. To a mixture of 63.09 g of (IIa) and 76.1 g of thiourea with heating on a boiling water bath and energetic mixing was added in drops 79.9 g (25.6 ml) of bromine in 45-50 min. The reaction mixture was heated an additional 6 h on a boiling water bath and left overnight. The mixture was dissolved in 1400 ml of hot water and filtered; the filtrate was treated with activated carbon, filtered again, and neutralized with aqueous ammonia. The base was filtered, washed with water, and dried. We obtained 52.9 g of (IVa), from which extraction with hot cyclohexane yielded 50.1 g (55%) of (IVa), mp 130.5° (from cyclohexane).

Salts of (IVa). To a solution of (IVa) in acetone was added an equivalent amount of concentrated acid. The precipitate was filtered, washed with acetone, and dried. Salts of (IVa) are presented in Table 3.

2-(2-Acetaminothiazolyl-4)-5-R-thiophenes (V). A mixture of 15 mmoles of (IVa-d, f), 3 ml of acetic anhydride, and 5 ml of glacial acetic acid was boiled for 30 min, then cooled, and diluted with water. The precipitate was filtered, washed with water, and dried. We obtained (Va-d, f).

The IR spectra of (Va-d, f) contain bands in the 3151-3157 cm^{-1} region (NH of amide in cis-configuration) and in the 1639-1640 cm^{-1} region (amide C=O [9]). IR spectra were taken on an IKS-14 instrument in pellets with potassium bromide in the 3700-660 cm^{-1} region.

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