SYNTHESIS OF 2-AMINO-4-(2-THIENYL)THIAZOLE AND ITS DERIVATIVES

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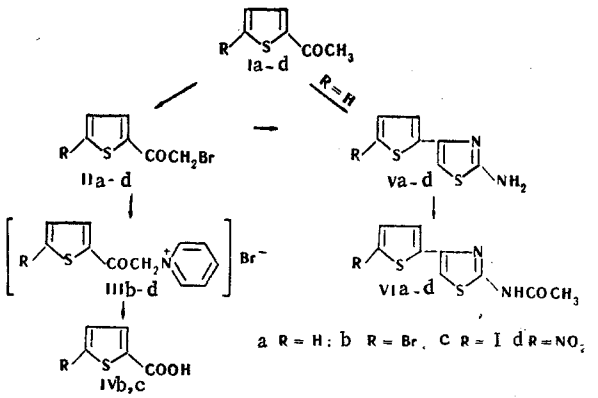
The bromination of substituted methyl 2-R-thienyl ketones with bromine in chloroform yielded bromomethyl 2-thienyl ketones. The latter were converted to quaternary pyridinium salts and 2-amino-4-(2-thienyl)thiazoles.

There has as yet been no systematic study of thienylthiazoles, and only individual representatives of compounds of this type are known [1,2], although many heteryl-substituted thiazoles are known to be physiologically active substances [3]. In addition, several thiophene derivatives also have known activity [4]. It therefore seemed of interest to us to synthesize several representatives of a new diheterocyclic system containing thiophene and thiazole rings for biological investigation. The starting bromomethyl ketones (IIa-d) were obtained by the bromination of methyl ketones Ia-d in chloroform at 20°C. The structures of IIb-d were confirmed by conversion to pyridinium salts IIIb-d and cleavage of the latter in alkali to the corresponding carboxylic acids (IV) by the method in [5]. Compound IIId proved to be an exception, since 5-nitrothiophene-2-carboxylic acid could not be isolated by alkaline cleavage.



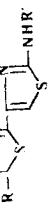
The corresponding aminothiazoles (Va-d) (see Table 1) were obtained by the reaction of IIa-d with thiourea. The hydrobromides of Vb-d are readily converted to bases on heating in alcohol, and mixtures of the bases and their hydrobromides are therefore obtained when the reaction is carried out in alcohol. The pure hydrobromides are conveniently obtained by using dry acetone as the solvent (method A). 2-Amino-4-(2-thienyl)thiazole (Va) was also obtained by treating a mixture of Ia and thiourea with bromine (method B).

The 2-acetamido-4-(2-thienyl)thiazoles (VIa-d) (see Table 1) are insoluble in water and quite soluble in aqueous alkali solutions.

Compound Va has selective antimicrobial activity with respect to several microorganisms. The introduction of bromine or iodine into the α position of the thiophene ring is accompanied by complete loss of the antimicrobial activity, while the selective antimicrobial activity is retained when a nitro group is introduced (Vd). The hydrobromides of Va-d are only slightly active, while the N-acetamido derivatives (VIa-d) are inactive with respect to the tests adopted for the microorganisms. The authors thank P. I. Buchin for his investigations of the antimicrobial activity of the synthesized compounds.

V. V. Kuibyshev Kuibyshev Polytechnic Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1369-1371, October, 1971. Original article submitted November 26, 1970.

TABLE 1



Compound	R	R′	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	S	C	H	S	
Va	H	H	130,5*	$C_7H_6N_2S_2$	46,0	3,5	35,3	46,1	3,3	35,2	85†
Vb	Br	H	148	$C_7H_5BrN_2S_2$	31,9	1,7	24,7	32,2	1,9	24,5	90
Vc	I	H	163	$C_7H_5IN_2S_2$	27,5	1,4	21,0	27,3	1,6	20,8	96
Vd	NO_2	H	267—269 (dec.)	$C_7H_5N_3O_2S_2$	37,1	2,1	28,1	37,0	2,2	28,2	91
Va·HBr	H	H	218	$C_7H_6N_2S_2$ HBr	32,2	2,9	24,6	32,0	2,7	24,4	88†
Vb·HBr	Br	H	190 ‡	$C_7H_5BrN_2S_2$ HBr	24,3	1,6	19,0	24,6	1,8	18,7	94
Vc·HBr	I	H	201—202 ‡	$C_7H_5IN_2S_2$ HBr	21,4	1,4	16,3	21,6	1,5	16,5	99
Vd·HBr	NO_2	H	230—232 ‡ (dec.)	$C_7H_5N_3O_2S_2$ HBr	27,5	2,1	20,8	27,3	2,0	20,8	94
VIa	H	$COCH_3$	210	$C_9H_8N_2OS_2$	48,4	3,8	28,4	48,2	3,6	28,6	98
VIb	Br	$COCH_3$	253	$C_9H_7BrN_2OS_2$	35,8	2,1	21,0	35,6	2,3	21,1	96
VIc	I	$COCH_3$	231	$C_9H_7IN_2OS_2$	30,6	1,8	18,5	30,8	2,0	18,3	97
VId	NO_2	$COCH_3$	335—340 (with charring)	$C_9H_7N_3O_3S_2$	40,3	2,4	23,7	40,1	2,6	23,8	94

* From cyclohexane.
† Yield via method A.
‡ Not recrystallized because of ready hydrolysis in water and alcohol. The remaining compounds were recrystallized from ethanol.

EXPERIMENTAL

Bromomethyl 5-Bromo-2-thienyl Ketone (IIb). A solution of 4 g (25 mmole) of bromine in 10 ml of chloroform was added to 5.13 g (25 mmole) of Ib in 20 ml of chloroform. The reaction was initiated by adding several drops of the bromine solution and heating the reaction mixture to 45-50° until the bromine coloration disappeared. The remaining amount of bromine was introduced in the course of 15-20 min at 20°. The mixture was stirred for another 30 min, and the solvent was removed by vacuum distillation. The residue (7.1 g, mp 80-82°) was recrystallized from ethanol in the presence of activated charcoal to give 4.8-5.1 g (68-72%) of large, colorless needles of IIb with mp 89-90°. Found: C 25.1; H 1.3; S 11.1%. $C_6H_4Br_2OS$. Calculated: C 25.4; H 1.4; S 11.3%.

Bromomethyl 5-Iodo-2-thienyl Ketone (IIc). This compound was similarly obtained in 60-64% yield and had mp 102° (from ethanol). Found: C 21.5; H 1.3; S 9.5%. C_6H_4IBrOS. Calculated: C 21.8; H 1.2; S 9.7%.

Bromomethyl 5-Nitro-2-thienyl Ketone (IId). This compound was similarly obtained in 60% yield and had mp 102-103° (from ethanol). Found: C 28.5; H 1.4; S 3.0%. $C_6H_4BrNO_3S$. Calculated: C 28.8; H 1.6; S 12.8%.

1-[(5-Bromo-2-thenoyl)methyl]pyridinium Bromide (IIIb). Dry pyridine (2 ml) was added to 0.57 g (2 mmole) of IIb, and the mixture was heated until a copious precipitate formed. The precipitate was removed by filtration, washed thoroughly with ether, and dried to give 0.67 g (92%) of IIIb with mp 210° (from water). Found: C 36.6; H 2.6; S 8.6%. $C_{11}H_9Br_2NOS$. Calculated: C 36.4; H 2.5; S 8.8%.

Compound IIIc was similarly obtained in 90% yield and had mp 226-228° (from water). Found: C 32.4; H 2.4; S 7.7%. $C_{11}H_9IBrNOS$. Calculated: C 32.2; H 2.2; S 7.8%.

Cleavage of Pyridinium Salt IIIb. A total of 3 ml of a 10% sodium hydroxide solution was added to a solution of 0.72 g (2 mmole) of IIIb in a mixture of 10 ml of ethanol and 20 ml of water, and the mixture was heated for 10 min on a boiling-water bath. Activated charcoal was added, and the mixture was filtered. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate was removed by filtration, washed with cold water, and dried to give 0.28 g (68%) of IVb with mp 141-142° (from ethanol) [6]. This product did not depress the melting point of the compound obtained by the method in [6].

Pyridinium salt IIIc was similarly cleaved to give 64% of IVc with mp 133-134° (from ethanol [6]).

2-Amino-4-(2-thienyl)thiazoles (Va-d). Method A. A solution of 0.76 g (10 mmole) of thiourea in 40 ml of acetone was added all at once to a solution of 10 mmole of IIa-d in 10 ml of acetone. The mixture was refluxed for 30 min and cooled. The precipitate was removed by filtration, washed with acetone, and dried to give the hydrobromide of V. The hydrobromide was suspended in a small amount of water and treated with ammonium hydroxide. Base V was removed by filtration, washed with water, and dried (see Table 1).

Bands corresponding to the NH_2 stretching vibrations at 3430-3440 and 3275-3290 cm^{-1}, to H_2N deformation vibrations at 1620-1630 cm^{-1}, to thiazole ring vibrations at 1550 and 1415-1425 cm^{-1}, and to thiophene ring vibrations at 1515-1525, 1345-1380, and 1225-1260 cm^{-1} [7, 8] are observed in the IR spectra of Va-d.

Method B. Bromine [79.9 g (0.5 mole)] was added dropwise in the course of 45-50 min to a mixture of 63.09 g (0.5 mole) of Ia and 76.1 g (1 mole) of thiourea with heating on a boiling-water bath and vigorous stirring. The reaction mixture was heated for another 6 h on a boiling-water bath and allowed to stand overnight. The mixture was dissolved in 1400 ml of hot water and filtered. The filtrate was treated with activated charcoal, filtered again, and neutralized with ammonium hydroxide. The base was removed by filtration, washed with water, and dried to give 52.9 g (58%) of product. The product was treated with hot cyclohexane, and 50.1 g (55%) of Va as slightly greenish needles with mp 130.5° was isolated from the cyclohexane extracts.

2-Acetamido-4-(2-thienyl)thiazoles (VIa-d). A mixture of 15 mmole of Va-d, 3 ml of acetic anhydride, and 5 ml of glacial acetic acid was refluxed for 30 min, cooled, and diluted with water. The precipitate was removed by filtration, washed with water, and dried to give VIa-d (see Table 1). Bands at 3150-3157 cm^{-1} (amide HN) and at 1640-1645 cm^{-1} (amide CO) [7] are observed in the IR spectra of VIa-d.

The IR spectra of KBr pellets were measured with an IKS-14 spectrometer.

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