3. Yu. G. Basova, S. M. Ramsh, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 8, 1046 (1981).
4. E. M. Peresleni, Yu. N. Sheinker, and N. P. Zosimova, Zh. Fiz. Khim., 39, 926 (1965).
5. A. A. Tsurkan, A. I. Frolova, N. I. Pospelov, and L. A. Dorofeeva, Khim.-Farm. Zh., No. 6, 12 (1975).
6. I. I. Chizhevskaya, A. I. Kharchenko, and N. N. Khovratovich, Khim. Geterotsikl. Soedin., No. 4, 642 (1967).
7. F. C. Brown, Chem. Rev., 61, 463 (1961).
8. T. Ueda, S. Kato, and S. Toyoshima, Japanese Patent No. 7811; Chem. Abstr., 54, 4620 (1960).
9. E. Akerblom, Acta Chem. Scand., 21, 843 (1967).
10. S. M. Ramsh, N. A. Smorygo, A. I. Ginak, and E. G. Sochilin, Zh. Org. Khim., 15, 1506 (1979).
11. F. B. Dains, L. M. Kinsett, C. O. Holmberg, and C. C. Robinson, Kansas Univ. Sci. Bull., No. 2, 15 (1936).
12. H. L. Wheeler and T. B. Johnson, Am. Chem. J., 28, 121 (1902).
13. R. Silverstein, G. Bassler, and T. Morrill, Spectrometric Identification of Organic Compounds, Wiley (1974).
14. A. N. Nesmeyanov and M. I. Kabachnik, Zh. Obshch. Khim., 25, 41 (1955).

BROMINATION OF 4-(2-THIENYL)THIAZOLES AND 2-(2-THIENYL)QUINOLINE

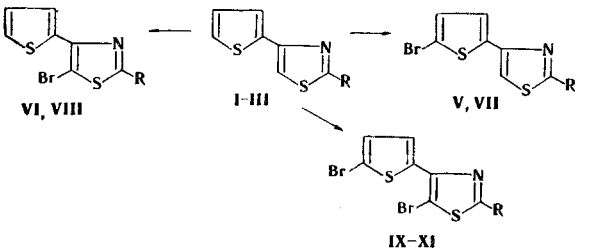
V. A. Smirnov, A. V. Zimichev, G. A. Lyzhova, and A. E. Lipkin

UDC 547.712.2'732'789'831:542.944.2:543.422

Depending on the substituent, the bromination of 4-(2-thienyl)thiazoles and 2-(2-thienyl)quinoline takes place in the 5 position of the thiophene or thiazole ring. When an amino group is present in the 2 position of the thiazole ring, bromination takes place in the 5 position of the thiazole ring. When excess brominating agent is present, a second bromine atom enters the 5 position of the free ring.

It is known that thiazole and its homologs with an unsubstituted 2 position are brominated with difficulty by both bromine and N-bromosuccinimide (NBS) [1-3]. Depending on the nature of the substituent in the 4 position, in the bromination of 2-amino- and 2-acetamidothiazoles bromine either enters the 5 position of the thiazole ring, or substitution takes place in the substituent [4-6]. At the same time, the bromination of thiophene and its homologs takes place readily and primarily in the α position of the ring [7-10].

In the present research we studied the bromination of 4-(2-thienyl)thiazole (I) and its 2-amino (II) and 2-acetamido (III) derivatives, as well as 2-(2-thienyl)quinoline (IV), with bromine and NBS in glacial acetic acid or acetic anhydride at 20, 40, 60, and 80°C.



We have previously shown [10] that the addition of acetic anhydride to glacial acetic acid in the bromination of thiophene with NBS leads to a 16% increase in the yield of 2-bromothiophene. We observed a similar effect in the bromination of I-IV: The yields of bromo deriva-

Kuibyshev Polytechnic Institute, Kuibyshev 443645. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 35-38, January, 1982. Original article submitted October 30, 1980.

 0009-3122/82/1801-0028$07.50

tives were 8-12% higher than in the case of the reaction without acetic anhydride. The initial products in the bromination of I and IV with bromine at 20°C are perbromides, which are slowly converted to monobromides V and XVII, and the bromination of I and IV is therefore effective only at temperatures above 40°C, under which conditions the perbromides are rapidly converted to monobromo-substituted compounds. A change in the reaction temperature from 20°C to 80°C has virtually no effect on the composition of the bromination products. The nature of the substituent has a decisive effect on the direction of substitution in monobromination. In the case of bromination of I and IV with one equivalent of bromine or NBS the halogen enters the 5 position of the thiophene ring. An increase in the nucleophilicity of the substituent by the introduction of an acetamido group in the 2 position leads to the formation of a mixture of monobromo-substituted compounds that contain halogen in the 5 position of both the thiophene (VII) and thiazole (VIII) rings. The introduction of an amino group (II) in the case of monobromination orients substitution exclusively in the thiazole ring. The bromination of I-III with a twofold amount of bromine or NBS leads to the formation of dibromides that contain bromine atoms in the 5 positions of the thiophene and thiazole rings (IX-XI) (see Table 1).

The structures of the products of bromination of I-IV were proved by alternative synthesis from the corresponding bromothienyl ketones and their bromomethyl-substituted derivatives.

Data from the PMR spectra of the compounds described in this paper are presented in Table 2. In the assignment of the signals in the PMR spectra we took into account the literature data on the effect of the substituents on the chemical shifts of the protons of the thiophene ring and the low sensitivity of the spin–spin coupling constants in thiophenes to a change in the character of the substituents [11]. For comparison, we synthesized XIII-XVI.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with an SF-4a spectrophotometer. The ratios of the isomers in the mixtures of crude products of the bromination of I-III were determined from data from the PMR spectra obtained from solutions in dimethyl sulfoxide (DMSO) with an RYa-2306 spectrometer (60 MHz) with tetramethylsilane (TMS) as the internal standard or, in the case of the products of bromination of IV, with a Tesla BS-487C spectrometer (80 MHz) with trifluoroacetic acid as the solvent. The course of the reactions and the individuality of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates in benzene–methanol (9:1), benzene–ether (1:1), and chloroform–acetic acid–methanol (91:5:4) systems.

We have previously described the synthesis of I-IV [12, 13].

Bromomethyl 3-Bromo-2-thienyl Ketone. This compound, with bp 155-156°C (5.3 hPa) and n_D^{20} 1.6644, was obtained in 47% yield by the method used to prepare bromomethyl 5-bromo-2-thienyl ketone [10]. Found: C 25.3; H 1.1; S 11.1%. $C_6H_4Br_2OS$. Calculated: C 25.4; H 1.4; S 11.3%.

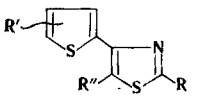
2-Amino-4-[5(and 4)-bromo-2-thienyl]thiazoles (XII, XIII). A solution of 0.76 g (10 mmole) of thiourea in 40 ml of acetone was added to a solution of 10 mmole of the corresponding ketone in 10 ml of acetone, and the mixture was refluxed for 30 min. It was then cooled, and the precipitate was removed by filtration, washed with acetone, and dried. The hydrobromide obtained was suspended in a small amount of water and neutralized with ammonia. The amine was removed by filtration, washed with water, and dried (see Table 1).

2-Amino-4-(3-bromo-2-thienyl)thiazole (XIV). A mixture of 2.84 g (10 mmole) of the ketone, 0.76 g (10 mmole) of thiourea, and 50 ml of acetone was refluxed for 1 h, after which it was cooled, and the acetone was decanted. Concentrated HCl (20 ml) was added to the oily residue, and the mixture was refluxed for 30 min, cooled, and neutralized with ammonia. The precipitate was removed by filtration, washed with water, and dried (see Table 1).

Bromination of I-III with Bromine. A solution of 1.6 g (10 mmole) of bromine in 5 ml of glacial acetic acid was added dropwise at 20°C to a solution of 10 mmole of I-III in 40 ml of glacial acetic acid, and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The precipitate was separated, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

Bromination of I-III with N-Bromosuccinimide (NBS). A 1.82-g (10.2 mmole) sample of NBS was added at 20°C to a solution of 10 mmole of I-III in 20 ml of a mixture of acetic anhydride

TABLE 1. Bromo Derivatives of 4-(2-Thienyl)thiazoles



Compound	R	R′	R″	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
					C	H	S		C	H	S	
V	H	5-Br	H	74—75	34,0	1,9	25,9	$C_7H_4BrNS_2$	34,2	1,6	26,1	95
VI	NH_2	H	Br	114—115	32,6	2,0	24,7	$C_7H_5BrN_2S_2$	32,2	1,9	24,5	70
VII	$NHCOCH_3$	5-Br	H	261	35,8	2,4	21,0	$C_9H_7BrN_2OS_2$	35,6	2,3	21,1	96
VIII	$NHCOCH_3$	H	Br	241	35,8	2,4	21,4	$C_9H_7BrN_2OS_2$	35,6	2,3	21,1	96
IX	H	5-Br	Br	63—64	26,1	1,1	19,8	$C_7H_3Br_2NS_2$	25,9	0,9	19,7	98
X	$NHCOCH_3$	5-Br	Br	258	28,4	1,7	17,0	$C_9H_6Br_2N_2OS_2$	28,3	1,6	16,8	96
XI	NH_2	5-Br	Br	161—162	25,0	1,3	19,1	$C_7H_4Br_2N_2S_2$	24,7	1,2	18,9	97
XII	NH	5-Br	H	151	32,4	2,1	24,7	$C_7H_5BrN_2S_2$	32,2	1,9	24,5	90
XIII	H	4-Br	H	158	32,5	1,9	24,6	$C_7H_5BrN_2S_2$	32,2	1,9	24,5	93
XIV	H	3-Br	H	148—150	32,5	2,1	24,3	$C_7H_5BrN_2S_2$	32,2	1,9	24,5	72
XV	$NHCOCH_3$	4-Br	H	254	35,8	2,5	20,8	$C_9H_7BrN_2OS_2$	35,6	2,3	21,1	97
XVI	$NHCOCH_3$	3-Br	H	255—256	36,0	2,6	20,9	$C_9H_7BrN_2OS_2$	35,6	2,3	21,1	98

TABLE 2. PMR Spectra of 4-(2-Thienyl)thiazoles

Compound	Chemical shifts, ppm						Spin–spin coupling constants, Hz			
	5′-H	4′-H	3′-H	5-H	2-H	NH_2	5′4′	4′3′	5′3′	5′2
I	7,31	6,97	7,48	7,64	8,97	—	5,0	3,6	1,2	2,1
II	7,19	6,84	7,19	6,62	—	6,99	5,2	3,8	1,0	—
III	7,31	6,92	7,34	7,23	—	—	5,3	3,4	1,1	—
V	—	6,99	7,21	7,74	8,94	—	—	4,0	—	2,0
VI	7,37	6,95	7,56	—	—	7,22	5,4	3,6	1,0	—
VII	—	7,01	7,16	7,28	—	—	—	4,2	—	—
VIII	7,47	7,00	7,64	—	—	—	5,2	3,7	1,3	—
IX	—	7,06	7,44	—	9,00	—	—	4,0	—	—
X	—	7,09	7,40	—	—	—	—	4,2	—	—
XI	—	7,06	7,34	—	—	7,29	—	4,1	—	—
XII	—	6,98	7,06	6,72	—	7,06	—	3,8	—	—
XIII	7,26	—	7,33	6,81	—	7,03	—	—	1,5	—
XIV	7,34	6,95	—	7,10	—	4,4	5,5	—	—	—
XV	7,38	—	7,43	7,40	—	—	—	—	1,1	—
XVI	7,46	7,01	—	7,64	—	—	5,3	—	—	—

and glacial acetic acid (1:1), and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The acetic anhydride was hydrolyzed, and the precipitate was removed by filtration, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

5-Bromo(5-bromo-2-thienyl)-2-R-thiazoles (IX, X, and XI). A) A solution of 1.6 g (10 mmole) of bromine in 5 ml of glacial acetic acid was added dropwise at 20°C to a solution of 10 mmole of V-VIII in 50 ml of acetic acid, and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The precipitate was separated, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

B) A 1.82-g (10.2 mmole) sample of NBS was added at 20°C to a solution of 10 mmole of V-VIII in 50 ml of a mixture of acetic anhydride with acetic acid (1:1), and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The acetic anhydride was hydrolyzed, and the precipitate was removed by filtration, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

C) A solution of 3.2 g (20 mmole) of bromine in 5 ml of glacial acetic acid was added dropwise at 20°C to a solution of 10 mmole of I-III in 30 ml of acetic acid, and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The precipitate was separated, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

D) A 3.6-g (20.2 mmole) sample of NBS was added at 20°C to a solution of 10 mmole of I-III in 50 ml of a mixture of acetic anhydride and acetic acid (1:1), and the mixture was maintained at 20°C for 30 min, after which it was poured into water. The acetic anhydride was hy-

drolyzed, and the precipitate was removed by filtration, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

2-(5-Bromo-2-thienyl)quinoline (XVII). A) A solution of 0.8 g (5 mmole) of bromine in 2.5 ml of acetic acid was added dropwise at 20°C to a solution of 0.53 g (2.5 mmole) of IV in 10 ml of acetic acid, and the mixture was maintained at 20°C for 1 h, after which it was poured into water and neutralized. The precipitate was removed by filtration, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

B) A 0.91-g (5.01 mmole) sample of NBS was added at 20°C to a solution of 0.53 g (2.5 mmole) of IV in 10 ml of a mixture of acetic anhydride with acetic acid (3:1), and the mixture was maintained at 20°C for 1 h, after which it was poured into water and neutralized with ammonia. The precipitate was removed by filtration, washed with water, dried, and analyzed. Bromination was carried out similarly at 40, 60, and 80°C.

C) A solution of 1.21 g (10 mmole) of 2-aminobenzaldehyde in 10 ml of alcohol and 10 mg of solid KOH were added to a solution of 2.05 g (10 mmole) of 5-bromoacetylthiophene in 10 ml of alcohol, and the mixture was refluxed for 1 h. Warm water was added dropwise to the hot solution until it became turbid, and the mixture was allowed to stand for crystallization. Workup gave 2.6 g (92.8%) of a product with mp 106-108°C (from aqueous alcohol). Found: C 59.5; H 3.0; S 11.7%. $C_{13}H_8BrNS$. Calculated: C 59.3; H 2.8; S 11.8%.

2-(4-Bromo-2-thienyl)quinoline (XVIII). This compound, with mp 128-130°C (from aqueous alcohol), was obtained in 95% yield by a method similar to that used to obtain XVII. Found: C 59.3; H 2.7; S 11.8%. $C_{13}H_8BrNS$. C 59.3; H 2.8; S 11.8%.

LITERATURE CITED

1. J. Wibaut and H. Jansen, Rec. Trav. Chim., 53, 77 (1934).
2. K. Ganapathi and K. Kulkarni, Curr. Sci. (India), 21, 314 (1952).
3. B. M. Mikhailov and V. P. Bronovitskaya, Zh. Obshch. Khim., 27, 726 (1957).
4. J. Garrean, Bull. Soc. Chim. Fr., No. 3, 564 (1954).
5. G. N. Mahapatra, J. Indian Chem. Soc., 33, 527 (1956).
6. E. P. Krysin, L. S. Krysina, and V. M. Ivanov, Tr. Vses. Nauchn. Issled. Inst. Khim. Reakt. Osobo Chistykh Khim. Veshchestva, No. 32, 73 (1970).
7. S. Clementi, P. Linda, and G. Marino, J. Chem. Soc., B, No. 6, 1153 (1970).
8. N. Buu-Hoi, Lieb. Ann., 556, 1 (1944).
9. R. Dittmer, R. Martin, W. Herz, and S. Cristol, J. Am. Chem. Soc., 71, 1201 (1949).
10. V. A. Smirnov and A. E. Lipkin, USSR Inventor's Certificate No. 341800; Byull. Izobret., No. 19, 101 (1972).
11. A. Katritzky, Physical Methods in the Chemistry of Heterocyclic Compounds, Academic Press (1963).
12. V. A. Smirnov and A. E. Lipkin, Khim. Geterotsikl. Soedin., No. 10, 1369 (1971).
13. A. V. Zimichev and A. E. Lipkin, in: The Structure and Properties of Molecules [in Russian], Kuibyshev (1976), p. 133.