THE BROMINATION OF 2-AMINO- AND 2-ACETYLAMINO-4-(2-FURYL)-THIAZOLES

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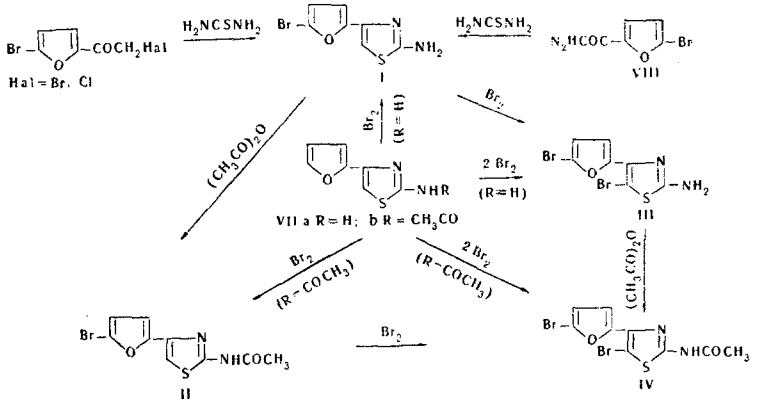
The bromination of 2-amino- and 2-acetylamino-4-(2-furyl)thiazoles has been studied, and it has been shown that bromination takes place first in the furan ring and then, with an excess of bromine, also in the thiazole ring in position 5.

It is known [1–3] that 4-substituted 2-aminothiazoles generally brominate readily in position 5 of the thiazole ring. However, in the bromination of 2-amino- and 2-acetylamino-4-(2-furyl)thiazoles (VIIa, b) the nature of the substituent, i.e., the furan ring, must naturally exert a fundamental influence on the direction of the reaction.

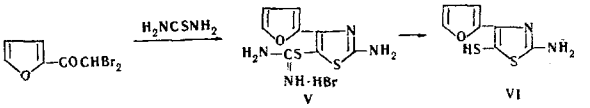


With the aid of chromatography, UV and PMR spectra, and independent synthesis we have shown that the bromination of VIIa and VIIb with an equimolecular amount of bromine takes place in position 5 of the furan ring. The constants of samples of 2-amino-4-(5-bromo-2-furyl)thiazole (I) obtained by the direct bromination of VIIa and by the reaction of 5-bromo-2-(halogenoacetyl)furans and 5-bromo-2-diazoacetylfuran (VIII) with thiourea, and also the constants of their derivatives, coincided completely.

2-Amino-5-bromo-4-(5-bromo-2-furyl)thiazole (III) and the corresponding 2-acetylamino compound (IV) were obtained both by brominating VIIa and VIIb and by brominating I and 2-acetylamino-4-(5-bromo-2-furyl)-thiazole (II). Compound IV was also obtained by the acetylation of III.

By analogy with Földi's work [4], we attempted by the reaction of 2-(dibromoacetyl)furan with thiourea to obtain 2-amino-5-bromo-4-(2-furyl)thiazole, but instead of this we isolated the thiouronium salt V. In ammoniacal solution, the latter is readily converted into 2-amino-4-(2-furyl)-5-mercaptothiazole (VI).

It may be assumed that 2-amino-5-bromo-4-(2-furyl)thiazole is formed first, but since halogen in position 5 of the 2-aminothiazoles is usually fairly mobile [5, 6], it immediately forms a thiouronium salt with an excess of thiourea, and from this the mercapto derivative can then be obtained.



The action of thiourea on I did not lead to the formation of thiouronium salts. This shows that bromine in position 5 of the furan ring is not mobile. When 5-bromo-2-(dibromoacetyl)furan was condensed with thiourea and the product was hydrolyzed with aqueous ammonia, a compound containing bromine and a mercapto group was obtained. In view of what has been said above, it may be assumed that the replacement of bromine by a mercapto group took place in the thiazole ring and not in the furan ring.

EXPERIMENTAL

2-Amino-4-(5-bromo-2-furyl)thiazole (I). a) With stirring, a solution of 4.8 g (30 mM) of bromine in 10 ml of glacial acetic acid was added dropwise at 40° C to 4.99 g (30 mM) of VIIa in 230 ml of glacial acetic acid, and the mixture was heated to 65° C, stirred for 10 min, and then left overnight. The excess acetic acid was distilled off in vacuum. The residue was treated with dilute aqueous ammonia. Yield 5.6 g (76%); mp 163–164° C (from ethanol). R_f 0.66 (system 1)*; R_f 0.62 (system 2). PMR spectrum**: $\tau \approx 6.4$ ppm (NH_2, broad singlet); $\tau = 3.35$ ppm (3, 4-H of a furan ring, singlet); $\tau = 3.16$ ppm (5-H of a thiazole ring, singlet); ratio of the intensities 2:2:1. λ_{max}, nm

*System 1: silica gel, benzene–alcohol (1:3); system 2: silica gel, methanol–chloroform (1:9).

**Working frequency, 40 MHz; solvent, dimethyl sulfoxide; internal standard cyclohexane.

(log ε)*: 247 (4.35), 293 (4.16). Found, %: C 34.26; H 2.16; Br 33.03; N 11.38. Calculated for $C_7H_5BrN_2OS$, %: C 34.30; H 2.06; Br 32.61; N 11.44.

b) A solution of 2.2 g (10 mM) of VIII in 20 ml of ethanol was treated with a solution of 0.76 g (10 mM) of thiourea in 25 ml of ethanol, and the mixture was boiled for 6 hr and left to stand overnight. Then 100 ml of water and 50 ml of 25% aqueous ammonia were added. The precipitate was filtered off. Yield 1.94 g (78%); mp 163–164° C (from ethanol). R_f 0.66 (system 1); R_f 0.62 (system 2). PMR spectrum: $\tau \approx 6.4$ ppm (NH_2, broad singlet); $\tau = 3.35$ ppm (3,4-H of a furan ring, singlet); $\tau = 3.16$ ppm (5-H of a thiazole ring, singlet); ratio of the intensities 2:2:1. λ_{max}, nm (log ε): 247 (4.35), 293 (4.17).

c) A solution of 6.7 g (30 mM) of 5-bromo-2-(chloroacetyl)furan or the corresponding amount of 5-bromo-2-(bromoacetyl)furan in 30 ml of ethanol was treated with a solution of 2.3 g (30 mM) of thiourea in 50 ml of ethanol. After 5 minutes' boiling, 100 ml of water and 5 ml of 25% aqueous ammonia were added. Yield 5.16 g (70%); mp 163–164° C (from ethanol).

The hydrochloride of I. This was obtained in a similar manner to I by method (c) but without the treatment with aqueous ammonia, with a yield of 60%. Mp 185–187° C (from anhydrous ethanol). Found, %: C 29.50; H 2.26; N 10.05; S 11.61. Calculated for $C_7H_5BrN_2OS \cdot HCl$, %: C 29.86; H 2.15; N 9.95; S 11.39.

Hydrobromide of I. This was obtained in a similar manner to I by methods (a) and (c) but without the treatment with aqueous ammonia, with a yield of 90%. Mp 169–171° C (decomp., from CH_3COOH). Found, %: C 25.88; H 1.99; Br 48.63; N 8.45. Calculated for $C_7H_5BrN_2OS \cdot HBr$, %: C 25.79; H 1.86; Br 49.02; N 8.59.

Picrate of I. Obtained from I by methods (a) and (b). Mp 206–208° C (from ethanol). Found, %: C 33.01; H 1.91; N 14.85. Calculated for $C_7H_5BrN_2OS \cdot C_6H_2(NO_2)_3OH$, %: C 32.92; H 1.70; N 14.77.

2-Acetylamino-4-(5-bromo-2-furyl)thiazole (II). a) A solution of 2.69 g (11 mM) of I obtained by method (a) or (b) in 50 ml of glacial acetic acid was treated with 2.25 g (22 mM) of acetic anhydride and boiled for 4 hr. Yield 2.98 g (95%). Mp 215° C (from CH_3COOH). R_f 0.79 (system 1); R_f 0.69 (system 2). λ_{max}, nm (log ε): 250 (4.30), 276 (4.36). Found, %: C 37.67; H 2.39; Br 28.09; N 9.32. Calculated for $C_9H_7BrN_2O_2S$, %: C 37.64; H 2.46; Br 27.83; N 9.76.

b) A solution of 8.3 g (40 mM) of VIIb in 300 ml of glacial acetic acid was treated with 6.4 g (40 mM) of bromine in 20 ml of glacial acetic acid. The further operations were similar to the preparation of I by method (a). Yield 9.62 g (84%). Mp 215° C (from CH_3COOH). R_f 0.79 (system 1); R_f 0.69 (system 2). λ_{max}, nm (log ε): 250 (4.30); 276 (4.36).

2-Amino-5-bromo-4-(5-bromo-2-furyl)thiazole (III). a) A solution of 2.9 g (12 mM) of I in 65 ml of glacial acetic acid was treated with 1.92 g (12 mM of bromine in 20 ml of glacial acetic acid. The further procedure was similar to the preparation of I by method (a). Yield 2.8 g (73%). Mp 138° C (from ethanol). λ_{max}, nm (log ε): 250 (4.39), 300 (4.17). Found, %: C 25.71; H 1.20; Br 49.96; N 8.64. Calculated for $C_7H_4Br_2N_2OS$, %: C 25.95; H 1.24; Br 49.33; N 8.65.

b) A solution of 4.99 g (30 mM) of VIIa in 230 ml of glacial acetic acid was treated with 9.95 g (60 mM) of bromine in 20 ml of glacial acetic acid. The further procedure was as for the preparation of I by method (a). Yield 8.6 g (88%). Mp 138° C (from ethanol). λ_{max}, nm (log ε): 250 (4.40), 300 (4.16).

Hydrobromide of III. This was obtained in similar manner to III, but without the neutralization with ammonia. Yield 90%; mp 171–173° C (decomp., from CH_3COOH). Found, %: C 20.96; H 1.22; Br 59.40; N 6.84; S 7.80. Calculated for $C_7H_4Br_2N_2OS \cdot HBr$, %: C 20.76; H 1.24; Br 59.21; N 6.92; S 7.92.

2-Acetylamino-5-bromo-4-(5-bromo-2-furyl)thiazole (IV). a) A solution of 3.24 g (10 mM) of III in 50 ml of acetic acid was treated with 1.42 ml (15 mM) of acetic anhydride and was boiled for 3 hr. The yield of product was 3.75 g (98%). Mp 225–226° C (from ethanol). Found, %: C 29.72; H 1.78; Br 43.96; N 7.80; S 8.70. Calculated for $C_9H_6Br_2N_2O_2S$, %: C 29.53; H 1.65; Br 43.66; N 7.65; S 8.76.

b) A solution of 2.08 g (10 mM) of VIIb in 150 ml of glacial acetic acid was treated with 3.2 g (20 mM) of bromine in 15 ml of glacial acetic acid. The subsequent procedure was similar to the preparation of I by method (c). Yield 3.06 g (84%). Mp 225–226° C (from ethanol).

S-[2-Amino-4-(2-furyl)thiazol-5-yl]thiouronium bromide (V). A mixture of 13.4 g (50 mM) of 2-(dibromoacetyl)furan and 7.6 g (100 mM) of thiourea in 70 ml of ethanol was boiled for 20 min. After cooling, a precipitate deposited. Yield 5.8 g (36%); mp 198–199° C (decomp., from ethanol). Found, %: C 29.84; N 2.83; N 17.33; S 20.11. Calculated for $C_8H_8N_4OS_2 \cdot HBr$, %: C 29.91; H 2.82; N 17.44; S 19.96.

2-Amino-4-(2-furyl)-5-mercaptothiazole (VI). A solution of 2.5 g of V in ethanol was treated with dilute aqueous ammonia. Yield 0.82 g (53%). Mp 169–171° C (decomp., from ethanol). Found, %: C 42.44; H 2.86; N 13.87; S 32.58. Calculated for $C_7H_6N_2OS_2$, %: C 42.40; H 3.05; N 14.13; S 32.35.

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*The UV spectra were taken on an SF-4 spectrophotometer in ethanolic solutions.

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