BROMINATION OF 2-THIAZOLYLHYDRAZONES

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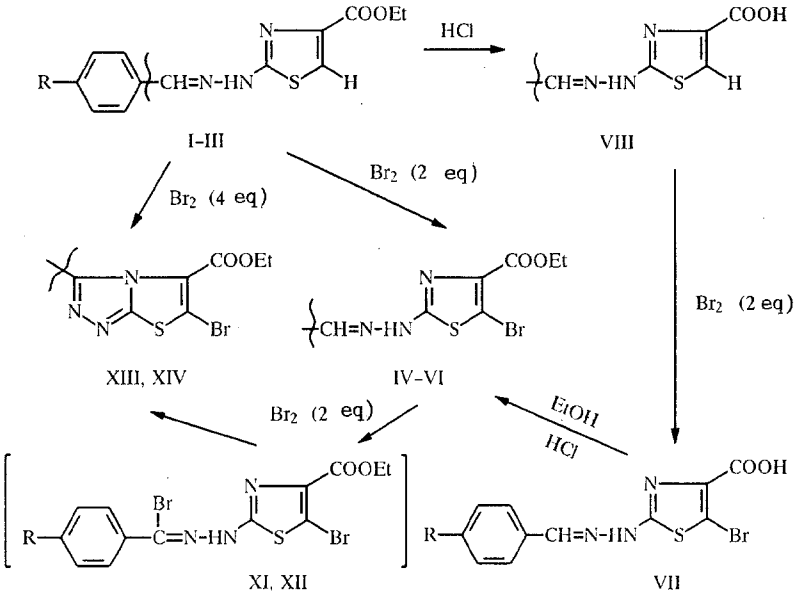
Bromination of the 4-carbethoxy- and 4-carboxy-2-thiazolylhydrazones of aldehydes and ketones occurs principally at the 5 position of the thiazole ring. In the case of aldehyde hydrazones an excess of bromine leads to substitution of the methine hydrogen atom and to intramolecular cyclization of the intermediate halohydrazone to 1,2,4-triazolo[3,4-b]thiazole.

Thiazole halohydrazones are of interest as precursors of biologically active compounds. We show that the bromination of some 4-carbethoxy- and 4-carboxy-2-thiazolylhydrazones can occur by substitution of the hydrogen both at the $C_{(5)}$ of the thiazole ring [1] and at the methine carbon atom [2].

The starting 2-benzylidene- (I) [3], 2-p-nitrobenzylidene- (II), and 2-p-methoxybenzylidenehydrazino-4-carbethoxythiazole (III) were prepared by treating ethyl bromopyruvate with thiosemicarbazide and the corresponding aldehyde in ethanol.

Treatment of I and II with two equivalents of bromine in acetic acid or chloroform leads to bromination at position 5 of the thiazole ring and formation of 2-benzylidene- (IV) and 2-p-nitrobenzylidenehydrazino-4-carbethoxy-5-bromothiazole (V), respectively. Bromination of the 2-p-methoxybenzylidene derivative (III) under various conditions gave a mixture of three compounds. One of these was identified as 2-p-methoxybenzylidenehydrazino-4-carbethoxy-5-bromothiazole (VI). This compound was also obtained by esterification of the 5-bromo derivative VII, which is the single reaction product from the bromination of 2-p-methoxybenzylidenehydrazino-4-carboxythiazole (VIII).



I, IV, XI, XIII R = H; II, V, XII, XIV R = NO_2; III, VI—VIII R = MeO

The structures of the compounds obtained were confirmed by spectroscopic data.

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TABLE 1. PMR Spectra of I-X and XIII-XXII

Compound	Chemical shift, δ, ppm (in DMSO-D_6)	
	5-H (1H, s)	other signals
I	7,74	8,0 (1H, c, HC=N); 7,7...7,3 (5H, m, Ph); 4,25 (2H, q, CH_2); 1,26 (3H, t, CH_3)
II	7,8	8,27 (2H,d, Ph); 8,13 (1H, s, HC=N); 7,9 (2H, d, Ph); 4,27 (2Hq., CH_2); 1,3 (3H, t, CH_3)
III	7,75	7,95 (1H, s, HC=N); 7,6 (2H, d, Ph); 7,0 (2H, d Ph); 4,25 (2H, q, CH_2); 3,8 (3H, s, OCH_3); 1,3 (3H, t, CH_3)
IV	—	8,0 (1H, s HC=N); 7,8...7,53 (2H, m, Ph); 7,5...7,3 (3H, m, Ph); 4,34 (2H, q CH_2); 1,35 (3H, t, CH_3)
V	—	8,27 (2H,d., Ph); 8,13 (1H, s, HC=N); 7,87 (2H,d., Ph); 4,3 (2H, q, CH_2); 1,3 (3H, т, CH_3)
VI	—	7,95 (1H, s HC=N); 7,6 (2H, d, Ph); 7,0 (2H, d Ph); 4,25 (2H, q, CH_2); 3,8 (3H, s OCH_3); 1,25 (3H, t, CH_3)
VII	—	7,97 (1H, s, HC=N); 7,6 (2H, d Ph); 6,95 (2H, d, Ph); 3,8 (3H, s, OCH_3)
VIII	7.65	8,0 (1H, s HC=N); 7,6 (2H, d Ph); 7,0 (2H, d Ph); 3,8 (3H, s, OCH_3)
IX	7,75	7,9...7,6 (2H, m, Ph); 7,55...7,3 (3H,m , Ph); 4,25 (2H, q CH_2); 2,35 (3H.s. CH_3); 1,26 (3H, t, CH_3)
X	7,52	8,7 (1H, s., NH); 4,8 (2H, s NH_2); 4,25 (2H,q., CH_2); 1,25 (3H, t, CH_3)
XIII*	—	7,52 (5H, s, Ph); 3,9 (2H,q , CH_2); 0,85 (3H, t, CH_3)
XIV	—	8,4 (2H,d , Ph); 7,9 (2H, d Ph); 3,95 (2H,q., CH_2); 0,85 (3H, t, CH_3)
XV	7,75	7,9 (1H,s., HC=N); 7,73...7,57 (2H, m, Ph); 7,5...7,27 (3H, m, Ph); 4,25 (2H,q., CH_2); 3,6 (3H,s, N—CH_3); 1,28 (3H, t, CH_3)
XVI	7,4	8,3 (1H, s HC=N); 7,8...7,6 (2Hm., Ph); 7,5...7,2 (3H,m., Ph); 4,27 (2H, q, CH_2); 3,63 (3H, s N—CH_3); 1,3 (3H, t, CH_3)
XVII	—	8,0 (1H,s , HC=N); 7,9...7,3 (5H,m , Ph); 4,3 (2H, q, CH_2); 3,6 (3H, s N—CH_3); 1,3 (3H,t., CH_3)
XVIII	7,7	7,8...7,2 (5H,m., Ph); 4,7 (2H,s., $BrCH_2$); 4,23 (2H, q, CH_2); 1,28 (3H, t, CH_3)
XIX	7,7	7,9...7,7 (2H,m , Ph); 7,57...7,3 (3H, m, Ph); 2,35 (3H,s., CH_3)
XX	—	7,8...7,2 (5H,m , Ph); 2,27 (3H, s, CH_3)
XXI	7,65	4,25 (2H, q, CH_2); 1,93 (3H, s, CH_3); 1,90 (3H,s , CH_3); 1,25 (3H, t, CH_3)
XXII	—	4,45...4,0 (4H, m, CH_2 + $BrCH_2$); 2,05 + 2,0 (3H, 2s, CH_3); 1,27 (3H, t, CH_3)

*$CDCl_3$ solvent.

The PMR spectra of the starting hydrazones I-III and VIII showed two one-proton signals to low field. By comparison with the spectra of the previously prepared [3, 4] 2-(1-phenyl)ethylidenehydrazino (XI) and 2-hydrazino-4-carbethoxythiazole (X) the singlet at lower field (δ= 8.0-8.15 ppm) can be assigned to the azomethine proton and the singlet at 7.7-7.8 ppm to the thiazole 5 proton.

In the PMR spectra of the bromo derivatives IV-VI and VII the signal for 5-H is absent and that for the azomethine proton is unchanged (see Table 1).

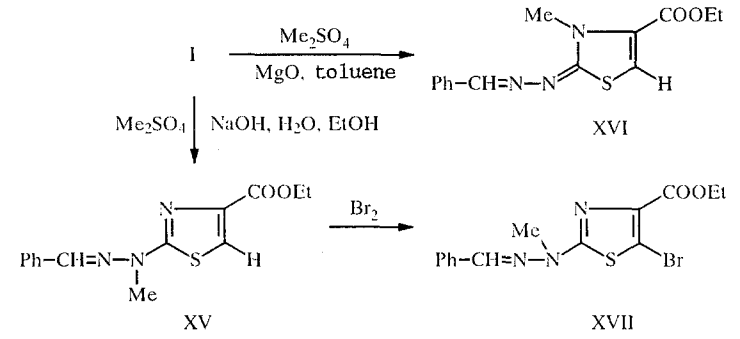
Further proof of the substitution position may be obtained from analysis of ^{13}C NMR spectroscopic data. Thus, the starting thiazole I shows carbon NMR signals for C=N, C=O, and for $C_{(2)}$, $C_{(4)}$, and $C_{(5)}$ which are split into doublets. In the spectrum of the 5-bromothiazole IV the azomethine carbon is also a doublet whereas the signals for the carbonyl carbon and the thiazole ring carbon are singlets. Moreover, halogen substitution causes the signal for $C_{(5)}$ to shift to higher field (δ = 104.72 ppm) than in the hydrazone I (δ = 118.8 ppm).

Further bromination of the 5-bromothiazoles IV and V and treatment of the 2-hydrazonothiazoles I and II with excess bromine (4-5 equivalents) in acetic acid leads to substitution on the methine carbon of the hydrazone fragment. However, the corresponding hydrazonyl bromides XI and XII under these reaction conditions undergo intramolecular cyclization to form an annelated 1,2,4-triazole ring. The reaction products were identified as 5-phenyl (XIII) and 5-p-nitrophenyl-2-bromo-3-carbethoxy-

1,2,4-triazolo[3,4-b]thiazole (XIV). This mechanism agrees with literature data [2, 5] concerning the intramolecular cyclization of hydrazonyl halides which contain a nucleophilic center in the molecule.

The PMR spectra of the triazolothiazoles XIII and XIV showed the absence of signals for the azomethine and thiazole protons. The signals for the ester protons were significantly shifted to higher field when compared with the analogous signals in the starting materials. The mass spectra of these derivatives show molecular ions (M^+ = 351, 353 for XIII and M^+ = 396, 398 for XIV) in agreement with the proposed structure.

We have studied the bromination of compounds for which cyclization to the annelated 1,2,4-triazole ring was not possible. We have synthesized hydrazones substituted on the nitrogen atom of the hydrazone or of the thiazole ring and also certain ketonic hydrazones.

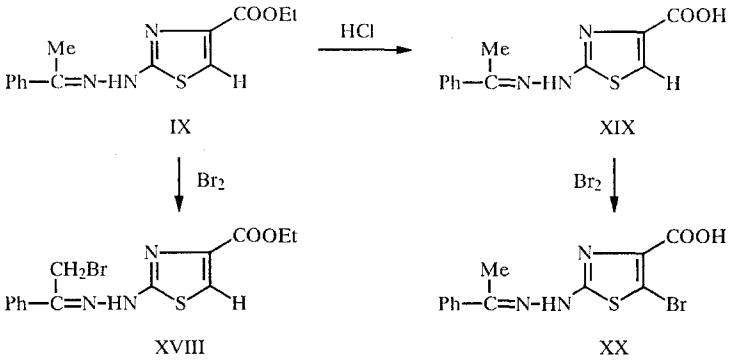


By alkylation of I using dimethyl sulfate in aqueous ethanol containing an equimolar amount of sodium hydroxide or in dry toluene with magnesium oxide (compare method [6]) we have obtained the isomeric 2-(N-benzylidene-N′-methyl)hydrazino-4-carbethoxythiazole (XV) and 2-benzylideneazino-3-N-methyl-4-carbethoxythiazoline (XVI).

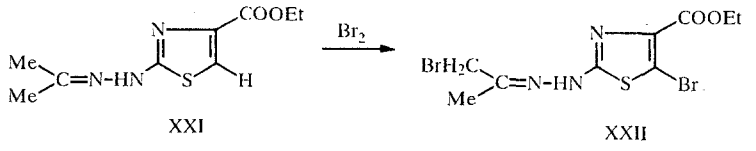
Bromination of thiazole XV in acetic acid both with two equivalents of bromine and in greater excess occurs only on the thiazole ring to give 2-(N-benzylidene-N′-methyl)hydrazino-4-carbethoxy-5-bromothiazole (XVII). Thiazole XVI is not brominated under these conditions.

Treatment of the acetophenone hydrazone IX with bromine in acetic acid leads to substitution of one of the methyl group hydrogens rather than the expected bromination at position 5 of the thiazole ring. The PMR spectrum of the obtained 2-(1-phenyl-2-bromo)ethylidenehydrazino-4-carbethoxythiazole (XVIII) shows signals for the protons of the thiazole ring and the $BrCH_2$ group.

By contrast, 2-(1-phenyl)ethylidenehydrazino-4-carbethoxythiazole (XIX) is readily brominated in the thiazole ring to form 2-(1-phenyl)ethylidenehydrazino-4-carboxy-5-bromothiazole (XX).



Bromination of 2-isopropylidenehydrazino-4-carbethoxythiazole (XXI) with two equivalents of bromine in chloroform gave simultaneous substitution at the thiazole 5 position and of a hydrazino methyl hydrogen to form 2-(1-bromomethyl)-ethylidenehydrazino-4-carbethoxy-5-bromothiazole (XXII).



This data shows that bromination of the thiazole hydrazone occurs preferentially at the 5 position of the thiazole ring.

EXPERIMENTAL

The reaction course and product purities were monitored by TLC on Silufol UV-254 plates using chloroform–ethanol (9:1) as eluting solvent. PMR spectra were obtained on a Perkin–Elmer R-12B instrument (60 MHz) and ^{13}C NMR spectra on a Bruker WH-90 (22.62 MHz) using TMS as internal standard and DMSO-D_6 as solvent. Mass spectra were measured on a Varian MAT-311A with an ionization energy of 70 eV and with direct introduction of the sample into the source.

2-Benzylidene (I), 2-(1-phenyl)ethylidenehydrazino-4-carbethoxythiazole (IX) and **2-(1-phenyl)ethylidenehydrazino-4-carboxythiazole (XIX)** were obtained as described in [3]. **2-Hydrazino-4-carbethoxythiazole (X)** and **2-isopropylidenehydrazino-4-carbethoxythiazole (XXI)** were synthesized by [4] and [7], respectively.

^{13}C NMR spectrum of **2-benzylidenehydrazino-4-carbethoxythiazole (I)**: 168.06 (d, ^3J = 8.54 Hz; C=O); 160.97 (d, ^3J = 8.32 Hz; $C_{(2)}$); 142.79 (d, ^1J = 32.2 Hz, HC=N); 141.89 (d, ^2J = 4.88 Hz; $C_{(4)}$); 134.13; 129.41; 128.74; 126.32 (phenyl); 118.80 (d, ^1J = 192.8 Hz; $C_{(5)}$); 60.28 (t.q, ^1J = 147.7 Hz; ^2J = 4.88 Hz; CH_2); 14.12 ppm (q.t, ^1J = 126.95 Hz; ^2J = 2.44 Hz; CH_3).

2-p-Nitrobenzylidenehydrazino-4-carbethoxythiazole (II, $C_{13}H_{12}N_4O_4S$). p-Nitrobenzaldehyde (8.3 g, 5.5 mmoles) and ethyl bromopyruvate (6.2 ml, 5.5 mmoles) were added to a suspension of thiosemicarbazide (5 g, 5.5 mmoles) in absolute ethanol (50 ml). The product was refluxed for 10 min, the precipitate filtered off, washed with ethanol, and recrystallized from DMF water to give the product (70%) with mp 304-306°C and R_f 0.9. M^+ 320.

2-p-Methoxybenzylidenehydrazino-4-carbethoxythiazole (III, $C_{14}H_{15}N_3O_3S$) was obtained similarly to II to give III (73%) with mp 206-208°C and R_f 0.9. M^+ 305.

2-Benzylidenehydrazino-4-carbethoxy-5-bromothiazole (IV, $C_{13}H_{12}N_3O_2SBr$). A solution of bromine (0.12 ml, 2.2 mmoles) in acetic acid (5 ml) was added dropwise with stirring to a suspension of I (0.3 g, 1.1 mmoles) in acetic acid (5 ml). The product was held for 1 h, filtered, and recrystallized from acetic acid. It was suspended in water and basified with concentrated ammonia to pH 7. The precipitate was then filtered, washed with water, and crystallized from ethanol to give product (80%) with mp 200-202°C and R_f 0.85. M^+ 353, 355. ^{13}C NMR spectrum: 166.60 (s, C=O); 160.49 (s, $C_{(2)}$); 142.92 (d, ^1J = 32.35 Hz; HC=N); 139.50 (s, $C_{(4)}$); 133.80; 129.65; 128.77; 126.44 (phenyl); 104.72 (s, $C_{(5)}$); 60.67 (t, ^1J = 148.32 Hz; CH_2); 13.99 ppm (q, ^1J = 127.23 Hz; CH_3).

2-p-Nitrobenzylidenehydrazino-4-carbethoxy-5-bromothiazole (V, $C_{13}H_{11}N_4O_4SBr$). Bromine (0.2 ml, 3.13 mmoles) in chloroform (5 ml) was added to a solution of II (0.5 g, 1.56 mmoles) in chloroform (5 ml). The product was stirred for 2 h and the precipitate filtered, washed with ether, and recrystallized from DMF–water to give product (49%) with mp 297-299°C and R_f 0.9.

2-p-Methoxybenzylidenehydrazino-4-carboxythiazole (VIII, $C_{12}H_{11}N_3O_3S$). A solution of III (2 g, 6.5 mmoles) in concentrated hydrochloric acid (10 ml) was refluxed for 2 h. The product was cooled and the precipitate filtered, washed with water, and recrystallized from DMF–water to give product (75%) with mp 260-262°C and R_f 0.02.

2-p-Methoxybenzylidenehydrazino-4-carboxy-5-bromothiazole (VII, $C_{12}H_{10}N_3O_3SBr$) was obtained similarly to V. Recrystallization from ethanol–water (1:1) gave product (65%) with mp 256-258°C and R_f 0.1.

2-p-Methoxybenzylidenehydrazino-4-carbethoxy-5-bromothiazole (VI, $C_{14}H_{14}N_3O_3SBr$). Hydrochloric acid (0.1 ml) was added to a solution of VII (0.2 g, 0.56 mmole) in absolute ethanol (20 ml). The product was refluxed for 3 h, evaporated in vacuo, and the residue recrystallized from 50% aqueous ethanol to give product (71%) with mp 180-182°C and R_f 0.85. M^+ 383, 385.

5-Phenyl-2-bromo-3-carbethoxy-1,2,4-triazolo[3,4-b]thiazole (XIII, $C_{13}H_{10}N_3O_2SBr$). Bromine (0.8 ml, 14.52 mmoles) in acetic acid (15 ml) was added to a suspension of I (1 g, 3.63 mmoles) in acetic acid (15 ml). The product was stirred for 24 h and the precipitate filtered, washed with ether, and recrystallized from acetic acid. After treatment with aqueous ammonia the product was filtered, washed with water, and crystallized from DMF–water to give product (31%) with mp 165-167°C and R_f 0.85. M^+ 351, 353.

5-p-Nitrophenyl-2-bromo-3-carbethoxy-1,2,4-triazolo[3,4-b]thiazole (XIV, $C_{13}H_9N_4O_4SBr$) was obtained similarly to XIII to give product (43%) with mp 311-313°C and R_f 0.9. M^+ 396, 398.

2-(N-Benzylidene-N'-methyl)hydrazino-4-carbethoxythiazole (XV, $C_{14}H_{15}N_3O_2S$). Sodium hydroxide (0.17 g, 4.3 mmoles) in water (2 ml) was added to a suspension of I (1 g, 3.63 mmoles) in ethanol (10 ml). The product was heated to 50°C

and dimethyl sulfate (0.41 ml, 4.3 mmoles) added with stirring. The reaction mixture was refluxed for 30 min, cooled, and the precipitate filtered and suspended in water. This suspension was filtered and the precipitate recrystallized from 50% aqueous ethanol to give product (53%) with mp 170-173°C and R_f 0.67.

2-Benzylideneazino-3-N-methyl-4-carbethoxythiazoline (XVI, $C_{14}H_{15}N_3O_2S$). A mixture of I (1 g, 3.63 mmoles), dimethylsulfate (0.41 ml, 4.3 mmoles), and magnesium oxide (0.6 g) in dry toluene (50 ml) was refluxed for 4-5 h. The product was cooled and the precipitate washed with toluene. The filtrate was washed with water, dried with calcium sulfate, the solvent evaporated, and the residue recrystallized from aqueous ethanol with addition of activated carbon. The yield was 57% with mp 130-131°C and R_f 0.79.

2-(N-Benzylidene-N'-methyl)hydrazino-4-carbethoxy-5-bromothiazole (XVII, $C_{14}H_{14}N_3O_2SBr$) was obtained similarly to IV. The product was held for 24 h and recrystallized from absolute ethanol with addition of activated carbon to give a yield of 59% with mp 120-123°C and R_f 0.67.

2-(1-Phenyl-2-bromo)ethylidenehydrazino-4-carbethoxythiazole (XVIII, $C_{14}H_{14}N_3O_2SBr$) was obtained similarly to IV in 52% yield with mp 190-195°C and R_f 0.59.

1-(1-Phenyl)ethylidenehydrazino-4-carboxy-5-bromothiazole (XX, $C_{12}H_{10}N_3O_2SBr$) was obtained similarly to IV in 54% yield with mp 190-193°C and R_f 0.54.

2-(1-Bromomethyl)ethylidenehydrazino-4-carbethoxy-5-bromothiazole (XXII, $C_9H_{11}N_3O_2SBr_2$). Bromine (0.3 ml, 4.4 mmoles) in chloroform (5 ml) was added to a solution of XXI (0.5 g, 2.2 mmoles) in chloroform (15 ml). The product was stirred for 2 h and evaporated in vacuo. The residue was treated with ether, suspended in acetone, and the precipitate filtered to give XXII (62%) with mp 140-142°C and R_f 0.9.

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