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Transformations of 1-Azinyl-4-ethoxycarbonyl Thiosemicarbazides. The Synthesis of 3-Ethoxycarbonylamino-s-triazolo[4,3-x]azines

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1-Azinyl-4-ethoxycarbonyl thiosemicarbazides **4**, **5**, and **12** and 1-azinyl-4-ethoxycarbonylmethyl thiosemicarbazide **17**, prepared from the corresponding heterocyclic hydrazino compounds and ethoxycarbonyl isothiocyanate or ethoxycarbonylmethyl isothiocyanate, were converted by oxidation with bromine in acetic acid into derivatives of fused 3-ethoxycarbonylamino-s-triazolo[4,3-a]pyridine **6**, -pyridazine **7**, and -pyrazine **13**, **18** and **20**. The thiosemicarbazide derivative **8** was transformed at 0 °C into bis-s-triazolo[4,3-b:3′,4′-f]pyridazine derivative **9**, while at room temperature 6-bromo-s-triazolo[4,3-b]pyridazine (**10**) was obtained. Further transformations of 8-substituted 3-ethoxycarbonylamino-s-triazolo[4,3-a]pyrazines **13** and **14** afforded derivatives of bis-s-triazolo[4,3-a:3′,4′-c]pyrazine **15** and s-triazolo[4,3-a]tetrazolo[1′,5′-c]pyrazine **16**.

(Keywords: 1-Azinyl-4-ethoxycarbonyl thiosemicarbazides; 3-Ethoxycarbonylamino-s-triazolo[4,3-x]azines; Oxidative cyclization with C—N *bond formation)*

Transformation von 1-Azinyl-4-ethoxycarbonylthiosemicarbaziden. Die Synthese von 3-Ethoxycarbonylamino-s-triazolo[4,3-x]azinen

Die aus den entsprechenden heterocyclischen Hydrazinverbindungen und Ethoxycarbonylmethylisothiocyanaten hergestellten 1-Azinyl-4-ethoxycarbonylthiosemicarbazide **4**, **5** und **12** und 1-Azinyl-4-ethoxycarbonylmethylthiosemicarbazid **17** wurden mittels Oxidation mit Brom in Essigsäure in die kondensierten Produkte 3-Ethoxycarbonylamino-s-triazolo[4,3-a]pyridin **6**, -pyridazin **7** und -pyrazine **13**, **18** und **20** übergeführt. Das Thiosemicarbazidderivat **8** wurde bei 0 °C in das Bis-s-trazolo[4,3-b:3′,4′-f]pyridazin-Derivat **9** transformiert, währenddessen bei Raumtemperatur 6-Brom-s-triazolo[4,3-b]pyridazin (**10**) erhalten wurde. Weitere Transformationen der 8-substituierten 3-Ethoxycarbonylamino-s-triazolo[4,3-a]pyrazine **13** und **14** ergaben Derivate von Bis-s-triazolo[4,3-a:3′,4′-c]pyrazin **15** und s-Triazolo[4,3-a]tetrazolo[1′,5′-c]pyrazin (**16**).

Introduction

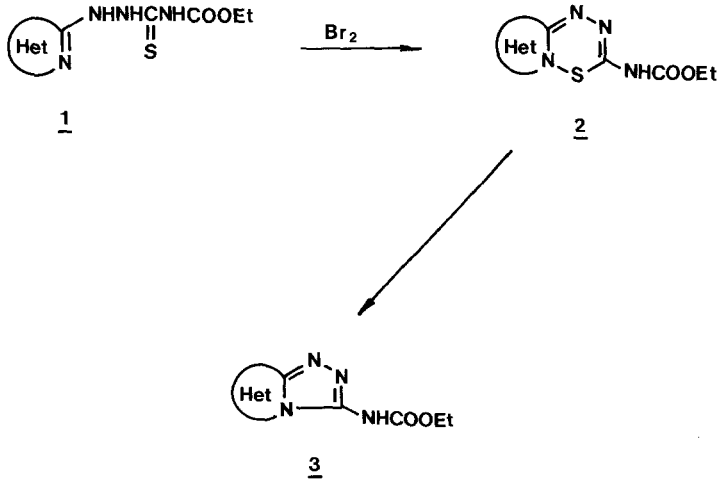
The cyclization of hydrazinoazines with one-carbon reagents is the most efficient method to prepare s-triazolo[4,3-x]azines. The substituent introduced at position 3 of the s-triazole ring depends on the nature of the reagent used for cyclization. With most reagents alkyl and aryl groups are introduced, 3-amino derivatives are obtained with cyanogen halides and 3-mercapto derivatives with carbon disulfide or phenyl isothiocyanate [1, 2].

Heterocyclic thiosemicarbazides are suitable intermediates for the preparation of various triazolo[4,3-x]azines. The first examples were observed in phthalazine [3] and pyridazine [4–6] series.

Results and Discussion

In continuation of our research in this area we expected that oxidative cyclization of 1-azinyl-4-ethoxycarbonyl thiosemicarbazides **1** with bromine in acetic acid would give the corresponding fused azinothiatriazine derivatives **2**. However, this ring system is most probably very unstable and extrusion of sulphur took place easily to give the corresponding 3-ethoxycarbonylamino-s-triazolo[4,3-x]azines **3** (Scheme 1). In this manner, 1-(pyridyl-2)-4-ethoxycarbonyl thiosemicarbazide (**4**) and 1-(6-chlorophyridazinyl-3)-4-ethoxycarbonylthiosemicarbazide (**5**) gave s-triazolo[4,3-a]pyridazine derivative **6** and s-triazolo[4,3-b]pyridazine derivative **7**, respectively. On the other hand, the oxidative cyclization of 1-(s-triazolo[4,3-b]pyridazinyl-6)-4-ethoxycarbonyl thiosemicarbazide

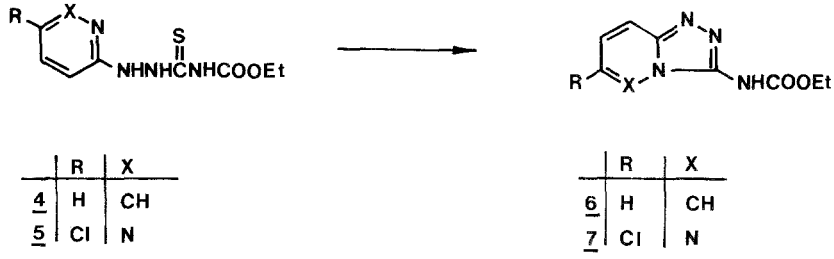
Scheme 1



1 **2** **3**

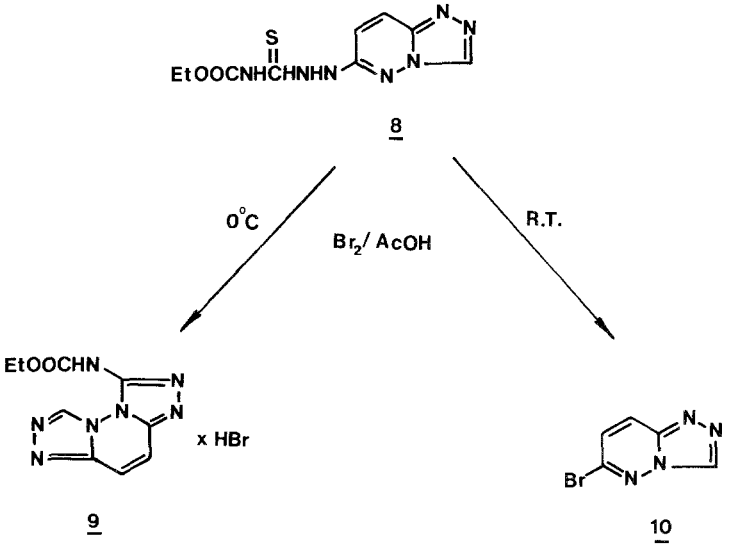
(**8**) with bromine in acetic acid is dependent on the reaction temperature. The oxidation at 0 °C produced bis-s-triazolo[4,3-b:3′,4′-f]pyridazine derivative **9**, while at 25 °C 6-bromo-s-triazolo[4,3-b]pyridazine derivative **10** was obtained, indicating that the side chain attached at position 6 of the bicyclic system was substituted with bromine (Scheme 2). Oxidative cyclization of 1-(chloropyrazinyl-2)-4-ethoxycarbonyl thiosemicarbazide (**12**), obtained from 2-chloro-3-hydrazinopyrazine (**11**) and ethoxycarbonyl isothiocyanate, gave 3-ethoxycarbonylamino-8-chloro-s-trazolo[4,3-a]pyrazine (**13**), which was with hydrazine hydrate transformed into the hydrazino derivative **14**. This compound gave by heating with triethyl orthoformate bis-s-triazolo[4,3-a:3′,4′-c]pyrazine derivative

Scheme 2

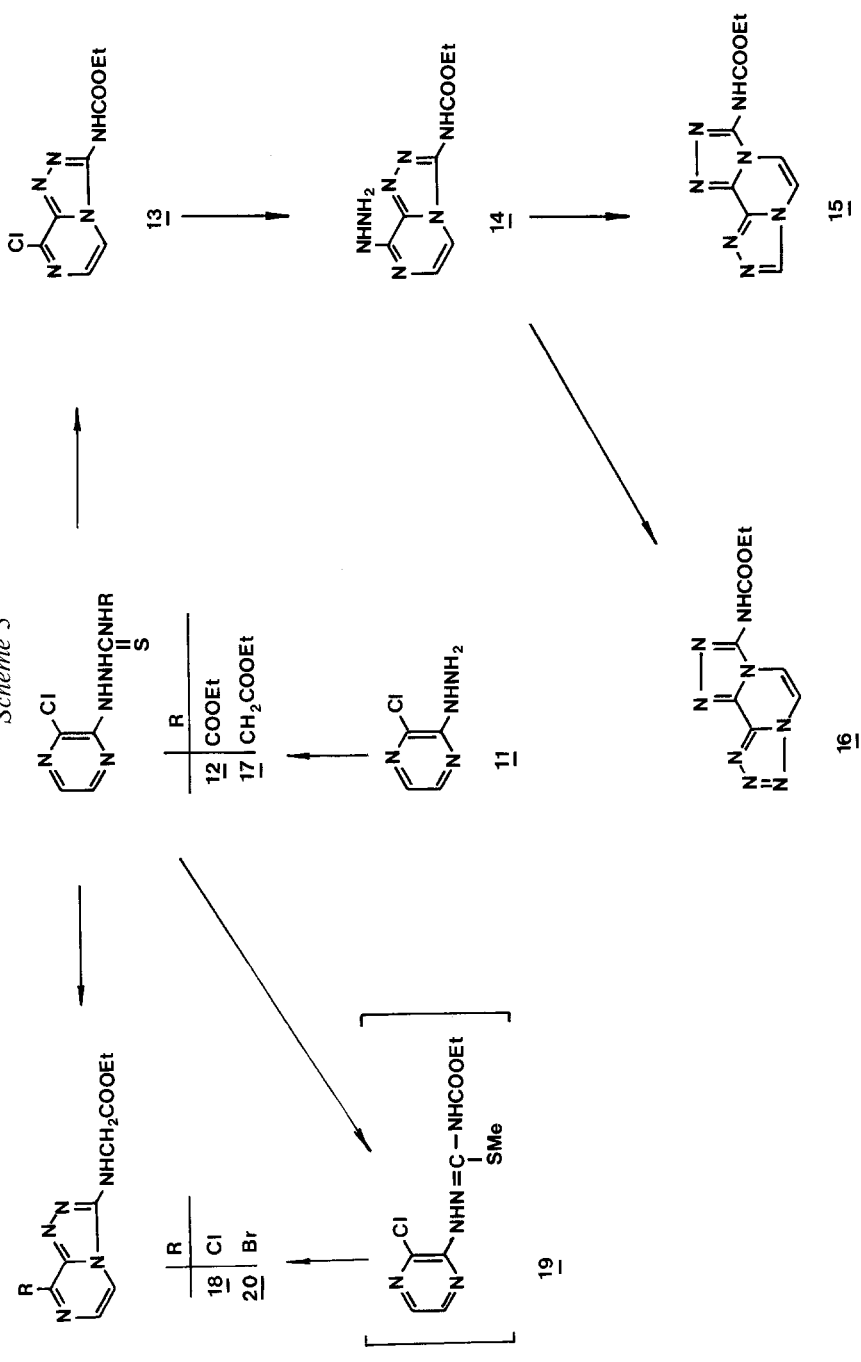


	R	X
4	H	CH
5	Cl	N

	R	X
6	H	CH
7	Cl	N



Scheme 3


NHCOOEt
Cl
13
NHNH2
14
15
16
NHNHCNHR
S
R
12 COOEt
17 CH2COOEt
11
NHCH2COOEt
R
18 Cl
20 Br
NHN=C–NHCOOEt
SMe
19

15, and by nitrosation with nitrous acid s-triazolo[4,3-a]tetrazolo[1',5'-c]pyrazine derivative **16**.

When ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)thiosemicarbazide (**17**) was treated with methyl iodide in the presence of sodium methoxide in methanol at room temperature 8-chloro-3-ethoxycarbonylmethylamino-s-triazolo[4,3-a]pyrazine (**18**) was formed most probably through the corresponding methylthio intermediate **19**. On the other hand, by oxidative cyclization of **17** with bromine in acetic acid besides the 8-chloro derivative **18** 8-bromo-3-ethoxycarbonylmethylamino-s-triazolo[4,3-a]pyrazine (**20**) was formed by substitution of chlorine at position 8 with bromide ion, judged on the basis of mass spectra. No attempts were made in order to separate both compounds (Scheme 3).

Acknowledgement

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Experimental [7]

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H NMR spectra were recorded on a JEOL C 60 HL spectrometer (*TMS* as internal standard, δ-values in ppm) and mass spectra on a Hitachi-Perkin-Elmer RMU-6L mass spectrometer. Elemental analyses (C, H, N) were obtained with a Perkin-Elmer Analyser 240 °C.

The following compounds were prepared according to literature references: 2-chloro-3-hydrazinopyrazine [8], 4-ethoxycarbonyl-1-(3-chloropyrazinyl-2)-thiosemicarbazide [9], and 4-ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)-thiosemicarbazide [9].

General synthesis of 4-ethoxycarbonyl- and 4-ethoxycarbonylmethyl-1-azinyl thiosemicarbazides

To a solution or suspension of 0.001 mol of the hydrazino compound in 5 ml of chloroform 0.001 mol of ethoxycarbonyl isothiocyanate or ethoxycarbonylmethyl isothiocyanate was added and the mixture was heated under reflux for one hour. Evaporation of the solvent afforded the crude 1,4-disubstituted thiosemicarbazide, which was recrystallized from an appropriate solvent. According to this procedure the following compounds were prepared:

4-Ethoxycarbonyl-1-(pyridyl-2)-thiosemicarbazide (**4**)

This compound was prepared from 2-hydrazinopyridine in 73% yield, m.p. 145–149 °C (from methanol). MS (*m/e*): 240 (M^+). NMR (*DMSO-d_6*): 1.17 (t, $MeCH_2$), 3.96 (q, $MeCH_2$), 6.41 (m, H_3, H_5), 7.14 (dd, H_4), 7.65 (ddd, H_6), 8.63 (br.s, NH), 10.5 (br.s, NH, NH), $J_{H_3,H_4} = J_{H_4,H_5} = 7.5$ Hz, $J_{H_4,H_6} = 1.8$ Hz, $J_{CH_2Me} = 6.9$ Hz.

$C_9H_{12}N_4O_2S$ (240.28). Calcd.: C 44.98 H 5.03 N 23.31.
Found: C 45.28 H 5.20 N 23.30.

4-Ethoxycarbonyl-1-(6-chloropyridazinyl-3)-thiosemicarbazide (**5**)

5 was prepared from 3-chloro-6-hydrazinopyridazine in 67% yield, m.p. 197–200 °C (from methanol). MS (*m/e*): 275 (M^+). NMR (*DMSO-d*$_6$): 1.20 (t, *Me*CH_2), 3.97 (q, *Me*$\mathbf{CH_2}$), 6.75 (d, H_5), 7.18 (d, H_4), 9.26 (br.s, NH), 10.73 (br.s, NH), 11.10 (br.s, NH), $J_{H_4,H_5} = 9.2$ Hz, $J_{CH_2Me} = 6.9$ Hz.

$C_8H_{10}ClN_5O_2S$ (275.72). Calcd.: C 34.85 H 3.65 N 25.40.
Found: C 35.01 H 3.68 N 25.37.

3-Ethoxycarbonylamino-s-triazolo[4,3-a]pyridine (**6**)

A solution of 160 mg of bromine in 1 ml of glacial acetic acid was slowly added to a solution of 4-ethoxycarbonyl-1-(pyridyl-2)-thiosemicarbazide (**4**) in 5 ml of glacial acetic acid. The mixture was left for 3 h at room temperature, then 5 ml of water were added and the mixture was neutralized with conc. aqueous ammonium hydroxide and filtered. The filtrate was extracted 3 times with 20 ml of chloroform and the combined extracts were dried over anhydrous sodium sulphate. Evaporation of the solvent in vacuo gave **6** in 21% yield, m.p. 146–149 °C (from a mixture of methanol and water). MS (*m/e*): 206 (M^+). NMR ($CDCl_3$): 1.27 (t, *Me*CH_2), 4.05 (q, *Me*$\mathbf{CH_2}$), 6.45 (ddd, H_6), 6.88 (ddd, H_7), 7.27 (dd, H_8), 7.64 (dd, H_5), 8.36 (br.s, NH), $J_{H_5,H_6} = 6.5$ Hz, $J_{H_5,H_7} = 1.5$ Hz, $J_{H_6,H_7} = 7.0$ Hz, $J_{H_6,H_8} = 2.5$ Hz, $J_{H_7,H_8} = 7.5$ Hz, $J_{CH_2Me} = 7.5$ Hz.

$C_9H_{10}N_4O_2$ (206.20). Calcd.: C 52.42 H 4.88 N 27.17.
Found: C 52.42 H 5.01 N 26.85.

In the same manner the following compounds were prepared:

6-Chloro-3-ethoxycarbonylamino-s-triazolo[4,3-b]pyridazine (**7**)

This compound was prepared from 275 mg of 4-ethoxycarbonyl-1-(6-chloropyridazinyl-3)-thiosemicarbazide (**5**) by oxidation with bromine in 28% yield, m.p. 177–180 °C. MS (*m/e*): 241 (M^+). NMR (*DMSO-d*$_6$): 1.18 (t, *Me*CH_2), 3.97 (q, *Me*$\mathbf{CH_2}$), 7.12 (d, H_7), 8.02 (d, H_8), 9.86 (br.s, NH), $J_{CH_2Me} = 6.9$ Hz, $J_{H_7,H_8} = 9.4$ Hz.

$C_8H_8ClN_5O_2$ (241.64). Calcd.: C 39.76 H 3.33 N 28.98.
Found: C 39.53 H 3.70 N 28.70.

4-Ethoxycarbonyl-1-(s-triazolo[4,3-b]pyridazinyl-6)-thiosemicarbazide (**8**)

8 was prepared from 6-hydrazino-s-triazolo[4,3-b]pyridazine [10] in 82% yield, m.p. 190–193 °C (from methanol). MS (*m/e*): 281 (M^+). NMR (*DMSO-d*$_6$): 1.23 (t, *Me*CH_2), 4.05 (q, *Me*$\mathbf{CH_2}$), 5.11 (br.s, NH, NH), 6.73 (d, H_7), 7.77 (d, H_8), 8.86 (s, H_3), 10.84 (br.s, NH), $J_{H_7,H_8} = 10$ Hz, $J_{CH_2Me} = 6.9$ Hz.

$C_9H_{11}N_7O_2S$ (281.29). Calcd.: C 38.56 H 3.57 N 34.98.
Found: C 38.62 H 3.85 N 35.35.

1-Ethoxycarbonylamino-bis-s-triazolo[4,3-b:3',4'-f]pyridazine hydrobromide (**9**)

This compound was prepared form 281 mg of 4-ethoxycarbonyl-1-(s-triazolo[4,3-b]pyridaninyl-6)-thiosemicarbazide (**8**) in 16% yield, m.p. 260–262 °C (from a mixture of *DMF*, methanol and water). MS (*m/e*): 247 (M^+). NMR (*DMSO-d*$_6$): 1.13 (t, *Me*CH_2), 3.92 (q, *Me*$\mathbf{CH_2}$), 6.67 (d, H_9), 7.71 (d, H_{10}), 8.60 (s, H_3), $J_{H_9,H_{10}} = 9.8$ Hz, $J_{CH_2Me} = 6.9$ Hz.

$C_9H_{10}BrN_7O_2$ (328.09). Calcd.: C 32.94 H 3.07 N 29.98.
Found: C 33.28 H 3.13 N 29.88.

6-Bromo-s-triazolo[4,3-b]pyridazine (**10**)

This compound was prepared from 4-ethoxycarbonyl-1-(s-triazolo[4,3-b]pyridazinyl-6)-thiosemicarbazide (**8**) in 16% yield, m.p. 219–220 °C (from methanol). MS (*m/e*): 199 (M^+). NMR (*DMSO-d*$_6$, 80 °C): 7.41 (d, H_7), 8.22 (d, H_8), 9.48 (s, H_3), $J_{H_7,H_8} = 10$ Hz.

$C_5H_3BrN_4$ (199.02). Calcd.: C 30.17 H 1.51 N 28.15.
Found: C 30.33 H 1.80 N 28.30.

8-Chloro-3-ethoxycarbonylamino-s-triazolo[4,3-a]pyrazine (**13**)

This compound was prepared from 275 mg of 4-ethoxycarbonyl-1-(3-chloropyrazinyl-2)-thiosemicarbazide (**12**) in 31% yield, m.p. 195–197 °C (from methanol). MS (*m/e*): 241 (M^+). NMR (*DMSO-d*$_6$): 1.25 (t, *Me*CH_2), 4.15 (q, *Me*$\mathbf{CH_2}$), 7.64 (d, H_6), 8.27 (d, H_5), $J_{H_5,H_6} = 5.4$ Hz, $J_{CH_2Me} = 6.9$ Hz.

$C_8H_8ClN_5O_2$ (241.64). Calcd.: C 39.76 H 3.33 N 28.98.
Found: C 40.05 H 3.39 N 28.95.

3-Ethoxycarbonylamino-8-hydrazino-s-triazolo[4,3-a]pyrazine (**14**)

To a solution of 241 mg of 8-chloro-3-ethoxycarbonylamino-s-triazolo[4,3-a]pyrazine (**13**) in 5 ml of ethanol 0.15 ml of hydrazine hydrate (80%) was added and the mixture was left at room temperature for 3 h. The precipitate was collected by filtration to give **14** in 53% yield, m.p. > 300 °C (from ethanol). MS (*m/e*) 237 (M^+). NMR (*DMSO-d*$_6$): 1.23 (t, *Me*CH_2), 3.29 (br.s, NH_2), 4.15 (q, *Me*$\mathbf{CH_2}$), 6.25 (br.s, NH, NH), 7.14 (s, H_5, H_6), $J_{CH_2Me} = 6.9$ Hz.

$C_8H_{11}N_7O_2$ (237.22). Calcd.: C 40.50 H 4.67 N 41.33.
Found: C 40.56 H 4.73 N 41.32.

3-Ethoxycarbonylamino-bis-s-triazolo[4,3-a:3',4'-c]pyrazine (**15**)

A mixture of 237 mg of 3-ethoxycarbonylamino-8-hydrazino-s-triazolo[4,3-a]pyrazine (**14**) and 3 ml of triethyl orthoformate was heated under reflux for 3 h. The precipitate was, after cooling, collected by filtration to give **15** in 30% yield, m.p. > 300 °C (from methanol). NMR (*DMSO-d*$_6$, 70 °C); 1.29 (t, *Me*CH_2), 4.27 (q, *Me*$\mathbf{CH_2}$), 7.85 (d, H_6), 8.20 (d, H_5), 9.36 (s, H_8), 10.59 (br.s, NH), $J_{H_5,H_6} = 6.3$ Hz, $J_{CH_2Me} = 7.1$ Hz.

$C_9H_9N_7O_2$ (247.22). Calcd.: C 43.72 H 3.67 N 39.66.
Found: C 43.53 H 3.81 N 39.79.

3-Ethoxycarbonylamino-s-triazolo[4,3-a]tetrazolo[1',5'-c]pyrazine (**16**)

To a solution of 120 mg of 3-ethoxycarbonylamino-8-hydrazino-s-triazolo[4,3-a]pyrazine (**14**) in 4 ml of hydrochloric acid (20%) a solution of 38 mg of sodium nitrite in 0.5 ml of water was added dropwise at 0 °C. After standing for half an hour at room temperature the solution was extracted three times with chloroform (10 ml each time). The combined extracts were dried over anhydrous sodium sulphate. The dry residue obtained after evaporation of chloroform in vacuo gave **16** in 37% yield, m.p. 178–180 °C. NMR (*DMSO-d*$_6$): 1.30 (t, *Me*CH_2), 4.23 (q, *Me*$\mathbf{CH_2}$), 6.45 (br, s, NH), 8.25 (d, H_6), 8.87 (d, H_5), $J_{H_5,H_6} = 6.1$ Hz, $J_{CH_2Me} = 7.1$ Hz.

$C_8H_8N_8O_2$ (248.21). Calcd.: C 38.71 H 3.25 N 45.15.
Found: C 38.71 H 3.43 N 44.85.

8-Chloro- (**18**) *and 8-bromo-3-ethoxycarbonylmethylamino-s-triazolo[4,3-a]pyrazine* (**20**)

a) To a solution of 289 g of 4-ethoxycarbonylmethyl-(3-chloropyrazinyl-2)-thiosemicarbazide (**17**) in 3 ml of glacial acetic acid a solution of 160 mg of bromine in 1 ml of glacial acetic acid was added dropwise at 0 °C. The mixture was left at room temperature for 1 h, diluted with 6 ml of water, neutralized with ammonium hydroxide solution (28%) and extracted three times with chloroform (10 ml each time). The combined extracts were dried over anhydrous sodium sulphate. The dry residue obtained after evaporation of the solvent in vacuo gave a mixture of **18** and **20**.

b) A mixture of 289 mg of 4-ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)-thiosemicarbazide (**17**), sodium methoxide, prepared from 23 mg of sodium in 5 ml of methanol, and 1 ml of methyl iodide was left at room temperature for 22 h. To the oily residue, obtained after evaporation of volatile components in vacuo 1 ml of water was added and the mixture was neutralized with solid sodium hydrogen carbonate and extracted three times with chloroform (5 ml each time). The dry residue obtained after evaporation of the solvent in vacuo gave **18** in 18% yield, m.p. 194–196 °C (from ethanol). MS (*m/e*): 255 (M^+). NMR (*DMSO-d*$_6$): 1.27 (t, *Me*CH_2), 4.24 (q, *Me*CH_2), 7.68 (d, H_6), 7.94 (t, $NHCH_2$), 8.41 (d, H_5), J_{H_5,H_6} = 5.6 Hz, J_{CH_2Me} = 7.5 Hz, J_{NHCH_2} = 5.2 Hz.

$C_9H_{10}ClN_5O_2$ (255.66). Calcd.: C 42.28 H 3.94 N 27.39.
Found: C 42.66 H 3.72 N 27.02.

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