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A NOVEL SYNTHESIS AND TRANSFORMATIONS OF 1H-PYRAZINO/2,3-e/-1,3,4-THIADIAZINE DERIVATIVES

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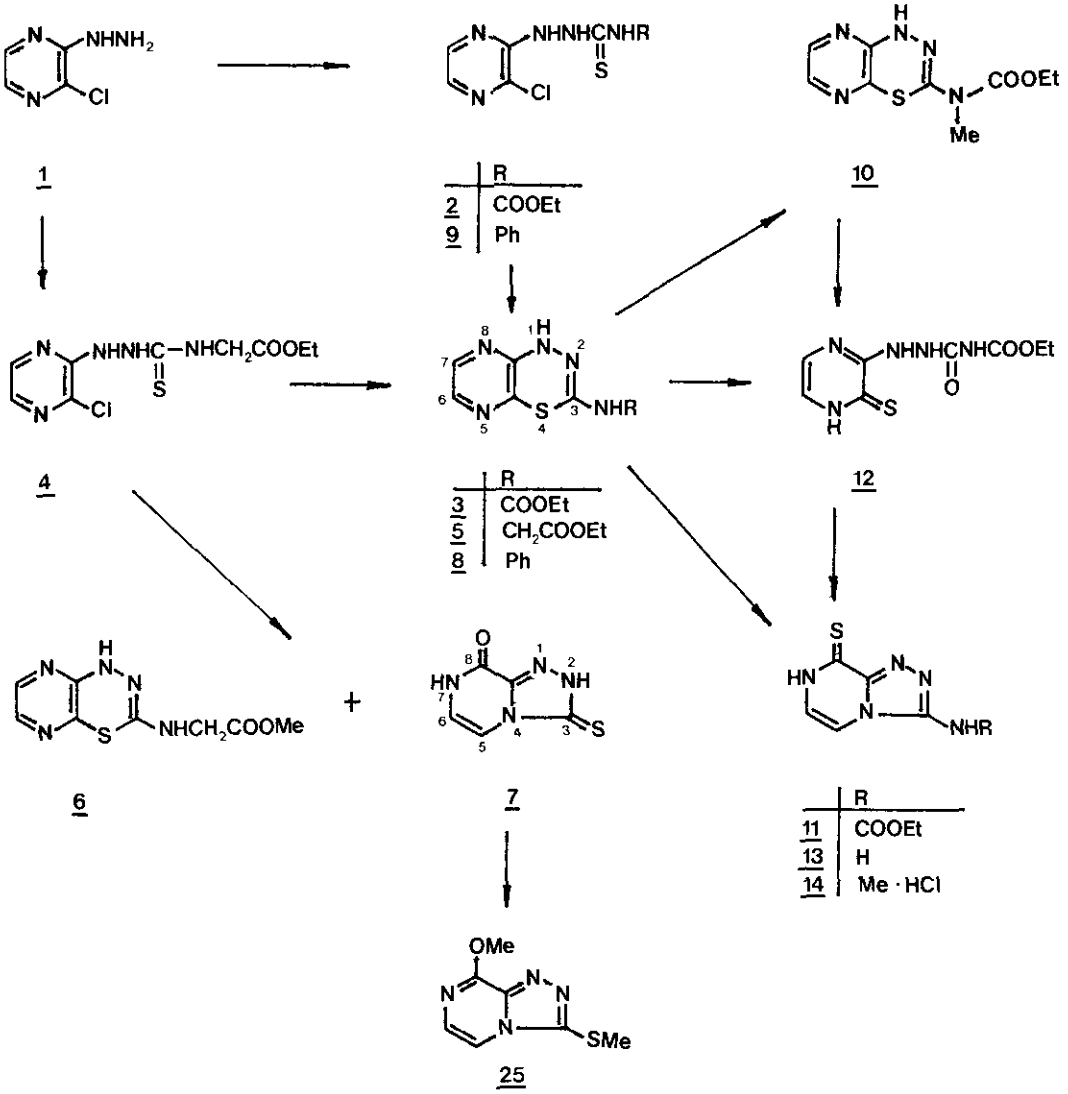
Abstract - 1,4-Disubstituted thiosemicarbazides 2, 4, and 9 cyclize thermally into 1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivatives 3, 5, 6 and 8. These can be converted under mild reaction conditions into derivatives of the same bicyclic system 10, 17, and 21. However, under acidic or alkaline conditions a cleavage of the C_3-S bond of the 1,3,4-thiadiazine ring is taking place to give either the 1,4-disubstituted *semicarbazide 12, or rearranged products, derivatives of s-*triazolo/4,3-b/pyrazine, 7, 11, 13, 14, 15, 16, 18, 22, 23 and 24.

Fused 1,3,4-thiadiazine systems are little known in the literature. A series of 4H-1,3,4-benzothiadiazines has been prepared by intramolecular substitutions of halides,[1-5] by oxidation of thiohydrazides,[6] by intramolecular nucleophilic attack of the thioether function on the electron deficient carbon atom of the nitrile imine function,[7] by diazotization of ethyl/(2-aminophenyl)sulphonyl/glyoxylate phenylhydrazone,[8] and by condensation reaction of N'-phenylbenzothiohydrazides and dithizone with a variety of activated aromatic and heteroaromatic 1,2-dihalogeno and 1-halogeno-2-nitro compounds.[9] The first derivatives of 1H-pyrazino/2,3-e/-1,3,4-thiadiazine system were prepared in 1980 from N'-phenylbenzothiohydrazide and 2,3-dichloro-5,6-dicyanopyrazine.[9]

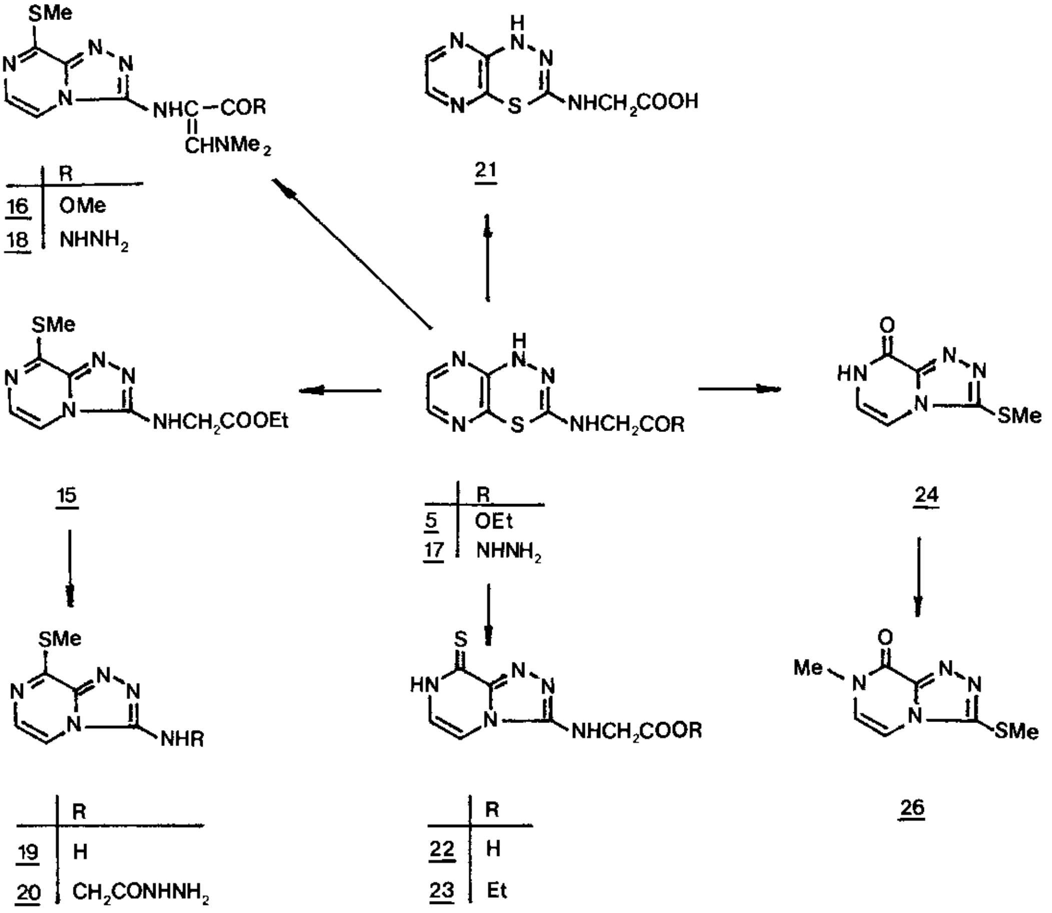
In continuation of our studies on the transformations of N-heteroaryl-N'-ethoxycarbonylthioureas and thiosemicarbazides[10-15] we report on a new approach to the synthesis of 1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivatives and some transformations of this relatively unknown heterocyclic system.

As starting material thiosemicarbazide 2, prepared from 3-chloro-2-hydrazinopyrazine (1)[16] and ethoxycarbonyl isothiocyanate was used. By an attempted crystallization



SCHEME 1

from hot methanol a cyclization of the compound 2 into 3-ethoxycarbonylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (3) took place, while the corresponding thiosemicarbazide 4, prepared from the compound 1[16] and ethoxycarbonylmethyl isothiocyanate, cyclized by heating in ethanol into the 1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivative 5. On the other hand, the thiosemicarbazide 4 gave by heating in methanol two products, 1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivative 6 and 3-thioxo-2,3-dihydro-s-triazolo/4,3-a/pyrazin-8(7H)-one (7). 3-Chloro-2-hydrazino-



SCHEME 2

pyrazine (1)[16] afforded by heating with phenyl isothiocyanate the corresponding 1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivative 8. The isolation of the intermediary thiosemicarbazide 9 was not successful. The reaction of the compound 3 with N,N-dimethylformamide dimethyl acetal (DMFDMA) gave the corresponding 3-(N-ethoxycarbonyl-N-methylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine derivative 10, while no reaction occurred by using either methyl iodide or diazomethane.

1H-Pyrazino/2,3-e/-1,3,4-thiadiazine system is relatively unstable, so that decomposition and rearrangements are taking place already under mild reaction conditions. Thus, the compound 3 was in alkaline medium transformed into triazolo /4,3-a/pyrazine derivative 11. In slightly acidic medium first the substituted semicarbazide 12 could be isolated and then further transformed into triazolo

/4,3-a/pyrazine derivative 13. Similarly, the derivative 10 gave in alkaline media 3-methylamino-8(7H)-thioxo-s-triazolo/4,3-a/pyrazine (14). This transformation is a convincing evidence that the methylation of the compound 3 with DMFDMA is taking place at the substituted amino group at position 3 and not at the ring nitrogen atom.

A general characteristic for all these transformations is the cleavage of the bond C_3-S, in which the semicarbazide 12 is formed as an intermediate. In the case of 3-ethoxycarbonylmethylamino derivative 5 the reaction with DMFDMA at room temperature afforded the triazolo/4,3-a/pyrazine derivative 15 as a consequence of a rearrangement and subsequent methylation.[17] By further heating in DMFDMA condensation of methylene group,[24] transesterification of ethyl ester into methyl ester and methylation of "mercapto" group at position 8 occurred to give the corresponding s-triazolo/4,3-a/pyrazine derivative 16. 3-Carbazoylmethylamino derivative 17, prepared from the ester 5 and hydrazine, reacted with DMFDMA at room temperature only at methylene group to give the compound 18.

8-Methylthio-3-ethoxycarbonylmethylamino-s-triazolo/4,3-a/pyrazine (15) was transformed in PPA into 3-amino-8-methylthio-s-triazolo/4,3-a/pyrazine (19), while by treatment with hydrazine the corresponding carbazoyl derivative 20 was obtained.

In dilute aqueous hydrochloric acid hydrolysis of the compound 5 gave the corresponding acid 21. On the other hand, in alkaline medium thiadiazine system was rearranged into s-triazolo/4,3-a/pyrazine derivative 22, while in DMF rearrangement into 23 took place. In methanol, saturated with dry hydrogen chloride, transformation of the thiadiazine derivative 5 into s-triazolo/4,3-a/pyrazine derivative 24 was observed. Methylation of thioxo compound 7 with DMFDMA produced 3-methylthio-8-methoxy derivative 25, while methylation of 3-methylthio derivative 24 gave the corresponding N-methyl product 26.

The structure determination of 1H-pyrazino/2,3-e/-1,3,4-thiadiazines and s-triazolo /4,3-a/pyrazines is based mainly on the nmr spectral characteristics. Namely, the chemical shift differences for protons H_6 and H_7 in 1H-pyrazino/2,3-e/-1,3,4-thiadiazines is very small, $\Delta\delta_{H_6,H_7} = 0.1$ ppm, with small coupling constant $J_{H_6,H_7} =$ 1.8-2.2 Hz. On the other hand, the chemical shift differences for the corresponding protons H_5 and H_6 in s-triazolo/4,3-a/pyrazines are larger, $\Delta\delta_{H_5,H_6} = 0.27 - 0.84$ ppm, with the coupling constant $J_{H_5,H_6} = 4.7 - 6.1$ Hz.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. ^{1}H nmr spectra were obtained on a JEOL JNM C60-HL spectrometer with TMS as internal standard, ir spectra on PERKIN-ELMER instrument 727B, mass spectra on a HITACHI-PERKIN-ELMER mass spectrometer RMU-6L, and elemental analyses for C,H, and N on a PERKIN-ELMER CHN Analyser 240C.

4-Ethoxycarbonyl-1-(3-chloropyrazinyl-2)thiosemicarbazide (2). - 3-Chloro-2-hydrazinopyrazine (1) was prepared according to the procedure described in lit.[16] To a solution of 3-chloro-2-hydrazinopyrazine (1)[16] (0.001 mole) in chloroform (5 ml) ethoxycarbonyl isothiocyanate (0.001 mole) was added and the mixture was heated under reflux (1 h). The solvent was evaporated in vacuo to give 2 in 67% yield, mp 175-183°C (the compound cyclized into 3 by attempted recrystallization from methanol), nmr (DMSO-d_6/TMS) δ: 1.17 (t, $CH_2\underline{CH_3}$), 3.84 (q, $\underline{CH_2}CH_3$), 2.27 (d) (H_5 and H_6), 8.67 (br s, NH), 10.57 (br s, NH), 10.84 (br s, NH), J_{H_5,H_6} = 2.3 Hz, $J_{CH_2CH_3}$ = 6.5 Hz.

4-Ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)thiosemicarbazide (4). This compound was prepared according to the above procedure from 3-chloro-2-hydrazinopyrazine (1)[16] and ethoxycarbonylmethyl isothiocyanate in 63% yield, mp 176-177°C, m/e 289 (M^+), nmr (DMSO-d_6/TMS) δ: 1.19 (t, $CH_2\underline{CH_3}$), 4.09 (q, $\underline{CH_2}CH_3$), 4.15 (d, $NH\underline{CH_2}$), 7.77 (d), 8.10 (d) (H_5 and H_6), 8.30 (t, $NHCH_2$), 9.14 (br s, NH), 9.50 (br s,NH), J_{H_5,H_6} = 3.0 Hz, $J_{CH_2CH_3}$ = 7.4 Hz, J_{NHCH_2} = 5.6 Hz.
Anal.Calcd. for $C_9H_{12}N_5O_2SCl$: C, 37.30; H, 4.17; N, 24.17. Found: C, 37.31; H, 4.42; N, 24.09.

3-Ethoxycarbonylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (3). - a) 4-Ethoxycarbonyl-1-(3-chloropyrazinyl-2) thiosemicarbazide (2) (0.001 mole) in methanol (5 ml) was heated under reflux (1 h). After cooling, the solid was collected by filtration to give the compound 3 in 25% yield, mp 188-190°C (from methanol), m/e 239 (M^+), nmr (DMSO-d_6/TMS) δ : 1.15 (t, $CH_2\underline{CH_3}$), 4.83 (q, $\underline{CH_2}CH_3$), 7.27 (s, H_6, H_7), 9.34 (br s, NH), 9.97 (br s, NH), $J_{CH_2CH_3}$ = 6.8 Hz.
Anal.Calcd. for $C_8H_9N_5O_2S$: C, 40.16; H, 3.79; N, 29.27. Found: C, 40.35; H, 3.80; N, 29.37.

b) The same compound was obtained also when the compound 2 was heated under reflux in acetic acid (3 h) or left at room temperature in a mixture of acetic acid (3 ml) and hydrobromic acid (0.5 ml).

3-Ethoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5). - 4-Ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)thiosemicarbazide (4) (0.001 mole) in ethanol (10 ml) was heated under reflux (30 min). To the residue, obtained after evaporation of solvent, water was added and the precipitate collected by filtration to give 5 in 44% yield, mp 146-147°C (from ethanol), m/e 253 (M^+), nmr (DMSO-d_6/TMS) δ : 1.19 (t, $CH_2\underline{CH_3}$), 4.08 (q, $\underline{CH_2}CH_3$), 3.84 (br s, $NH\underline{CH_2}$), 6.97 (br s, $\underline{NH}CH_2$), 7.74 (d), 7.81 (d) (H_6,H_7), 10.5 (br s, NH), J_{H_6,H_7} = 1.8 Hz, $J_{CH_2CH_3}$ = 7.1 Hz.
Anal.Calcd. for $C_9H_{11}N_5O_2S$: C, 42.67; H, 4.37; N, 27.65. Found: C, 42.74; H, 4.44; N, 27.53.

3-Methoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (6). - A solution of 4-ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)-thiosemicarbazide (4) (0.001 mole) in methanol (10 ml) was heated under reflux (1 h). Addition of water (5 ml) to the residue,obtained after evaporation of the solvent in vacuo,gave 6 in 40% yield, mp 158-159°C (from ethanol), m/e 239 (M^+).
Anal.Calcd. for $C_8H_9N_5O_2S$: C, 40.16; H, 3.79; N, 29.27. Found: C, 39.87; H, 4.06; N, 28.95.

3-Thioxo-2,3-dihydro-s-triazolo/4,3-a/pyrazin-8(7H)-one (7). - a) Ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)thiosemicarbazide (4) (289 mg) was heated in methanol (5 ml) under reflux (3 h). Water (5 ml) was added to the residue obtained after evaporation of methanol in vacuo and the precipitate collected by filtration to give 7 in 37% yield, mp 300°C (from methanol), nmr (DMSO-d_6/TMS) δ : 6.60 (d, H_6), 7.25 (d, H_5), 12.93 (br s, NH), J_{H_5,H_6} = 5.5 Hz.
Anal.Calcd. for $C_5H_4N_4OS$: N, 33.31. Found N, 33.70.

b) 3-Phenylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (8) (243 mg) in an aqueous hydrochloric acid (10%, 2 ml) was heated under reflux (45 min). The precipitate was after cooling collected by filtration to give 7. The ir spectrum was identical with that of the compound obtained under a).

3-Phenylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (8). - A mixture of 3-chloro-2-hydrazinopyrazine (1)[16] (0.001 mole) and phenyl isothiocyanate (0.001 mole) in methanol (3 ml) was heated under reflux (3 h). Evaporation of the solvent in vacuo gave 8 in 45% yield, mp 285°C (decomp)(from ethanol), m/e 243 (M^+), nmr ($DMSO-d_6$/TMS) δ: 7.74 (d), 7.82 (d) ($H_6.H_7$), 8.95 (br s, NH), 9.70 (br s, NH), 7.17 (m, Ph), J_{H_6,H_7} = 1.8 Hz).
Anal.Calcd. for $C_{11}H_9N_5S.H_2O$: C, 50.56; H, 4.24; N, 26.80. Found: C, 50.42; H, 3.97; N, 26.80.

3-(N-Ethoxycarbonyl-N-methylamino)-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (10). - 3-Ethoxycarbonylaminopyrazino/2,3-e/-1,3,4-thiadiazine (3) (239 mg) in DMFDMA (2 ml) was heated under reflux (2 h). After evaporation of volatile components in vacuo, methanol (2 ml) was added and the precipitate collected by filtration to give 10 in 36% yield, mp 195-197°C (from methanol), m/e 253 (M^+), nmr ($DMSO-d_6$/TMS) δ: 1.27 (t, $CH_2\underline{CH_3}$), 3.20 (s, CH_3), 4.21 (q, $\underline{CH_2}CH_3$), 7.95 (d), 8.04 (d) (H_6,H_7), 10.44 (br s, NH), J_{H_6,H_7} = 2.2 Hz, $J_{CH_2CH_3}$ = 7.2 Hz.
Anal.Calcd. for $C_9H_{11}N_5O_2S$: C, 42.67; H, 4.37; N, 27.65. Found: C, 42.89; H, 4.38; N, 27.34.

3-Ethoxycarbonylamino-8(7H)-thioxo-s-triazolo/3,4-a/pyrazine (11). - 3-Ethoxycarbonylaminopyrazino/2,3-e/-1,3,4-thiadiazine (3) (250 mg) in aqueous potassium hydroxide solution (3%, 5 ml) was heated under reflux (2 h). The precipitate obtained after neutralization with aqueous hydrochloric acid was collected by filtration to give 11 in 29% yield, mp>300°C (from ethanol), m/e 239 (M^+), nmr ($DMSO-d_6$/RMS δ: 1.26 (t, $CH_2\underline{CH_3}$), 4.18 (q, $\underline{CH_2}CH_3$), 5.70 (br s, NH), 7.01 (d, H_6), 7.06 (br s, NH), 7.63 (d, H_5), J_{H_5,H_6}= 5.8 Hz, $J_{CH_2CH_3}$ = 7.2 Hz.
Anal.Calcd. for $C_8H_9N_5O_2S.HCl.1/2\ H_2O$: C, 38.70; H, 4.60; N, 28.20. Found: C, 38.16; H, 3.64; N, 28.51.

3-Amino-8(7H)-thioxo-s-triazolo/4,3-a/pyrazine (13). - a) 3-Ethoxycarbonylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (3) (400 mg) in DMF (3 ml) was heated (150°C, 4 h). To the residue, obtained after evaporation of the solvent in vacuo, methanol (2 ml) was added and the precipitate collected by filtration to give 13 in 30% yield, mp>300°C (from ethanol), m/e 167 (M^+), nmr ($DMSO-d_6$/TMS) δ: 3.47 (br s, NH_2), 6.73 (d, H_6), 6.79 (br s, NH), 7.57 (d, H_5), J_{H_5,H_6} = 5.0 Hz.

Anal.Calcd. for $C_5H_7N_5OS$: C, 32.69; H, 3.80; N, 37.81. Found: C, 32.53; H, 3.79; N, 35.89.

b) The same compound was obtained when 3 (100 mg) was heated (1 h) in aqueous hydrochloric acid (15%, 1 ml). The precipitate was dissolved in water and neutralized with aqueous solution of potassim hydroxide (4%). Precipitate was collected by filtration to give 13; ir spectrum was identical with that of the compound obtained under a).

4-Ethoxycarbonyl-1-/2-pyrazinyl-3(4H)-thioxo/semicarbazide (12). - a) 3-Ethoxycarbonylaminopyrazino/2,3-c/-1,3,4-thiadiazine (3) (300 mg) in methanol saturated with hydrogen chloride (5 ml) was heated under reflux (2 h). The precipitate was collected by filtration to give 12 in 32% yield, mp 237-238°C, m/e 257 (M^+), nmr ($DMSO-d_6$/TMS) δ: 1.28 (t, $CH_2\underline{CH_3}$), 4.22 (q, $\underline{CH_2}CH_3$), 6.81 (d), 6.95 (d) (H_5,H_6), 9.15 (br s, NH), 11.50 (br s, NH), J_{H_5,H_6} = 1.5 Hz, $J_{CH_2CH_3}$ = 7.1 Hz.
Anal.Calcd. for $C_8H_{11}N_5O_3$: C, 37.34; H, 4.30; N, 27.22. Found: C, 37.42; H, 4.40; N, 26.91.

3-Methylamino-8(7H)-thio-s-triazolo/4,3-a/pyrazine hydrochloride (14). - 3-(N-Ethoxycarbonyl-N-methylamino)pyrazino/2,3-e/-1,3,4-thiadiazine (10) (100 mg) in aqueous potassium hydroxide solution (4%, 3 ml) was heated under reflux (4 h).The solution was acidified with aqueous hydrochloric acid to pH 1, and the precipitate was collected by filtration to give 14 in 67% yield, mp>300°C (from ethanol), m/e 181 (M^+), nmr (CF_3COOH/TMS) δ : 3.25 (s, CH_3), 6.99 (d, H_6), 7.52 (d, H_5), J_{H_5,H_6}=5.8Hz.
Anal.Calcd. for $C_6H_{11}N_5ClOS$: C, 30.57; H, 4.27; N, 29.71. Found: C, 31.11; H,4.38; N, 29.84.

3-Ethoxycarbonylmethylamino-8-methylthio-s-triazolo/4,3-a/pyrazine (15). - 3-Ethoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) in DMFDMA (2 ml) was left at room temperature (22 h). The oily residue, obtained after evaporation of volatile components, crystallized on standing at room temperature to give 15 in 36% yield, mp 207-209°C (from methanol), m/e 267 (M^+), nmr ($DMSO-d_6$/TMS) δ: 1.21 (t, $CH_2\underline{CH_3}$), 2.59 (s, CH_3), 4.09 (q, $\underline{CH_2}CH_3$), 4.18 (d,$NH\underline{CH_2}$), 7.50 (d, H_6), 7.54 (br s, $\underline{NH}CH_2$), 7.92 (d, H_5), J_{H_5,H_6} = 5.1 Hz, $J_{CH_2CH_3}$ = 7.3 Hz, J_{NHCH} = 5.2 Hz.

Anal.Calcd. for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.19. Found: C, 44.96; H, 4.89; N, 26.35.

Methyl 2-/N-(8-methylthio-s-triazolo/4,3-a/pyrazinyl-3/amino-3-diethylamino-propenoate (16). - 3-Ethoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) in DMFDMA (2 ml) was heated under reflux (2 h). The volatile components were evaporated in vacuo and a mixture of methanol and water (1:1, 5 ml) was added to the residue. The precipitate was collected by filtration to give 16 in 22% yield, mp 124-126°C (from ethanol), m/e 308 (M^+), nmr (DMSO-d_6/TMS) δ : 2.56 (s, SCH_3), 2.99 (s, NMe_2), 3.28 (s, OMe), 7.37 (s, CH=C), 7.51 (d, H_6), 7.73 (br s, NH), 8.02 (s, H_5), J_{H_5,H_6} = 4.9 Hz.
Anal.Calcd. for $C_{12}H_{16}N_6O_2S$: C, 46.74; H, 5.23; N, 27.25. Found: C, 46.51; H, 5.49; N, 26.91.

3-Carbazoylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (17). - 3-Ethoxycarbonylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) and hydrazine hydrate (80%, 3 ml) in ethanol (5 ml) was heated under reflux (45 min). The residue, obtained after evaporation of solvent, gave 17 in 57% yield, mp 225-227°C (from ethanol), m/e 239 (M^+), nmr (DMSO-d_6/TMS) δ: 3.66 (d, NH$\underline{CH}_2$), 3.95 (br s, NH_2), 6.75 (t, N$\underline{H}$$CH_2$), 7.70 (d), 7.79 (d) ($H_6$,$H_7$), 9.45 (br s, NH), J_{H_6,H_7} = 1.8 Hz, J_{NHCH_2} = 5.4 Hz.
Anal.Calcd. for $C_7H_9N_7OS$: C, 35.14; H, 3.79; N, 40.97. Found: C, 34.97; H, 3.88; N, 40.61.

2-/N-(1H-Pyrazino/2,3-e/-1,3,4-thiadiazinyl-3)/amino-3-dimethylaminopropenoic acid hydrazide (18). - A solution of 3-carbazoylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (17) (239 mg) in DMFDMA (2 ml) was left at room temperature (7 h).The precipitate was collected by filtration to give 18 in 21% yield, mp 214-216°C (from ethanol), m/e 294 (M^+), nmr (DMSO-d_6/TMS) δ: 2.74 (s, NMe_2), 7.5 (br s, NH), 7.64 (d), 7.79 (d) (H_6,H_7), 7.74 (s, CH=C), 9.45 (br s, NH_2), 9.5 (br s, NH), 10.2 (br s, NH), J_{H_6,H_7} = 1.8 Hz.
Anal.Calcd. for $C_{10}H_{14}N_8OS$: C, 40.80; H, 4.79; N, 38.07. Found: C, 40.88; H, 4.75; N, 37.79.

3-Amino-8-methylthio-s-triazolo/4,3-a/pyrazine (19). - 3-Ethoxycarbonylamino-8-methylthio-s-triazolo/4,3-a/pyrazine (15) (267 mg) was heated in PPA (2 g, 130°C, 9 h). After cooling, water (20 ml) was added, neutralized with the solid sodium hydrogen carbonate and extracted with chloroform (3 times, 20 ml each time). Evaporation of combined extracts gave 19 in 24% yield, mp 251°C (decomp) (from methanol), m/e 181 (M^+), nmr DMS-d_6/TMS) δ : 2.54 (s, SMe), 6.65 (br s, NH_2), 7.43 (d, H_6), 7.82 (d, H_5), J_{H_5,H_6} = 4.7 Hz.
Anal.Calcd. for $C_6H_9N_5OS$: C, 36.17; H, 4.55; N, 35.15. Found: C, 36.80; H, 3.83; N, 35.06.

3-Carbazoylmethylamino-8-methylthio-s-triazolo/4,3-a/pyrazine (20). - 3-Ethoxycarbonylmethylamino-8-methylthio-s-triazolo/4,3-a/pyrazine (15) (267 mg) and hydrazine hydrate (80%, 60 mg) in ethanol (3 ml) was left at room temperature (14 h). The precipitate was collected by filtration to give 20 in 35% yield, mp>300°C (from ethanol), m/e 253 (M^+), nmr (DMSO-d_6/TMS) δ: 2.65 (s, SMe), 3.42 (br s, NH_2), 4.11 (d, $NHCH_2$), 7.55 (t, $N\underline{H}CH_2$), 7.70 (d, H_6), 8.13 (d, H_5), 9.5 (br s, NH), J_{H_5,H_6} = 5.2 Hz, J_{NHCH_2} = 6.1 Hz.
Anal.Calcd. for $C_8H_{11}N_7OS.1/2\ H_2O$: C, 36.63; H, 4.61; H, 37.83. Found: C, 36.10; H, 4.52; N, 37.53.

3-Carboxymethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (21). - Ethoxycarbonylmethylaminopyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) in aqueous hydrochloric acid (1:1,3 ml) was left at room temperature (6 h). The precipitate was collected by filtration to give 21 in 34% yield, mp 220-222°C, m/e 225 (M^+), nmr (DMSO-d_6/TMS) δ: 3.72 (s, $NH\underline{CH_2}$), 7.65 (d), 7.75 (d) (H_6,H_7), J_{H_6,H_7} = 2.2 Hz.
Anal.Calcd. for $C_7H_8N_5ClO_4S$: C, 31.05; H, 3.35; N, 25.87. Found : C, 31.05; H, 3.40; N, 25.40.

3-Carboxymethylamino-8(7H)-thioxo-s-triazolo/4,3-a/pyrazine (22). - a) 3-Ethoxycarbonylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) in aqueous solution of potassium hydroxide (4%, 3 ml) was heated under reflux (1 h). The solution was after cooling neutralized with aqueous hydrochloric acid (1:1) and precipitate was collected by filtration to give 22 in 21% yield, mp>300°C (from a mixture of DMF, methanol and water), m/e 225 (M^+), nmr (DMSO-d_6/TMS) δ: 4.25 (br s, $NH\underline{CH_2}$), 6.55 (br s, $N\underline{H}CH_2$), 6.62 (d, H_6), 6.78 (d, H_5), 10.27 (br s, NH), J_{H_5,H_6} = 5.1 Hz.

Anal. Calcd. for $C_7H_7N_5O_2S$: C, 37.32; H, 3.13; N, 31.09. Found: C, 37.51; H, 3.27; N, 31.73.

3-Ethoxycarbonylmethylamino-8(7H)-thioxo-s-triazolo/4,3-a/pyrazine (23). - 3-Ethoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) was heated in DMF (3 ml) under reflux (11 h). The solution was allowed to cool and the precipitate was collected by filtration to give 23 in 43% yield, mp>300°C (from ethanol), m/e 253 (M^+), nmr (DMSO-d_6/TMS) δ : 1.23 (t, $CH_2\underline{CH_3}$), 4.14 (q, $\underline{CH_2}CH_3$), 4.19 (t, $NH\underline{CH_2}$), 6.90 (d, H_6), 7.64 (br s, $N\underline{H}CH_2$), 7.65 (d, H_5), J_{H_5,H_6} = 5.6 Hz, $J_{CH_2CH_3}$ = 7.6 Hz, J_{NHCH_2} = 6.1 Hz.

Anal.Calcd. for $C_9H_{13}N_5O_3S$: C, 39.90; H, 4.78; N, 25.85. Found: C, 39.67; H, 4.78; N, 25.85.

3-Methylthio-s-triazolo/4,3-a/pyrazin-8(7H)-one (24). - a) 3-Ethoxycarbonylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (5) (253 mg) in methanol, saturated with hydrogen chloride (5 ml), was heated under reflux (3 h). The precipitate was collected by filtration to give 24 in 32% yield, mp 272-275°C (from ethanol), m/e 182 (M^+), nmr (DMSO-d_6/TMS) δ : 2.69 (s, Me), 6.87 (d, H_6), 7.20 (d, H_5), 12.0 (br s, NH), J_{H_5,H_6} = 5.4 Hz.

Anal.Calcd. for $C_6H_6N_4OS$: C, 39.55; H, 3.31; N, 30.74. Found: C, 39.31; H, 3.55; N, 30.46.

b) 3-Carbazoylmethylamino-1H-pyrazino/2,3-e/-1,3,4-thiadiazine (17) (239 mg) in methanol saturated with hydrogen chloride (5 ml) was heated under reflux (15 min). The precipitate was collected by filtration to give 24 in 41 % yield. The ir spectrum was identical with that of the compound described under a).

8-Methoxy-3-methylthio-s-triazolo/4,3-a/pyrazine (25). - 3-Thioxo-2,3-dihydro-s-triazolo/4,3-a/pyrazin-8(7H)-one (7) (168 mg) in DMFDMA (1 ml) was left at room temperature (14 h). The precipitate was collected by filtration to give 25 in 24% yield, mp 163-164°C (from ethanol), m/e 196 (M^+), nmr ($CDCl_3$/TMS) δ : 2.64 (s, SMe), 3.70 (s, OMe), 7.37 (s, H_5, H_6).

Anal.Calcd. for $C_7H_8N_4OS$: C, 42.84; H, 4.10; N, 28.55. Found: C, 42.87, H, 4.08; N, 28.45.

7-Methyl-3-methylthio-s-triazolo/4,3-a/pyrazin-8(7H)-one (26). - 3-Methylthio-s-triazolo/4,3-a/pyrazin-8(7H)-one (24) (182 mg) and DMFDMA (1.5 ml) was heated under reflux (30 min). The precipitate was, after cooling, collected by filtration to give 26 in 27% yield, mp 185-187°C (from ethanol), m/e 196 (M^+), nmr ($CDCl_3$/TMS) δ: 2.81 (s, SMe), 3.56 (s, NMe), 6.67 (d, H_6), 6.93 (d, H_5), J_{H_5,H_6} = 6.1 Hz.
Anal.Calcd. for $C_7H_8N_4OS$: C, 42.84; H, 4.10; N, 28.55. Found: C, 42.95; H, 4.15; N, 28.36.

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