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TRANSFORMATIONS OF 1,2,4-THIADIAZOLO/2,3-x/AZINES

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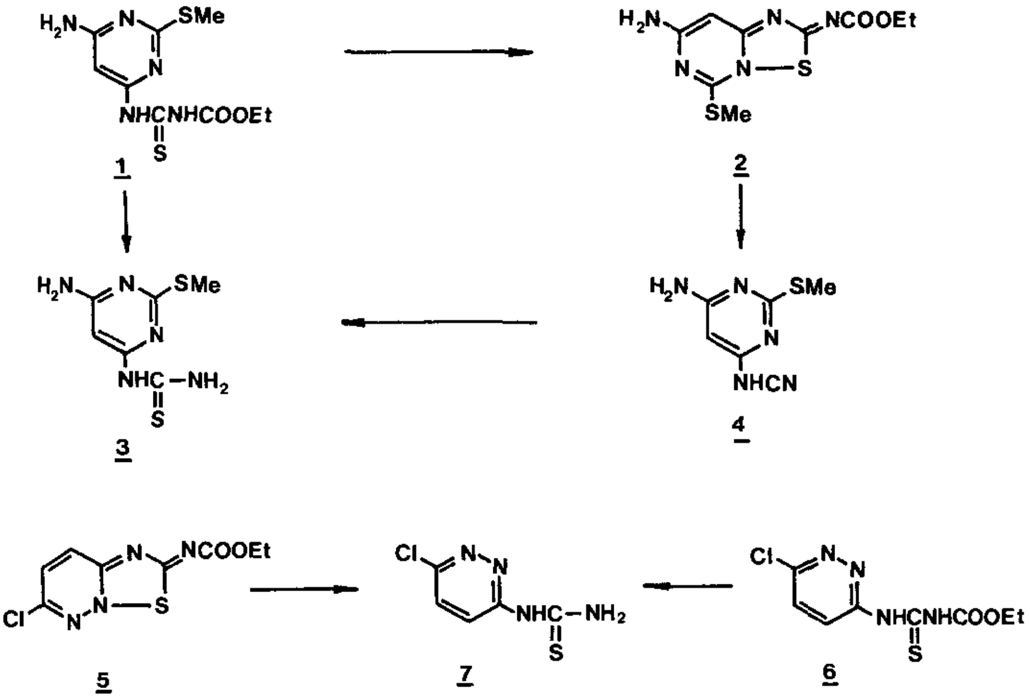
Abstract - Hydrolysis of 1,2,4-thiadiazolo/2,3-c/pyrimidine derivative 2 produced cyanoaminopyrimidine 4, while treatment of 1,2,4-thiadiazolo/2,3-b/pyridazine 5 with hydrazine hydrate gave thiourea derivative 7. 1,2,4-Thiadiazolo/2,3-a/pyridine 8 and 1,2,4-thiadiazolo//2,3-a/pyrazine 9 gave by alkaline hydrolysis the corresponding pyridopyrimidine 10 and pteridine 11, respectively. The compound 10 was converted with phenacyl bromide into 14 and further cyclized in PPA into pyrido/2,3-d/thiazolo/2,3-a/pyrimidine 15. Pyrazinylthiourea derivative 16 was cyclized in acidic solution into thiazolo/4,5-b/pyrazine 17, which was converted by hydrolysis and decaroxylation into amino derivative 20. This gave with ethyl acetoacetate pyrazino/2',3':4,5/thiazolo /3,2-a/pyrimidine 23. 1,2,4-Thiadiazoloazines 24 and N-ethoxycarbonyl-N'-azinylthioureas 25 were transformed with hydrogen peroxide into urea derivatives 26.

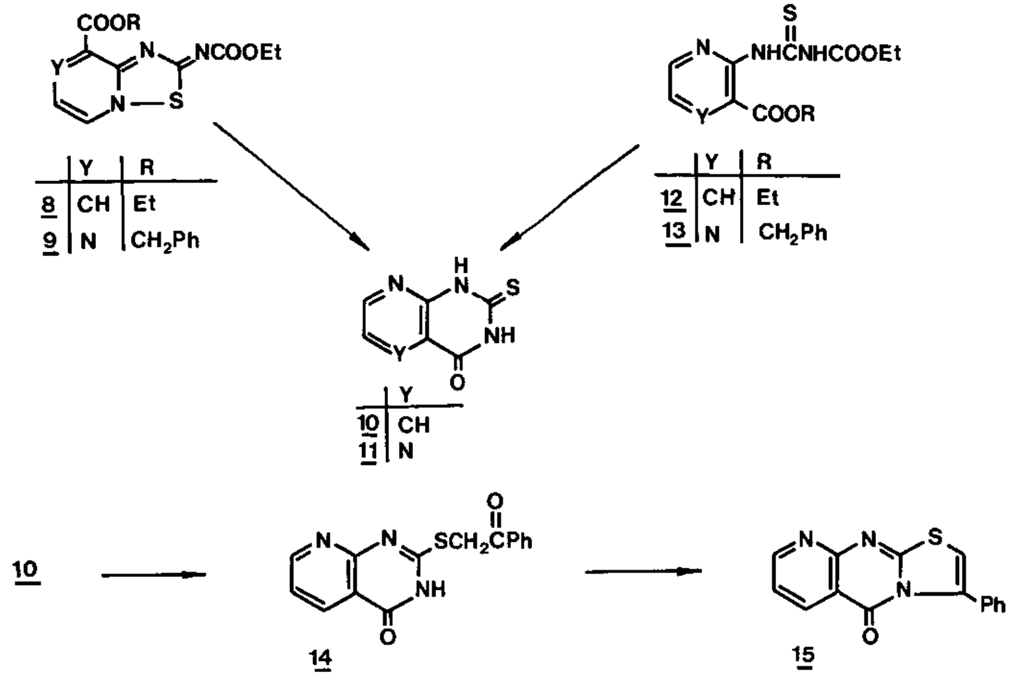
The synthesis and some transformations of 1,2,4-thiadiazolo/2,3-a/azines have been the interest of our previous investigations.[1-3] We found that fused 1,2,4-thiadiazoles are not stable compounds. In alkaline medium the S_3-N_4 bond is easily cleaved to give various products. 2-Ethoxycarbonylimino-1,2,4-thiadiazolo/2,3-a/pyridine gave N-(2-pyridayl)thiourea and 2-cyanopyridine,[1] while in the case of 2-ethoxycarbonylamino-1,2,4-thiadiazolo/2,3-a/pyrimidine, the pyrimidine ring is cleaved to give 3-amino-ethoxycarbonylamino-1,2,4-thiadiazole.[1] A similar reaction was also observed in the case of 2-ethoxycarbonylimino-s-triazolo/5,1-c/-1,2,4-thiadiazolo-/2,3-a/pyrazine.[3]

In this paper we report some new transformations of 1,2,4-thiadiazolo/2,3-x/ azines. The alkaline hydrolysis of 7-amino-2-ethoxycarbonylimino-5-methylthio-1,2,4-thiadiazolo/2,3-c/pyrimidine (2) prepared from the corresponding ethoxycarbonylthiourea (1), gave 6-amino-4-cyanoamino-2-methylthiopyrimidine (4) as the only product.

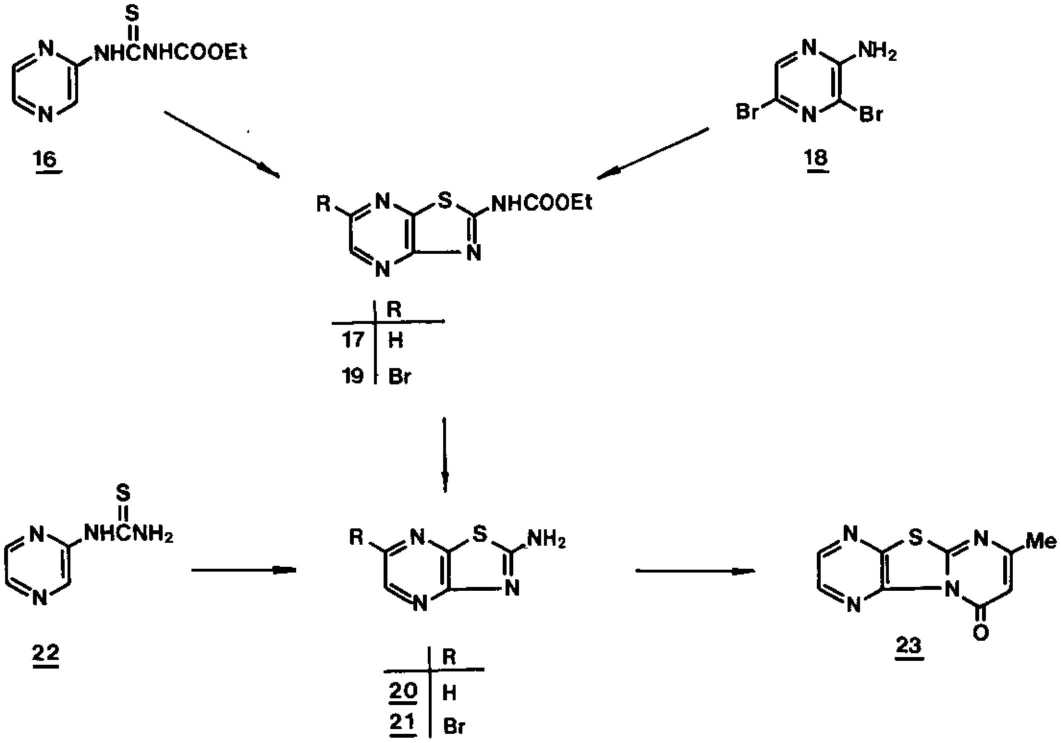


Scheme 1

This was further converted with sodium *hydrogen sulphide into N-(6-amino-2-methyl*thiopyrimidinyl-4)thiourea (3). The same compound was also obtained by alkaline hydrolysis, followed by decarboxylation, of 1. Attempts to substitute chlorine in 6-chloro-2-ethoxycarbonylimino-1,2,4-thiadiazolo/2,3-b/pyridazine (5) or in the corresponding N-ethoxycarbonyl-N'-(6-chloropyridazinyl-3)thiourea (6) with hydrazine resulted in the formation of N-(6-chloropyridazinyl-3)thiourea (7). (Scheme 1). Hydrolysis of 2-ethoxycarbonylimino-8-ethoxycarbonyl-1,2,4-thiadiazolo/2,3-a/pyridine (8) and of 2-ethoxycarbonylimino-8-benzyloxycarbonyl-1,2,4-thiadiazolo/2,3-a/pyrazine (9) gave 2-thioxopyrido/2,3-d/pyrimidin-4-one (10) and 2-thioxotetrahydropteridin-4-one (11), respectively. The reaction proceeds first as a cleavage of the S_3-N_4 bond of the fused thiadiazole systems 8 and 9 followed by cyclization of the resulting ethoxycarbonylthiourea derivatives 12 and 13 with the ester group at ortho position. The same products were obtained also by cyclization of the thiourea derivatives 12 and 13. The pyridopyrimidine derivative 10 *was transformed with phenacyl* bromide into 2-phenacylthiopyrido/2,3-d/pyrimidin-4-one (14) which was cyclodehydrated



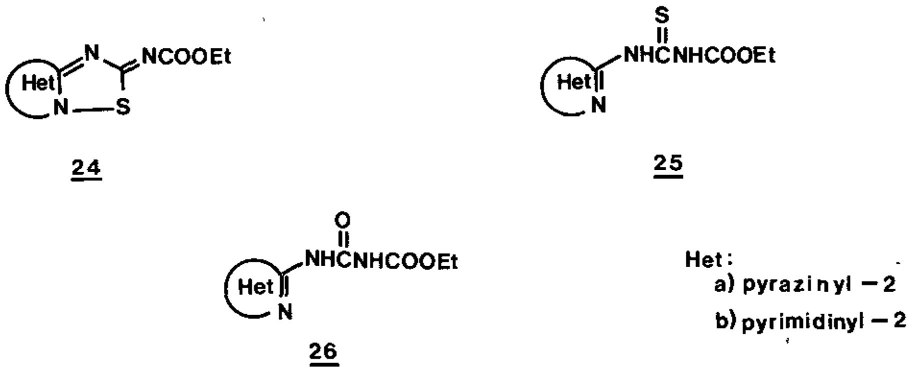
Scheme 2



Scheme 3

in PPA to give 3-phenylpyrido/2,3-*d*/thiazolo/3,2-a/ pyrimidin-5-one (15). (Scheme 2). There is not very much known about the thiazolo/4,5-*b*/pyrazine system. The derivatives of this system have been previously prepared by cyclization of 2-amino-3-mercaptopyrazines.[4] We describe here two new approaches to this system. *N*-Ethoxycarbonyl-*N'*-(pyrazinyl-2)thiourea (16) cyclized in aqueous hydrochloric acid into 2-ethoxycarbonylaminothiazolo/4,5-*b*/pyrazine (17). On the other hand, 2-amino-3,5-dibromopyrazine (18) reacted with ethoxycarbonyl isothiocyanate to give the 6-bromo derivative of the bicyclic system 19 without isolation of the corresponding thiourea intermediate. Hydrolysis of the compounds 17 and 19 under alkaline conditions gave 2-aminothiazolo/4,5-*b*/pyrazines 20 and 21, respectively. Bromination of 17 with bromine in acetic acid is taking place at position 6 to give 6-bromo derivative 21, identical with the compound obtained from 19 by hydrolysis and decarboxylation of ethoxycarbonyl group. An attempt to prepare 2-aminothiazolo/4,5-*b*/pyrazine (20) from the corresponding 2-pyrazinylthiourea 22 was unseccessful. 2-Aminothiazolo/4,5-*b*/pyrazine (20) reacted with ethyl cyanoacetate in PPA to give a derivative of a tricyclic system 7-methylpyrazino/2',3':4,5/thiazolo/3,2-*a*/pyrimid-9-one (23). (Scheme 3).

An attempt to use hydrogen peroxide as a reagent for cyclization of *N*-heteroarylthioureas into fused thiadiazoloazines has been unsuccessful, since only the corresponding ureas have been isolated. The reaction proceeds most probably through S-oxides and sulphones, which have been previously isolated in some other examples.[5,6] Furthermore, when 1,2,4-thiadiazoloazines (24) were treated with hydrogen peroxide the corresponding azinyl ureas 26 were produced, identical with the compounds obtained by treatment of *N*-ethoxycarbonyl-*N'*-azinylthioureas 25 with hydrogen peroxide. (Scheme 4).



Scheme 4

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 a PERKIN-ELMER instrument RMU-6L, 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.

The Synthesis of N-Ethoxycarbonyl-N'-azinylthioureas. General Method. To a solution of aminoazine (0.001 mole) in chloroform (5 ml) ethoxycarbonyl isothiocyanate (0.001 mole) was added and the mixture was heated under reflux (30 min). The precipitate was, after cooling, filtered and recrystallized from an appropriate solvent. The following compounds were prepared according to this method.

N-Ethoxycarbonyl-N'-(6-amino-2-methylthiopyrimidinyl-4)-thiourea (1).- This compound was prepared from 4,6-diamino-2-methylthiopyrimidine in 83% yield, mp 193-195°C (from methanol), m/z 287 (M^+), nmr (DMSO-d_6/TMS) δ: 1.28 (t, OCH_2Me), 2.46 (s, Me), 4.26 (q, OCH_2Me), 7.13 (br s, NH_2), 7.33 (s, H_5), 11.79 (br s, NH), 12.12 (br s, NH), J_{CH_2Me} = 7.1 Hz. Anal.Calcd.for $C_9H_{13}N_5O_2S_2$: C, 37.61; H, 4.56; N, 24.37. Found: C, 37.55; H, 4.59; N, 24.15.

N-Ethoxycarbonyl-N'-(3-benzyloxycarbonylpyrazinyl-2)-thiourea (13). This compound was prepared from benzyl 2-aminopyrazine-3-carboxylate in 78% yield, mp 159-162°C (from methanol), m/z 360 (M^+), nmr (DMSO-d_6/TMS) δ: 1.26 (t, OCH_2Me), 4.25 (q, OCH_2Me), 5.40 (s, CH_2), 7.49 (m, br s, Ph), 8.77 (s), 8.88 (s) (H_5,H_6), 11.94 (br s, NH), J_{H_5,H_6} = 2.4 Hz, J_{CH_2Me} = 7.4 Hz. Anal.Calcd.for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.47; N, 15.54. Found: C, 53.39; H, 4.42; N, 15.32.

The following 1,2,4-thiadiazoloazines were prepared according to the procedure described in lit.[2]

7-Amino-2-ethoxycarbonylimino-5-methylthio-1,2,4-thiadiazolo/2,3-c/pyrimidine (2). - This compound was prepared from 1 in 67% yield, mp 247-250°C (decomp.)(from methanol), m/z 285 (M^+), nmr (DMSO-d_6/TMS, 120°C) δ: 1.26 (t, OCH_2Me), 2.74 (s, Me), 4.27 (q, OCH_2Me), 6.19 (s, H_8), 7.25 (br s, NH), J_{CH_2Me} = 7.0 Hz. Anal.Calcd.for $C_9H_{11}N_2O_2S_2$: C, 37.87; H 3.88; N, 24.54. Found: C, 37.62; H, 4.10; N, 24.29.

8-Benzyloxycarbonyl-2-ethoxycarbonylimino-1,2,4-thiadiazolo/2,3-a/pyrazine (9). - This compound was prepared from 13 in 52% yield, mp 227-230°C (from methanol), m/z 258 (M^+), nmr (DMSO-d_6/TMS, 100°C) δ: 1.32 (t, OCH_2Me), 4.35 (q, OCH_2Me), 5.49 (s, CH_2), 7.43 (m, Ph), 8.35 (d, H_6), 9.12 (d, H_5), $J_{H_5H_6}$ = 4.1 Hz, J_{CH_2Me} = 7.4 Hz.

Anal.Calcd.for: $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.93; N, 15.63. Found: C, 53.61; H, 3.81; N, 15.54.

N-(6-Amino-2-methylthiopyrimidinyl-4)-thiourea (3). - a) The compound 4 (181 mg) was heated in an aqueous saturated solution of sodium hydrogen sulphide (3 h). The precipitate was filtered to give 3 in 47 % yield, mp 207-210°C (from methanol), m/z 215 (M^+), nmr (DMSO-d_6/TMS) δ: 2.43 (s, Me), 5.92 (s, H_5), 8.97 (br s, NH, 10.41 (br s, NH). Anal.Calcd.for $C_6H_9N_5S_2$: C, 33.47; H, 4.21; N, 32.48. Found: C, 33.70; H, 4.25; N, 32.52.

b) The compound 1 (287 mg) in aqueous solution of sodium hydroxide (5 %, 5 ml) was left at room temperature (12 h). The precipitate was filtered to give 3 in 4 % yield. The ir spectrum was identical with that of the compound described under a).

6-Amino-4-cyanoamino-2-methylthiopyrimidine (4). - The compound 2 (285 mg) was heated in an aqueous solution of sodium hydroxide (5 %, 10 ml, 3 h). The solution was neutralized (1 M aqueous hydrochloric acid) and the precipitate was filtered to give 4 in 26 % yield, mp 250°C (decomp.), m/z 181 (M^+), nmr (DMSO-d_6/TMS) δ: 2.51 (s, Me), 5.69 (s, H_5), 7.24 (br s, NH). Anal.Calcd.for $C_6H_8N_5SCl$: C, 33.10; H, 3.70; N, 32.17. Found: C, 32.75; H, 3.32; N, 32.49.

N-(6-Chloropyridazinyl-3)-thiourea (7). - a) To a solution of 5[2] (230 mg) in ethanol (5 ml) hydrazine hydrate (80 %, 2 ml) was added and the mixture was left at room temperature (12 h). The precipitate was filtered to give 7 in 33 % yield, mp 223-226°C (from methanol), m/z 188 (M^+), nmr (DMSO-d_6/TMS) δ: 7.06 (d, H_5), 7.34 (d, H_4), 8.58 (br s, NH), 9.26 (br s, NH_2), J_{H_4,H_5} = 9.0 Hz. Anal.Calcd.for $C_5H_5N_4SCl$: C, 31.83; H, 2.67; N, 29.70. Found: C, 31.79; H, 3.05; N, 29.78.

b) A mixture of 6[2] (260 mg) and hydrazine hydrate (80 %, 2 ml) in ethanol (10 ml) was left at room temperature (5 h). The precipitate was filtered to give 7 in 36 % yield. The ir spectrum of it was identical with that of the compound described under a).

2-Thioxo-2,3-dihydropyrido/2,3-d/pyrimidin-4(1H)-one (10). - A solution of 8[2] (295 mg) in aqueous sodium hydroxide (5 %, 3 ml) was heated under reflux (1 h). The mixture was neutralized with hydrochloric acid (1 M), and the precipitate was filtered to give 10 in 61 % yield, mp>300°C, ir spectrum of which was identical with that of an authentic sample.[9]

4-Oxo-2-thioxo-1,2,3,4-tetrahydropteridine (11). - A solution of 13 (720 mg) and sodium ethoxide, prepared from sodium (46 mg) in ethanol (10 ml), was heated under reflux (30 min). The solvent was evaporated in vacuo, water (5 ml) was added to the residue and neutralized with hydrochloric acid to give 11 in 48 % yield, mp>300°C, lit.[8] mp>300°C.

2-Phenacylthiopyrido/2,3-d/pyrimidin-4(3H)-one (14). A mixture of 10 (179 mg) and phenacyl bromide (211 mg) in solution of sodium methoxide, prepared from sodium (23 mg) in methanol (10 ml), was left at room temperature (3 h). The precipitate was filtered to give 14 in 42 % yield, mp 219-221°C, m/z 297 (M^+), nmr (DMSO-d_6/TMS) δ: 4.96 (s,CH_2), 7.36 (dd, H_6), 7.59 (m, 3H, Ph), 8.06 (m, 2H, Ph), 8.39 (dd, H_5), 12.95 (br s, NH), J_{H_5,H_6} = 7.6 Hz, J_{H_6,H_7} = 4.6 Hz, J_{H_5,H_7} = 1.5 Hz. Anal.Calcd.for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.72; N, 14.13. Found: C, 60.65; N, 3.85; N, 14.19.

3-Phenylpyrido/2,3-d/thiazolo/2,3-a/pyrimidin-5-one (15). - The compound 14 (297 mg) was heated in PPA (1.5 g, 100°C, 4 h). The mixture was, after cooling, diluted with water (6 ml) and neutralized with solid sodium hydrogen carbonate. The precipitate was filtered and purified by sublimation (235°C, 1 torr) to give 15 in 33 % yield, mp 307-314°C, m/z 279 (M^+), nmr (DMSO-d_6/TMS, 35°C) δ: 7.04 (s, H_2), 7.29 (dd, H_7), 7.35 (m, Ph), 8.39 (dd, H_6), 8.83 (dd, H_8), J_{H_7,H_8} = 4,6 Hz, J_{H_6,H_7} = 7.6 Hz, J_{H_6,H_8} = 1.5 Hz. Anal. Calcd. for $C_{15}H_9N_3CS$: C, 64.50; H, 3.24; N, 15.04. Found: C, 64.79; H, 3.42; N, 14.92.

2-Ethoxycarbonylaminothiazolo/4,5-b/pyrazine (17). - The compound 16[2] (200 mg) was heated in hydrochloric acid (20%, 6 ml, 2h). The precipitate was filtered to give 17 in 58 % yield, mp>300°C (from a mixture of DMF and water), m/z 224 (M^+), nmr (DMSO-d_6/TMS, 100°C) δ: 1.29 (t, OCH_2Me), 4.24 (q, OCH_2Me), 8.26 (d), 8.43 (d), (H_5,H_6), J_{H_5,H_6} = 2.6 Hz. J_{CH_2Me} = 7.0 Hz. Anal.Calcd.for $C_8H_8N_4O_2S$: C, 42.85; H, 3.59; N, 24.98. Found: C, 42.70; H, 3.72; N, 25.14.

6-Bromo-2-ethoxycarbonylaminothiazolo/4,5-b/pyrazine (19). - A mixture of 18 (253 mg) and ethoxycarbonyl isothiocyanate (2 ml) was heated (10 min, 100°C). Methanol (5 ml) was added and the solution was heated under reflux (30 min). The precipitate was, after cooling, filtered to give 19 in 41 % yield, mp 252-254°C (from a mixture of DMF and water), m/z 302 (M^+), nmr (DMSO-d_6/TMS) δ: 1.30 (t, OCH_2Me), 4.25 (q, OCH_2Me), 8.71 (s, H_5), J_{CH_2Me} = 7.1 Hz. Anal.Calcd.for $C_8H_7BrN_4O_2$: C, 31.69; H, 2.32; N,18.48. Found: C, 31,50; H, 2.63; N, 18.94.

2-Aminothiazolo/4,5-b/pyrazine (20). - The compound 17 (200 mg) was heated in an aqueous solution of sodium hydroxide (50 %, 6 ml, 5 h). The solution was neutralized with hydrochloric acid (1:1) and the precipitate was filtered to give 20 in 54 %

yield, mp 203°C (decomp.) (from methanol), m/z 152 (M^+), nmr ($DMSO-d_6$)δ: 8.08 (d), 8.30 (d), (H_5, H_6), 8.49 (br s, NH_2), J_{H_5,H_6} = 2.7 Hz. Anal.Calcd.for $C_5H_4N_4S$: C, 39.46; H, 2.64; N, 36.81. Found: C, 39.12; H, 2.83; N, 37.03.

2-Amino-6-bromothiazolo/4,5-b/pyrazine (21). - a) The compound 19 (135 mg) was heated in aqueous solution of sodium hydroxide (10 %, 5 ml, 5 h). The mixture was, after cooling, neutralized with hydrochloric acid (1 M) and the precipitate was filtered to give 21 in 71 % yield, mp 284-286°C (from ethanol), m/z 231 (M^+), nmr ($DMSO-d_6$/TMS) δ: 8.27 (s, H_5), 8.57 (br s, NH_2). Anal.Calcd.for $C_5H_3BrN_4S$: C, 25.98; H, 1.30; N, 24.24. Found: C, 26.26; H, 1.30; N, 24.17.

b) To a solution of 20 (80 mg) in glacial acetic acid (2 ml) bromine (80 mg) in glacial acetic acid (1 ml) and sodium acetate (180 mg) were added and the suspension was left at room temperature (2h). Water (5 ml) was added and the mixture was neutralized with ammonium hydroxide (28 % aqueous solution). The precipitate was filtered to give 21 in 15 % yield. The ir spectrum of the compound was identical with that of the compound described under a).

N-(Pyrazinyl-2)thiourea (22). - The compound 16[2] (226 mg) was heated under reflux in an aqueous solution of sodium hydroxide (1 M, 3 ml, 3h). The precipitate was, after cooling, filtered to give 22 in 49 % yield, mp 236-238°C (from methanol), m/z 154 (M^+). Anal.Calcd.for $C_5H_6N_4S$: C, 38.95; H, 3.92; N, 36.34. Found: C, 39.12; H, 3.75; N, 36.15.

7-Methylpyrazino/2',3':4,5/thiazolo/3,2-a/pyrimidin-9-one (23). - A mixture of 20 (152 mg) and ethyl acetoacetate (160 mg) was heated (85°C, 3 h) in PPA (5 g). After cooling, water (5 ml) was added and the solution was neutralized with solid sodium hydrogen carbonate. The resulting mixture was extracted with chloroform (3 times, 20 ml each time) and the combined extracts were dried over anhydrous sodium sulphate. The evaporation of the solvent in vacuo gave 23 in 35 % yield, mp 280-281°C (from ethanol), m/z 218 (M^+), nmr ($DMSO-d_6$/TMS, 100°C) δ: 2,27 (s, Me), 6.20 (s, H_8), 8.59 (s, H_2,H_3). Anal.Calcd.for $C_9H_6N_4OS$: C, 49.53; H, 2.77; N, 25.67. Found: C, 49.73; H, 2.55; N, 25.96.

General Method for the Conversion of 1,2,4-Thiadiazoloazines into N-Heteroarylureas. - To a solution of 1,2,4-thiadiazoloazine (0.001 mole) in glacial acetic acid (2 ml) a solution of hydrogen peroxide (30 %, 2 ml) in glacial acetic acid (3 ml) was added. The mixture was stirred at room temperature (30 min), water (5 ml) was added and the solution neutralized with solid sodium hydrogen carbonate. The mixture was extracted with chloroform (3 times, 20 ml each time) and the combined extracts dried over anhydrous sodium sulphate. The evaporation of chloroform in vacuo gave the corresponding urea derivative. The following compounds were prepared according to this procedure.

N-Ethoxycarbonyl-N'-(pyrazinyl-2)-urea (26a).- This compound was prepared from 2-ethoxycarbonylimino-1,2,4-thiadiazolo/2,3-a/pyrazine 24a[2] in 47 % yield, mp 207-209^{o}C (from ethanol), m/z 210 (M^+). Anal.Calcd.for $C_8H_{10}N_4O_3$: C, 54.71; H, 4.79; N, 26.65. Found: C, 54.67; H, 4.83; N, 26.50

N-Ethoxycarbonyl-N'-(pyrimidinyl-2)-urea (26b).- This compound was prepared from 2-ethoxycarbonylimino-1,2,4-thiadiazolo/2,3-a/pyrimidine 24b[1] in 63 % yield, mp 198-200^{o}C (from ethanol), m/z 210 (M^+). Anal.Calcd.for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.79; N, 26.65. Found: C, 45.84; H, 4.51; N, 26.69.

An analogous procedure was used for the conversion of N-ethoxycarbonyl-N'-azinylthioureas 25 with hydrogen peroxide into the corresponding urea derivatives 26 in essentially the same yields.

ACKNOWLEDGEMENT

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