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# Studies on Pyrazine Derivatives, XLVI: The Synthesis of New Pyrazine Derivatives with *N′*-(Pyrazine-2-carbonyl)-hydrazinecarbodithioic Acid Methyl Ester Usage

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*4-Ω-alkylsubstituted derivatives of 1,2,4-triazole-2-thiones* ***2–7*** *were obtained using the high reactivity of* N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester* ***1*** *towards amines. In the reaction with cysteamine 1,3-thiazaethylene-1,2,4-triazole* ***8*** *formed. Aromatic amines and N-aminocycloalkylamines gave thiosemicarbazide derivatives* ***9–12*** *under the same conditions. The solution of sodium hydroxide caused the decomposition of compounds* ***11*** *and* ***12*** *and resulted in 4-piperidino- and 4-morpholino-thiosemicarbazides* ***13*** *and* ***14****. Compounds* ***11*** *and* ***12*** *were cyclized to appropriate 4-substituted 1,2,4-triazole-2-thiones* ***16*** *and* ***17*** *under the influence of DBU or potassium carbonate solution. The heating of derivative* ***12*** *with sulfuric acid led to disubstituted 1,3,4-thiadiazole* ***18****.*

**Keywords** 1,2,4-triazoles; 4-N-cycloakylamino-thiosemicarbazides; dithiocarboxylic acid esters; pyrazine derivatives; tuberculostatic activity

## INTRODUCTION

Our previous research has shown that *N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **1** is a perfect substrate for the synthesis of heterocyclic systems like 1,3,4-oxadiazole and

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1,2,4-triazole with substituents of an arrangement that has a difficult access or is unattainable.[1,2] The example of that synthesis is the reaction of pyrazinoylcarbodithioic acid methyl ester with the ethanolamine, which forms 4-(2-hydroxyethyl)-[1,2,4]triazole-2-thione with the pyrazine moiety in the 5-position.[2]

The subject of this work was the study of the reactivity of **1** in reactions with primary aliphatic and aromatic amines and N-aminocycloalkylamines.

## RESULTS AND DISCUSSION

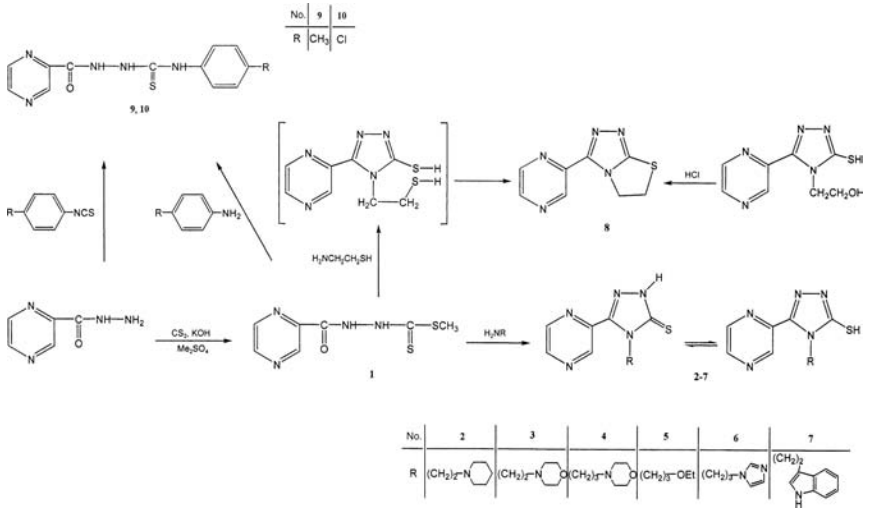
The starting *N′*-(pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **1** was obtained in the reaction of pyrazine-2-caboxylic acid hydrazide with carbon disulfide and dimethyl sulfate in a solution alkalized with potassium hydroxide.

Compound **1** and the amines 2-piperidinoethylamine, 4-(2-aminoethyl)morpholine, 4-(3-aminopropyl)morpholine, 3-ethoxypropylamine, 1-(3-aminopropyl)imidazole, and tryptamine reacted during heating in pyridine to 4-substituted 1,2,4-triazole-2-thiones **2**–**7**.

In the reaction with cysteamine, the cyclization occurred and the condensed system of triazole with thiazoline formed as 1,3-thiazaethylene-[1,2,4]triazole **8**. Its structure was confirmed by the additional synthesis by the heating of 4-$\beta$-hydroxyethylene-5-pyrazin-2-yl-[1,2,4]-triazole-2-thiol in hydrochloric acid solution, which is the method described earlier.[3]

Under the same condition reaction with aromatic amines, p-methyl- and p-chloroaniline did not lead to the cyclization to triazole, and the products are thiosemicarbazide derivatives. The treatment of hydrazide with isothiocyanates confirmed the structure of the obtained products as we reported previously[4] (Scheme 1).

An unexpected result was acquired in the reaction of compound **1** with 1-aminopiperidine and 4-aminomorpholine. The first step of that reaction occured according to our expectation, and compounds **11** and **12** were obtained as a result of the thiomethyl group substitution. The probe of their cyclization in 10% sodium hydroxide solution to 4-N-cycloalkyl-triazole-thiones of compound **16** type was unsuccessful because the molecule decomposed, and finally 4-N-piperidinethiosemicarbazide **13** and 4-(4′-morpholine)-thiosemicarbazide **14** were obtained. $^1$H NMR spectra and an additional MS spectrum for derivative **14** corroborated that course of the reaction. The product of the condensation of **14** with p-chlorobenzaldehyde gave **15**. The structure of derivative **14** was also confirmed by its synthesis



**SCHEME 1**

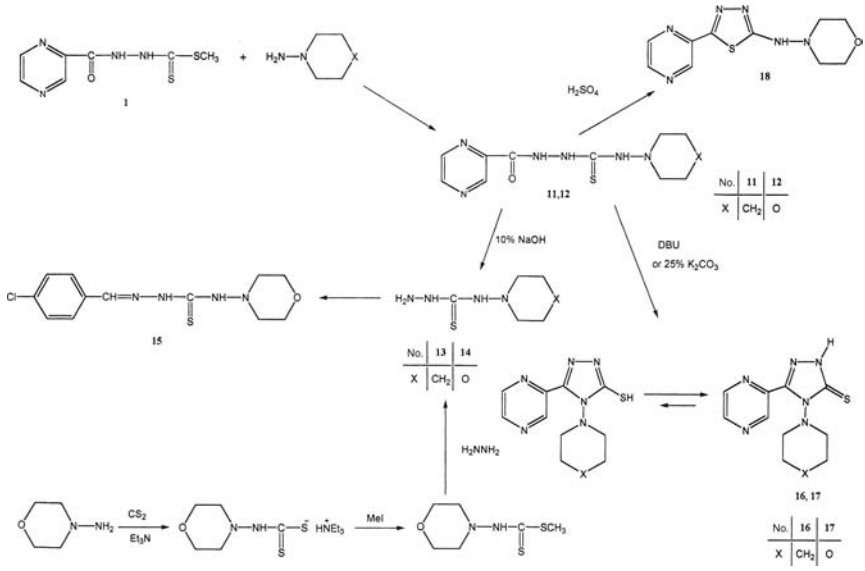
according to a simplified method of Podgornaya:[5] Ammonium gas was replaced with triethylamine.

Compound **11** in water-alkaline solution decomposed to product **13**, and only the cyclization in an anhydride medium in the presence of DBU led to 4-piperidin-1-yl-5-pyrazin-2-yl-2,4-dihydro[1,2,4]triazole-3-thione **16**. The structure of that product was confirmed by IR, $^1$H NMR, and MS spectra. $^1$H NMR spectrum determined for that compound indicated an equilibrium state between thione–thiol tautomeric forms existing in DMSO-$d_6$ solution. The similar reaction performed for derivative **12** resulted in compound **17**.

Compounds **16** and **17** were also obtained by the cyclization of the appropriate substrate **11** and **12** under the influence of 25% potassium carbonate solution. Derivative **12** also underwent cyclization in concentrated sulfuric acid, but the reaction led to a completely different product: morpholine-4-yl-(5-pyrazin-2-yl-[1,3,4]-thiadiazol-2-yl)-amine **18** (Scheme 2).

## MICROBIOLOGY

The tuberculostatic properties of the newly synthesized derivatives were examined towards the *Mycobacterium tuberculosis* $H_{37}$Rv strain and two "wild" strains isolated from tuberculotic patients: one (Spec. 210) resistant to p-aminosalicic acid (PAS), isonicotinic acid hydrazide



**SCHEME 2**

(INH), and etambutol (ETB) and rifampicine (RFP), another (Spec. 192) fully sensitive to the administrated drugs. In vitro investigations were performed by a classical test-tube method of successive dilution with Youman's liquid medium containing 10% of bovine serum.[6] The determined Minimum Concentrations (MIC) inhibiting the growth of tuberculous strains for all the tested compounds were within the limits of 25–50 $\mu$g/mL, which indicates low antituberculosis activity.

## EXPERIMENTAL

All materials and solvents were of analytical reagent grade. Thin-layer chromatography was performed on Merck Kieselgel $60F_{254}$ plates and visualized with UV. The results of elemental analyses (% C, H, N) for all the compounds obtained were in good agreement with the data calculated. $^1$H NMR spectra in $CDCl_3$ or DMSO-$d_6$ were recorded on Varian Gemini (200 MHz) and Varian Unity Plus (500 MHz) instruments. IR Spectra (KBr) were determined as KBr pellets of the solids on a Satellite FT-IR spectrophotometer. Mass spectra for compounds **14** and **16** were taken on Finngan MAT 95 (70 eV). Melting points were determined on a BOETIUS apparatus and were uncorrected. Reaction yields, physical constants, and spectral data of the compounds are given in Table I.

**TABLE I Characteristics of the Newly Synthesized Compounds**

| Compound no. | M.P.[°C] Solvent for crystallization | Yield [%] | Formula MW | IR [$cm^{-1}$] | $^1H$ NMR $\delta$ [ppm] MS [m/z (%)] |
|---|---|---|---|---|---|
| **2** | 207–208 EtOH | 35 | $C_{13}H_{18}N_6S$ 290 | 413, 572, 756, 857, 942, 1017, 1103, 1290, 1315, 1379, 1456, 1526, 2933 | $CDCl_3$: 1.42 and 2.63 (2m, 10H, piperidine); 2.91 and 4.87 (2s, 4H, $2CH_2$); 8.68 and 9.29 (2s, 3H, pyrazine); |
| **3** | 112–114 $H_2O$ | 47 | $C_{12}H_{16}N_6OS$ 292 | 411, 584, 848, 870, 907, 1007, 1046, 1114, 1312, 1387, 1466, 1507, 1523, 2848 | DMSO-$d_6$: 2.25 and 3.19 (2s, 8H, morpholine); 2.54 and 4.55 (2s, 4H, $2CH_2$); 8.76 and 9.17 (2s, 3H, pyrazine); 14.28 (brs, 1H, NH) |
| **4** | 152–153 EtOH | 43 | $C_{13}H_{18}N_6OS$ 306 | 408, 567, 753, 825, 961, 1016, 1116, 1272, 1298, 1372, 1462, 1493, 1560, 1624, 2960 | $CDCl_3$: 2.70 and 3.77 (2s, 8H, morpholine); 2.04, 2.16 and 4.65 (3m, 6H, $3CH_2$); 8.63, 8.67 and 9.29 (3s, 3H, pyrazine); 11.33 (brs, 1H, NH) |
| **5** | 85–87 Benzene/cyclohexane | 32 | $C_{11}H_{15}N_5OS$ 265 | 405, 567, 776, 857, 945, 987, 1017, 1068, 1125, 1187, 1255, 1284, 1465, 1494, 2927, 3094 | $CDCl_3$: 1.11 (t, 3H, $CH_3$); 2.11 (q, 2H, $CH_2$); 3.38, 3.50 and 3.77 (3m, 6H, 3 $CH_2$); 8.67, 8.71 and 9.33 (3s, 3H, pyrazine) |
| **6** | 215–216 MeOH | 61 | $C_{12}H_{13}N_7S$ 287 | 409, 581, 941, 1018, 1094, 1174, 1220, 1299, 1393, 1467, 1511, 1625, 3097, 3155 | DMSO-$d_6$: 2.18, 4.08 and 4.37 (3m, 6H, $3CH_2$) 6.89, 7.17 and 7.65 (3s, 3H, imidazole); 8.61, 8.79 and 9.16 (3s, 3H, pyrazine); 14.30 (brs, 1H, NH) |
| **7** | 233–236 MeOH | 96 | $C_{16}H_{14}N_6S$ 322 | 409, 491, 583, 742, 962, 1018, 1100, 1181, 1462, 1496, 1521, 1556, 1619 | DMSO-$d_6$: 3.07 and 4.69 (2t, 4H, $2CH_2$); 6.85, 6.91, 7.0 and 7.17 (4m, 4H, phenyl); 7.39 and 8.51 (2m, 3H, pyrazine); 10.70 (s, 1H, CH, pyrrole); 14.24 (s, 1H, NH) |

*(Continued on next page)*

**TABLE I Characteristics of the Newly Synthesized Compounds *(Continued)***

| Compound no. | M.P.[°C] Solvent for crystallization | Yield [%] | Formula MW | IR [$cm^{-1}$] | $^1H$ NMR $\delta$ [ppm] MS [m/z (%)] |
|---|---|---|---|---|---|
| **8** | 206–207 MeOH | 20 | $C_8H_7N_5S$ 205 | 405, 465, 507, 758, 858, 986, 1015, 1240, 1419, 1438, 1463, 1485, 1530 | $CDCl_3$: 4.05 and 4.68 (2t, 4H, $2CH_2$); 8.54, 6.60 and 5.91 (3s, 3H, pyrazine) |
| **11** | 193–194 EtOH | 62 | $C_{11}H_{16}N_6OS$ 280 | 467, 785, 916, 1021, 1267, 1397, 1460, 1482, 1519, 1540, 1697, 2819, 2947, 3155, 3312 | DMSO-$d_6$: 1.04, 2.40 and 2.92 (3brs, 10H, piperidine); 8.77, 8.89 and 9.16 (3s, 3H, pyrazine); 9.34, 9.68 and 10.64 (3s, 3H, 3NH) |
| **12** | 215–216 EtOH | 38 | $C_{10}H_{14}N_6O_2S$ 282 | 426, 614, 862, 912, 1021, 1073, 1108, 1220, 1262, 1301, 1395, 1459, 1495, 1531, 1691, 2837, 2977, 3135, 3207 | DMSO-$d_6$: 2.75 and 3.70 (2d, 8H, morpholine); 8.77, 8.90 and 9.16 (3s, 3H, pyrazine); 9.40, 9.88 and 10.67 (3s, 3H, 3NH) |
| **13** | 169–170 $H_2O$ | 76 | $C_6H_{14}N_4S$ 174 | 466, 585, 672, 763, 809, 875, 993, 1027, 1260, 1335, 1514, 2803, 3154 | DMSO-$d_6$: 1.00, 2.37 and 2.76 (3brs, 10H, piperidine); 4.59 (s, 2H, $NH_2$); 8.70 and 8.89 (2s, 2H, 2NH) |
| **14** | 194–195 MeOH | 96 | $C_5H_{12}N_4OS$ 176 | 505, 594, 687, 768, 826, 866, 919, 996, 1068, 1106, 1266, 1508, 1645, 2826, 3188 | DMSO-$d_6$: 2.63 (s, 4H, 2 $NCH_2$); 3.60 (d, 4H, 2 $OCH_2$); 4.61 (s, 2H, $NH_2$); 8.78 and 9.13 (2s, 2H, 2NH)<br>MS: $M^+$- 176 (63), 101 (29), 87 (17), 86 (100), 85 (13), 57 (37), 56 (21), 55 (11), 44 (13), 42 (10) |

| | | | | | |
|---|---|---|---|---|---|
| **15** | 173–174<br>EtOH | 38 | $C_{12}H_{15}ClN_4OS_2$<br>306.5 | 510, 518, 659, 786, 827, 865, 904, 1011, 1090, 1121, 1241, 1332, 1404, 1489, 1538, 1595, 2834, 2967, 3192 | $CDCl_3$: 3.03 (s, 4H, $2NCH_2$); 3.89 (s, 4H, $2OCH_2$); 7.38 (d, 2H, 2ArH); 7.60 (d, 2H, 2ArH); 8.00 (s, 1H, ArCH=N); 8.11 (brs, 1H, NH) |
| **16** | 290–294<br>DMF/MeOH | 63 | $C_{11}H_{14}N_6S$<br>262 | 513, 637, 697, 840, 898, 958, 1055, 1276, 1316, 1301, 1384, 1415, 1502, 2854, 2930 | DMSO-$d_6$: 1.16, 1.32, 1.55, 1.65, 3.07 and 4.24 (6m, 20H, 2 × piperidine); 8.80 and 9.02 (d and s, 3H, pyrazine); 14.07 (s, 1H, NH)<br>MS: $M^+$- 262 (3.5), 180 (90.2), 179 (10.2), 115 (22.6), 106 (11.9), 84 (100), 83 (84.9), 82 (12.8), 55 (63.8), 42 (18), 41 (10.7) |
| **17** | 283–285<br>DMF | 62 | $C_{10}H_{12}N_6OS$<br>264 | 636, 714, 844, 852, 913, 958, 1047, 1104, 1273, 1299, 1316, 1381, 1391, 1416, 1500, 2720, 2856, 3053, 3096 | DMSO-$d_6$: 3.04 and 3.35 (2s, 4H, $NCH_2$); 3.82 and 4.52 (2s, 4H, $OCH_2$); 8.85 (s, 1H, pyrazine); 9.08 (s, 1H, pyrazine); 14.19 (s, 1H, NH) |
| **18** | 234–236<br>EtOH | 77 | $C_{10}H_{12}N_6OS$<br>264 | 413, 641, 743, 580, 872, 1010, 1082, 1112, 1153, 1265, 1404, 1443, 1499, 1590, 2835, 2930, 3049, 3178 | DMSO-$d_6$: 2.88 (d, 4H, $NCH_2$); 3.66 (d, 4H, $OCH_2$); 8.67 (s, 2H, pyrazine), 9.27 (s, 1H, pyrazine); 9.68 (s, 1H, NH) |

## 4-Substituted 5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thiones (2–7)

### *General Method*

*N′*-(Pyrazine-2-carbonyl)-hydrazinecarbodithioic acid methyl ester **1** (5 mmol) and appropriate amine (6 mmol) were heated under reflux in 2 mL of pyridine for 1.5 h. Then the solvent was evaporated, 5 mL of water were added, and the mixture was acidified with glacial acetic acid. The precipitate was filtered after cooling and recrystallized.

## 3-Pyrazin-2-yl-5,6-dihydro-thiazolo[2,3-*c*][1,2,4]triazole (8)

A quantity of 5 mmol of compound **1** was refluxed with 6 mmol of cysteamine in 2 mL of pyridine for 1.5 h. Pyridine was evaporated, and 5 mL of water was added. The solid in an amount of 1 mmol was filtered and recrystallized.

## Pyrazinoylthiosemicarbazide Derivatives (9, 10)

### *General Methods*

*A.* Compound **1** (5 mmol) was heated under reflux with an appropriate amine (6 mmol) in 2 mL of pyridine for 1.5 h. Pyridine was evaporated in vacuum. The oily residue was dissolved in 3 mL of methanol, and the product was precipitated from the solution by water addition. Then water was decanted, and the crude product was treated with chloroform and filtered.

*B.* Pyrazine-2-carboxylic acid hydrazide (1 mmol) was dissolved in 5 mL of ethanol and treated with an appropriate isothiocyanate (1 mmol). The mixture was refluxed for 15 min, and the product was filtered after cooling (m.p. was in agreement with literature data[5]).

## Pyrazinoylthiosemicarbazide Derivatives (11, 12)

A quantity of 5 mmol of **1** was heated under reflux with 6 mmol of 1-aminopyridine or 1-aminomorpholine in 2 mL of pyridine. After the removal of pyridine, 10 mL of water was added, and the mixture was acidified with acetic acid. The precipitate was filtered after cooling and recrystallized.

## 4-N-Cycloalkylaminothiosemicarbazides (13, 14)

*A.* Derivative **11** or **12** (1 g) was refluxed for 2 h in 10 mL of 10% solution of sodium hydroxide. After cooling, if the solution was not clear,

then it was filtered and acidified with acetic acid. The solid was filtered and recrystallized.

*B (for compound 14).* 4-Aminomorpholine (2.55 mL, 25 mmol) was added to 10 mL of ethanol then treated with triethylamine (4 mL, 30 mmol) and carbon disulfide (1.6 mL, 25 mmol). The reaction mixture was stirred for 15 min, and about 5 mL of water was added to dissolve the precipitate. Then methyl iodide (1.55 mL, 25 mmol) was added dropwise, and the product precipitated immediately. The mixture was stirred for about 15 min, and the solid of S-methyl derivative (4 g, 83%) was filtered after cooling. That compound was next dissolved in 50 mL of ethanol, and 3 mL of 100% hydrazine hydrate was added. The reaction mixture was refluxed for 1.5 h and cooled, and the precipitate was filtered and recrystallized (m.p. was in agreement with literature data[4]).

## 1-(4-Chlorobenzylidene)-4-N-morpholinothiosemicarbazone (15)

Equimolecular amounts of compound **14** and p-chlorobenzaldehyde were refluxed in 10 mL of ethanol for 30 min. Then the mixture was cooled in an ice bath, and the product was filtered and recrystallized.

## 4-Piperidin-1-yl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (16)

*A.* Compound **11** (0.7 g, 2.5 mmol) and DBU (1 mL) were heated under reflux in 5 mL of n-butanol for 2 h. Then the mixture was condensed, ice was added, and the solution was acidified with acetic acid.

*B.* Compound **11** (1.5 g, 5 mmol) was dissolved in 20 mL of 25% potassium carbonate water solution. The mixture was refluxed for 4 h and then cooled. The precipitate was dissolved by an addition of a small amount of water. The clear solution was acidified with acetic acid, and the product was filtered and recrystallized. Yield 72% (0.53 g).

## 4-Morpholin-4-yl-5-pyrazin-2-yl-2,4-dihydro-[1,2,4]triazole-3-thione (17)

*A.* Compound **12** (0.2 g, 0.7 mmol) was refluxed with 1 mL of DBU in 2 mL of pyridine for 4 h. Then 15 g of ice was added, and the mixture was acidified with hydrochloric acid. The precipitate was filtered and recrystallized.

*B.* The synthesis was performed according to Method B described for compound **16** from (0.55 g, 2 mmol) of **12**.Yield 75% (0.39 g).

## 2-Aminomorpholin-4-yl-5-pyrazin-2-yl-[1,3,4]thiadiazole (18)

A quantity of 0.22 g (0.78 mmol) of compound **12** was heated in 2 mL of concentrated sulfuric acid at 90°C for 30 min. Then the mixture was poured onto ice and alkalized with ammonium hydroxide. The precipitate was filtered and recrystallized.

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