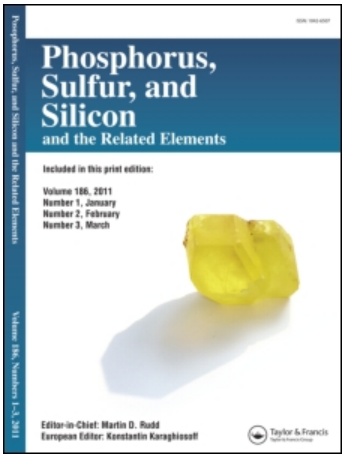

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STUDIES ON PYRAZINE DERIVATIVES. XXXI. SYNTHESIS AND REACTIONS OF ALKYL 3-PYRAZINOYLDITHIOCARBAZATES AND S,S'-DIALKYLDITHIOCARBONATE PYRAZINOYLHYDRAZONES TOWARDS AMINES AND HYDRAZINES

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STUDIES ON PYRAZINE DERIVATIVES. XXXI. SYNTHESIS AND REACTIONS OF ALKYL 3-PYRAZINOYLDITHIO-CARBAZATES AND S,S′-DIALKYLDITHIO-CARBONATE PYRAZINOYLHYDRAZONES TOWARDS AMINES AND HYDRAZINES

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Alkyl 3-pyrazinoyldithiocarbazates and S,S′-dialkyldithiocarbonate pyrazinoylhydrazones were obtained. Their chemical reactions with some primary and secondary amines, diamines and hydrazines were studied.

Keywords: pyrazines; 3-alkyldithiocarbazate esters; S,S′-dialkyldithiocarbonates; 1,2,4-triazoles; 1,3,4-oxadiazoles; 1,3-dithione; 1,3-dithiolan; 1,3-diazacycloalkanes; 1,2-diazirane

Dedicated to Prof. Józef Sawlewicz on the occasion of his 90th birthday.

INTRODUCTION

4-Mono- and 4-disubstituted 1-pyrazinoyl and pyridoyl thiosemicarbazides showed high tuberculostatic activity in our previous studies [1–3]. These compounds were prepared from 1,3,4-oxadiazol-2-thiones upon treatment with primary and secondary amines. This method, however, was not applicable to all amines. Some monosubstituted acylthiosemicarbazides may be obtained upon action of isothiocyanates on acid hydrazides[3].

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The scope of the present study was making use of alkyl 3-pyrazinoyldithiocarbazates, which in the reactions with amines would give, by methanethiol elimination, the expected 4-substituted thiosemicarbazides. The reactions of 3-acyldithiocarbazate esters with amines have not been reported yet, except the one with hydrazine, which gave 4-amino-1,2,4-triazolethiols[4]. Since in the course of the syntheses of mono alkyl 3-pyrazinoyldithiocarbazates some dialkyl derivatives were obtained as well, we decided to investigate their synthesis and to determine their behaviour towards primary and secondary amines, as well as hydrazines.

In the chemical literature there is just one reference[5] to S,S'-dimethyl-dithiocarbonate 2- and 4-pyridylhydrazones, yet as byproducts. The chemical properties of these compounds have not been reported.

RESULTS AND DISCUSSION

Preliminary attempts to synthesize the methyl 3-pyrazinodithiocarbazate ester **1** were made as reported for the syntheses of the analogous benzoyl-[6] and isonicotinoyl esters[5,7]. Though the reagents were used in stoichiometric amounts, mixtures of mono- **1** and dimethyl **2a** derivatives were obtained, and their separation by fractional crystallization failed. Pure compound **1** was obtained while using dimethyl sulphate as a methylating agent.

Bulky substituents were thought to form a steric hindrance big enough to preclude the formation of dialkyl derivatives. It appeared, nevertheless, that the only product of the reaction with benzyl chloride was dibenzyl compound **2c**. The reaction with iso-propyl iodide, which had to be carried out at elevated temperature, gave a mixture of products, which was difficult to separate. The use of two moles of alkyl iodide per one mole of pyrazine hydrazide resulted in the formation of dialkyl derivatives **2a** and **2b** in very good yields.

Seeing that dialkyl compounds **2a-c** were easily formed, we tried to obtain the cyclic compounds: 1,3-dithiolane **3a** and 1,3-thione **3b**; monohalogeno derivatives were replaced with the suitable dibromoalkanes.

In the next step of this study the reactivities of the compounds **1** and **2a** towards morpholine and ethanoloamine were examined.

The product of the reaction with morpholine strongly depended on the reaction conditions. At ambient and elevated temperatures, in alcoholic solutions, with stoichiometric amounts of the substrates, only the salt **4** was formed, which upon acidyfying produced the starting compound. Prolonged heating at boiling with excess amine led to 5-pyrazinyl-1,3,4-oxadiazolo-2-thione **5**.

Compound **1** refluxed in neat morpholine for 5 minutes gave the morpholine derivative of thiosemicarbazide **9**. Extension of the heating time up to 2 hours produced 2-morpholino-5-pyrazinylo-1,3,4-oxadiazole **6**.

Reaction of compound **1** with ethanoloamine gave 4-(2-hydroxyethylo)-5-pyrazinyl-1,2,4-triazolo-3-thione 7, which upon methylation gave an S-methyl derivative **8**.

In the subsequent part of this study the susceptibility of dimethyl derivative **2a** to the reactions with amines and hydrazines was examined. Upon heating with morpholine in ethanolic solution the compound remained unchanged. However, dissolved in excess morpholine it gave upon heating 2-morpholino-1,3,4-oxadiazole **6** in very good yield.

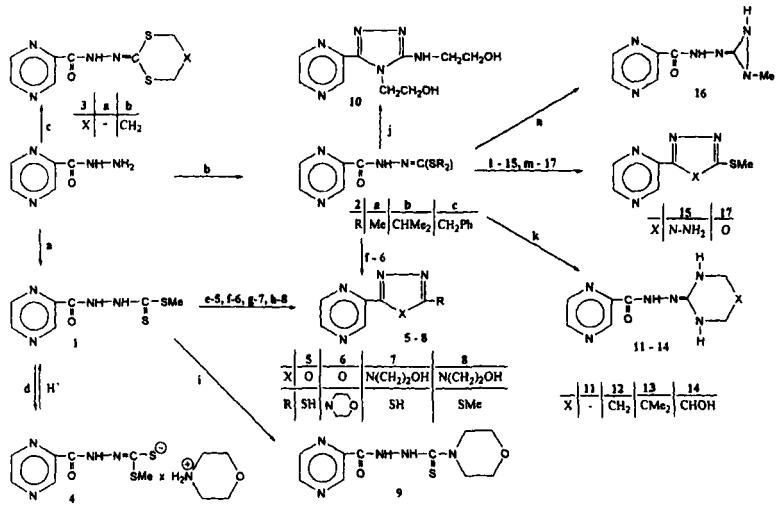
The reaction of compound **2a** with ethanoloamine proceeded only as a result of the direct heating. This reaction produced 3-[(2-hydroxyethyl)amino]-4-(2-hydroxyethyl)-5-pyrazinyl-1,2,4-triazole **10**.

N′-(diazacycloalkano-2-ylideno)-pyrazine derivatives **11 – 14** were produced in the reactions of compound **2a** with diamines: 1,2-diaminoethane, 1,3-diaminopropane, 1,3-diamino-2,2-dimethylopropane and 1,3-diamino-2-propanol.

The reactions of compound **2a** with hydrazines gave very interesting results. The long-drawn heating led to the formation of 4-amino-3-methylthio-5-pyrazinyl-1,2,4-triazole 15, and N′2-(1-methyl-1,2-diaziran-3-yliden)-2-pyrazine carbohydrazide **16** – with hydrazine and methylhydrazine, respectively.

N,N-dimethylhydrazine, as a strong base, gave only an intramolecular elimination of one mercaptan molecule, which resulted in the formation of 2-methylthio-5-pyrazinyl-1,3,4-oxadiazole **17**. The analogous attempt of cyclization reaction of compound **2a** in the presence of pyridine failed. Pyridine basicity was obviously too weak to produce the reaction of this type.

The reactions performed with compound **2a** show thus, that it can be a valuable starting material for the syntheses of the heterocyclic systems **6, 10 – 17**.



a) CS_2, EtOH/H_2O, KOH, Me_2SO_4; b) CS_2, EtOH, Et_3N, 2RI; c) CS_2, EtOH, KOH, $BrCH_2XCH_2Br$; d) EtOH, I⁻, morpholine; e) EtOH, I 2,5 morpholine, boiling, H⁺; f) morpholine, boiling; g) $H_2NCH_2CH_2OH$, H⁺; h) 7 EtOH, KOH, MeI; i) morpholine, boiling 5 min, H⁺; j) $H_2NCH_2CH_2OH$, boiling; k) EtOH, $H_2NCH_2XCH_2NH_2$; l) EtOH, H_2NNH_2; m) EtOH, Me_2NNH_2; n) EtOH, MeHN-NH_2

SCHEME 1

EXPERIMENTAL

Melting poins were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with a Specord IR-75 spectrophotometer. The ^{1}H-NMR spectra were taken with a Tesla Spectrometer BS-487 c, 80 MHz, (and the mass spectra – with Varian MAT 711 apparatus, at electron beam energy of 70 eV). The results of elemental analyses (%C, H) for all the compounds obtained were in a good agreement with the data calculated. Reaction yields and the physical constans of the compounds obtained are given in Table I.

Methyl 3-pyrazinoyldithiocarbazate (1)

To a solution of KOH (2 g) in water (20 ml) and ethanol (20 ml) pyrazine hydrazide [8] (2.1 g, 15 mmole) was added, followed by carbon disulphide (neat, 0.9 g, 15 mmole). The reaction mixture was stirred for 30 min and Me_2SO_4 (0.71 g, 7.5 mmole) was added dropwise. After 30 min the reaction was quenched with acetic acid, and the resulting precipitate was collected and purified by recrystallization.

TABLE I Characteristics of the newly synthesized pyrazinyl compounds

Compound No	*M.p. [°C] Solvent for crystalization*	*Yield [%]*	*Formula*	*IR [cm^{-1}] MS [m/z (%)]*	*^{1}H-NMR δ [ppm]*
1	163 – 165 MeOH	70	$C_7H_8N_4OS_2$	IR: 912, 975, 1104, 1163, 1295, 1332, 1392, 1453, 1672, 3163, 3312, 3403	d_6-DMSO: 2.75(s,3H,SCH_3); 9.15; 9.25 and 9.6(3s,3H pyrazine)
2a	150 – 152 MeOH	95	$C_8H_{10}N_4OS_2$	IR: 640, 880, 960, 1072. 1155, 1392, 1504, 1683, 3472 MS: M^+- 195(100), 106(23.5), 79(41.5), 74(11.7), 52(27.5)	$CDCl_3$: 2.55(s,6H,2SCH_3): 8.57; 8.8 and 9.48(3s,3H pyrazine); 10.9 (b,s,1H,NH)
2b	85 – 87 MeOH	85	$C_{12}H_{18}N_4OS_2$	IR: 672, 752, 944, 1024, 1104, 1155, 1303, 1392, 1455, 1643, 3240	$CDCl_3$: 1.7(d,12H,4CH_3); 4.25 and 4.65(2m,2H,2CH); 9.9; 10.1 and 10.85(3s,3H pyrazine); 12.9(b.s. 1H,NH)
2c	132 – 134 MeOH	95	$C_{20}H_{18}N_4OS_2$	IR: 704, 763, 1072, 1403, 1503, 1695, 3403	$CDCl_3$: 4.7 and 5.0(2s,4H,2CH_2); 8.35(m,10H,2 phenyl); 9.7; 10.0 and 10.8(3s,3H pyrazine); 12.6(s,1H,NH)
3a	171 – 172 MeOH	50	$C_8H_8N_4OS_2$	IR: 443, 560, 944, 1055, 1160, 1280, 1403, 1520, 1552, 1695, 3455	d_6-DMSO: 4.02(s,4H,2CH_2); 9.15; 9.22 and 9.57(3s,3H pyrazine); 11.08(b.s,1H,NH)
3b	146 – 148 MeOH	60	$C_9H_{10}N_4OS_2$	IR: 443, 592, 752, 783, 895, 975, 1024, 1055, 1120, 1152. 1312, 1403, 1504, 1563, 1680, 3280	$CDCl_3$: 1.0(m,2H,CH_2); 1.8(m,4H. 2CH_2); 7.3; 7.5 and 8.2(3s,3H pyrazine); 9.5(b.s,1H,NH)
4	174 – 175 EtOH/Et_2O	95	$C_{10}H_{15}N_5O_2S_2$	IR: 672, 895, 1072, 1104, 1264, 1395, 1424, 1472, 1483, 1563, 1652, 2963, 3163, 3392	
5	212–213 EtOH [10]	85	$C_6H_4N_4S_2$		
6	184 – 185 EtOH/H_2O [1]	65	$C_{10}H_9N_5O_2$		
7	230 – 321 MeOH/H_2O	60	$C_8H_9N_5OS$	IR: 843, 963, 1044, 1183, 1243, 1295, 1312, 1344, 1455, 1515, 1563, 2895, 3200, 3500	d_6-DMSO: 3.75 and 4.7(2t, 4H, 2CH_2); 8.9 and 9.22(2s,3H pyrazine)

Compound No	*M.p. [°C] Solvent for crystalization*	*Yield [%]*	*Formula*	*IR [cm^{-1}] MS [m/z (%)]*	*^{1}H-NMR δ [ppm]*
8	178 – 179 MeOH	70	$C_9H_{11}N_5OS$	IR: 683, 976, 1072, 1155, 1403, 1520, 3224	d_6-DMSO: 2.9(s,3H, SCH_3); 3.85 and 4.65(2m,4H,$2CH_2$); 8.9 and 9.47(2s,3H pyrazine)
9	184- 185 MeOH [1]	40	$C_{10}H_{13}N_5O_2S$		
10	207 – 209 EtOH	50	$C_{10}H_{14}N_6O_2$	IR: 752, 864, 1064, 1163, 1424, 1463, 1540, 1584 MS: M^+ – 250(6.1), 177(31.7), 175(47.6), 163(100), 106(47), 79(46.9)	d_6-DMSO: 3.75 and 4.6(2m,8H, $4CH_2$); 8.9 and 9.42(2s,3H pyrazine)
11	240 – 242 EtOH	60	$C_8H_{10}N_6O$	IR: 652, 1024, 1055, 1160, 1323, 1472, 1543, 1690, 1704, 3184. MS: M^+ – 206 (47.3), 127(10.2), 99(100), 81(13.8), 79 (20.5)	d_6-DMSO: 3.4(s,4H,$2CH_2$); 8.7 and 9.2(2s,3H pyrazine)
12	227 – 229 MeOH	55	$C_9H_{12}N_6O$	IR: 804, 1072, 1155, 1264, 1360, 1523, 1630, 1663, 2880, 3152, 3292	d_6-DMSO 2.1(m,2H,CH_2); 3.55(s,4H,$2CH_2$)
13	241 – 243 MeOH	70	$C_{11}H_{16}N_6O$	IR: 683, 1055, 1160, 1180, 1312, 1360, 1392, 1575, 1664, 1705. MS: M^+ – 248(25.5), 230(14.4), 215(21.4), 141(100)	d_6-DMSO: 1.1(s,6H,$2CH_3$); 3.1(s, 4H,$2CH_2$);8.51(m,2H,2NH); 8.80; 8.95 and 9.25(3s,3H pyrazine); 9.4 (s,1H,NH)
14	268 – 270 H_2O	40	$C_9H_{12}N_6O_2$	IR: 684, 732, 1152, 1200, 1260, 1392, 1472, 1564, 1685, 1664, 3200.	d_6-DMSO: 3.35(s,4H,$2CH_2$); 3.9- 4.2((m,1H,CH); 8.4–8.6(m,2H pyrazine); 9.35(s,1H pyrazine)
15	177 – 178 MeOH	65	$C_7H_8N_6S$	IR: 683, 864, 1003, 1163, 1243, 1403, 1543, 1632, 3312. MS: M^+ – 208(100), 192(73.1), 108(24.9)	d_6-DMSO: 2.8(s,3H,SCH_3); 6.9(b.s, 2H,NH_2); 8.9; 9.4(2s,3H pyrazine)
16	141 – 142 MeOH	50	$C_7H_8N_6O$	IR: 735, 895, 1043, 1072, 1163, 1215, 1403, 1443, 1584, 1664, 3072, 3283, 3450. MS: M^+ – 192(100), 147(27.5), 106(30.7), 79(70.5)	d_6-DMSO: 3.45(s,3H,CH_3); 4.7(b.s. 2H,2NH); 8.9 and 9.35(2s,3H pyrazine)
17	110 – 112 MeOH	60	$C_7H_6N_4OS$	IR: 752, 1003, 1083, 1203, 1412, 1456, 1504. MS: M^+ – 194(100), 147(43), 123(33), 107(30.2)	$CDCl_3$: 2.95(s,3H,SCH_3); 8.97 and 9.47(2s,3H pyrazine)

S,S′-Dimethyl- and S,S′-dibenzyldithiocarbonate (2a, 2c)

To a suspension of pyrazine hydrazide (2.1 g, 15 mmole) in ethanol (20 ml), triethylamine (4.2 ml, 30 mmole) and carbon disulphide (0.9 ml, 15 mmole) were added, stirred until homogenization, and then methyl iodide (1.86 ml, 30 mmole), or benzyl chloride (3.43 ml, 30 mmole) was added portionwise. While stirring for 30 min the crystalline products precipitated, which, after cooling down of the mixture, were collected and purified by recrystallization.

S,S′-Diisopropyldithiocarbonate (2b)

Compound **2b** was obtained as described for **2a** and **2c**, but after addition of isopropyl iodide (1.5 ml, 15 mmole) the mixture was refluxed for 30 min and concentrated. After adding water the resulting precipitate was collected and purified by recrystallization.

N′-(1,3-dithiolan-2-ylideno)-pyrazine hydrazide (3a), and N′-(1,3-dithian-2-ylideno)-pyrazine hydrazide (3b)

To a suspension of pyrazine hydrazide (1.4 g, 10 mmole) in ethanol (20 ml) and water (2 ml), triethylamine (1.56 ml, 11 mmole) and carbon disulphide (0.6 ml, 10 mmole) were added. The mixture was stirred upon clarification, and there were added, respectively:

- for **3a** - ethylene bromide (0.86 ml, 10 mmole); the mixture was allowed to stand for 1 h, and on cooling down the precipitate was filtered off;
- for **3b** - propylene bromide (1.02 ml, 10 mmole); the mixture was allowed to stand for 1 h, then 10 ml of water was added and, on cooling with ice, the crystalline product was filtered off.

Methyl ester (1) morpholine salt (4)

Compound **1** (10 mmole), ethanol (10 ml) and morpholine (0.9 g, 10 mmole) were heated to reflux and allowed to stand. The product was precipitated with anhydrous diethyl ether. The precipitate of salt **4** on dissolving in water and acicifying with acetic acid gave the compound **1** back.

5-Pyrazinyl-1,3,4-oxadiazolo-2-thione (5)

Compound **1** (10 mmole) and morpholine (2 ml) dissolved in ethanol (10 ml) were refluxed for 4 h. The solvent was distilled off, then 5 ml of water was added and the mixture was acidified with acetic acid. The precipitate was collected and recrystallized. Its mp and IR spectrum were as in ref. [9].

2-Morpholino-5-pyrazinyl-1,3,4-oxadiazole (6)

Compound **1** or **2a** (10 mmole) and morpholine (2 ml) were refluxed for 2 h. On cooling down 20 ml of water was added. The mixture was extracted with chloroform, dried ($MgSO_4$), concentrated and the residue purified by recrystallization. Physical constans were as in ref.[1].

4-(2-Hydroxyethyl-5-pyrazinyl- 1,2,4-triazolo-3-thione (7)

Compound **1** (10 mmole) and ethanoloamine (3 ml, 50 mmole) were refluxed for 1 h. On cooling down, water (10 ml) and acetic acid (3.5 ml) were added. The mixture was ice-cooled, the precipitate collected and recrystallized.

4-(2-Hydroxyethyl-5-pyrazinyl-1,2,4-triazolo-3-methylthione (8)

Compound **7** (1.1 g, 5 mmole) was added to a solution of KOH (0.3 g, 5 mmole) in ethanol (15 ml), then methyl iodide (0.3 ml, 5 mmole) was added and the mixture refluxed for **2** h. To the concentrated mixture 5 ml of water was added. The precipitate was filtered off.

N′-Carbothiomorpholinopyrazine hydrazide (9)

Compound **1** (10 mmole) and morpholine (2 ml) were refluxed for 5 min. On cooling down 10 ml of water was added and acidified with acetic acid. The precipitate was collected and purified by recrystalization from ethanol.

3-[(2-Hydroxyethyl)amino]-4-(2-hydroxyethyl)-5-pyrazinyl-1,2,4-triazole (10)

Compound **2a** (1.2 g, 5 mmole) and ethanoloamine (2 ml, 30 mmole) were refluxed for 3 h. Upon cooling down, 5 ml of water was added and the precipitate filtered off.

N′-(1,3-diazacycloalkano-2-ylideno)-pyrazine hydrazides (11 – 14)

Compound **2a** (10 mmole), ethanol (10 ml) and an appropriate alkylodiamine (20 mmole) were refluxed for 4 h. After cooling down, the precipitates were collected and recrystallized.

4-Amino-3-methylthio-5-pyrazinylo-1,2,4-triazole (15)

Compound **2a** (1.2 g, 5 mmole) and 100% hydrazine hydrate (0.15 g, 15 mmole) disolved in ethanol (10 ml) were refluxed for 10 h, then alcohol was evaporated, water added and the precipitate of compound **15** filtered off.

N′2-(1 -methyl-1,2-diaziran-3-yliden)-2-pyrazinecarbohydrazide (16)

Compound **2a** (1.2 g, 5 mmole), ethanol (10 ml) and methylhydrazine (1 ml, 20 mmole) were refluxed for 20 h. Upon concentration, 1 ml of methanol was added, then the product was precipitated with diethyl ether and purified by recrystallization.

2-Methylthio-5-pyrazinylo-1,3,4-oxadiazole (17)

To compound **2a** (1.2 g, 5 mmole), ethanol (10 ml) and N,N-dimethylhydrazine (1.15 ml, 15 mmole) were added and refluxed for 10 h. On cooling down the precipitate was collected and recrystallized.

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