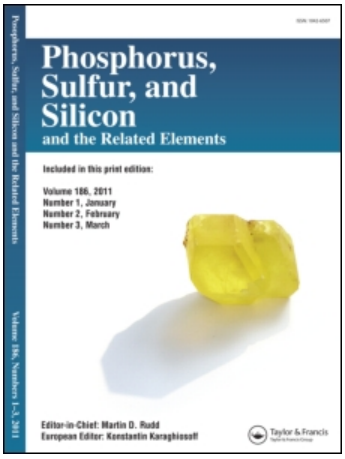


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

STUDIES ON PYRAZINE DERIVATIVES. XL. SYNTHESIS, REACTIVITY, AND TUBERCULOSTATIC ACTIVITY OF 4-HYDROXYALKYL-5-PYRAZINYL4H-[1,2,4]-TRIAZOLE-3-THIONES

Henryk Foks[a]; Mieczysław Janowiec[b]; Zofia Zwolska[b]; Ewa Augustynowicz-Kopeć[b]
[a] Department of Organic Chemistry, Medical University of Gdańsk, Poland [b] Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, Warsaw, Poland

Online publication date: 16 August 2010

To cite this Article Foks, Henryk , Janowiec, Mieczysław , Zwolska, Zofia and Augustynowicz-Kopeć, Ewa(2004) 'STUDIES ON PYRAZINE DERIVATIVES. XL. SYNTHESIS, REACTIVITY, AND TUBERCULOSTATIC ACTIVITY OF 4-HYDROXYALKYL-5-PYRAZINYL4H-[1,2,4]-TRIAZOLE-3-THIONES', Phosphorus, Sulfur, and Silicon and the Related Elements, 179: 12, 2519 — 2526
To link to this Article: DOI: 10.1080/10426500490485534
URL: http://dx.doi.org/10.1080/10426500490485534

Phosphorus, Sulfur, and Silicon, 179:2519–2526, 2004

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500490485534

Taylor & Francis
Taylor & Francis Group

STUDIES ON PYRAZINE DERIVATIVES. XL. SYNTHESIS, REACTIVITY, AND TUBERCULOSTATIC ACTIVITY OF 4-HYDROXYALKYL-5-PYRAZINYL-4H-[1,2,4]-TRIAZOLE-3-THIONES

Henryk Foks,[a] *Mieczysław Janowiec,*[b] *Zofia Zwolska,*[b] *and Ewa Augustynowicz-Kopeć*[b]
Department of Organic Chemistry, Medical University of Gdańsk, Poland;[a] *and Department of Microbiology, Institute of Tuberculosis and Pulmonary Diseases, Warsaw, Poland*[b]

(Received April 15, 2004; accepted May 11, 2004)

In the reactions of pirazinoyldithiocarbazoic acid monoester with aminoalcohols, 4-hydroxyalkyl-1,2,4-triazole-3-thiones were obtained. Their susceptibility to alkylation, as well as the condensed heterocyclic 1,3-thiazacycloalkyl[3,2-b]-1,2,4-thiazoles[1] formation ability, were examined. Some of the compounds obtained were tested for their tuberculostatic activity.

Keywords: 1,3-Thiazacycloalkyl[3,2-b]-1,2,4-triazoles; 4H-[1,2,4]-triazole-3-thiol; hydrazinedithioic acid ester; pyrazines; tuberculostatic

INTRODUCTION

The reactions of acyldithiocarbazoic acid monoester with aminoethanol were found useful to the syntheses of 4-(2-hydroxyethyl)-1,2,4-triazole-3-thiones, as reported before.[1,2] An extensive examination of these reactions was the main view of the present study. A considerable number of the aminoalcohols had to be used initially, then the possibility of obtaining the triazolothione derivatives, in particular through the cyclization of triazole with 1,3-thiazacycloalkanes to the condensed systems, was studied.

Address correspondence to Henryk Foks, Department of Organic Chemistry, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80416 Gdańsk, Poland. E-mail: hfoks@farmacja.amg.gda.pl

CHEMISTRY

The synthesis of methyl pyrazinoyldithiocarbazate **1** was reported elsewhere.[1] The reaction of this ester was conducted either in an excess of the corresponding amine (neat), or in dimethylformamide solution with double stoichiometric amine excess. The product formation depended on the amine structure, not on the reaction conditions. The use of ethanolamines, 3-amino-1-propanol, 1-amino-2-propanol, 4-amino-1-butanol, and 3-amino-1,2-propandiol gave the corresponding 5-pyrazinyl-4-hydroxy-alkyl-1,2,4-triazole-3-thiones **2a–e**. In the first stage of these reactions, the salts of the corresponding triazolothiones with the amine used were formed, and then upon acidification free thiones were obtained.

A different reaction course was observed in the case of aminoalcohols having their amine groups bound to the secondary or tertiary carbon atoms. The pyrazinoyldithiocarbazoic ester was not subject to cyclization under the influence of amines such as 2-amino-2-methyl-1-propanol, L-2-amino-1-phenyl-1-propanol, L-2-amino-3-phenyl-1-propanol, or both (+ and −) 2-amino-2-butanol enantiomers, but to the cleavage only. Pyrazinohydrazide and most likely 1,3-dihydroxyalkylthioureas were the reaction products. In the case of analogous compounds, the same reaction course and mechanism were already reported.[3]

The examination of cyclization conditions of the 4-hydroxyalkyl derivatives **2a–e** to the condensed systems **3a–e** was the next step of the present study. The reactions proceeded in the solutions of both concentrated hydrochloric and polyphosphoric acid. The reaction yields were almost the same, but for preparative reasons it was easier to obtain the products with hydrochloric acid.

The cyclization of 4-hydroxyalkylthiones in the acidic media was confirmed by the reactions of compound **1** with 2-bromoethylamine and 3-bromopropylamine. The products thus obtained were identical to the earlier prepared ones; however, the yields were smaller. The last-mentioned reaction is another example of dithiocarbazates use in heterocyclic systems syntheses.

4-Hydroxyalkyltriazolthioles **2a–e** were changed, in good yields, into S-substituted derivatives **4–9** upon action of active halogen-containing compounds in basic media. Compound **6a** was used to synthesizes of the amide derivative **10a** and of the hydrazide **11a**.

The replacement reactions of a thiocarboxyethyl group by a hydrazine arrangement (in compound **5a**) and of SMe group by the morpholine one (in compound **4a**) were unsuccesful. In the former case, the triazolothione **2a**, and in the latter one small amounts of the condensed

heterocyclic rings (compound **3a**), were isolated instead of the products expected.

The reactions realized are shown in Scheme 1. The IR, ^{1}H NMR, and mass spectra, as well as the results of elementary analyses, supplied the documentary evidence for the structures of the products.

EXPERIMENTAL

Melting points were determined with the Reichert apparatus and are uncorrected. The IR spectra were taken with a Satellite spectrophotometer. The ^{1}H NMR spectra were taken with a Varian Gemini 200 spectrometer BS-487c, MS-LKB 900 S instrument (electron impact at 70 eV). Reaction yields and the physical constants of the compounds obtained are given in Table I. The results of elemental analyses for C and H for all the compounds obtained are in good agreement with the data calculated.

4-Hydroxyalkyl-5-pyrazinyl-1,2,4-triazole-3-thiones (2a–e)

Compound **1** (10 mmole, 2.3 g) and the corresponding amine (50 mmole) were refluxed for 0.5 h. After cooling, water (10 ml) was added and the mixture acidified with concentrated HCl to pH 5. The products precipitated at ambient temperature or upon cooling in a freezer.

1,3-Thiazacycloalkyl[3,2-b]1,2,4-triazole (3a–e)

Method A

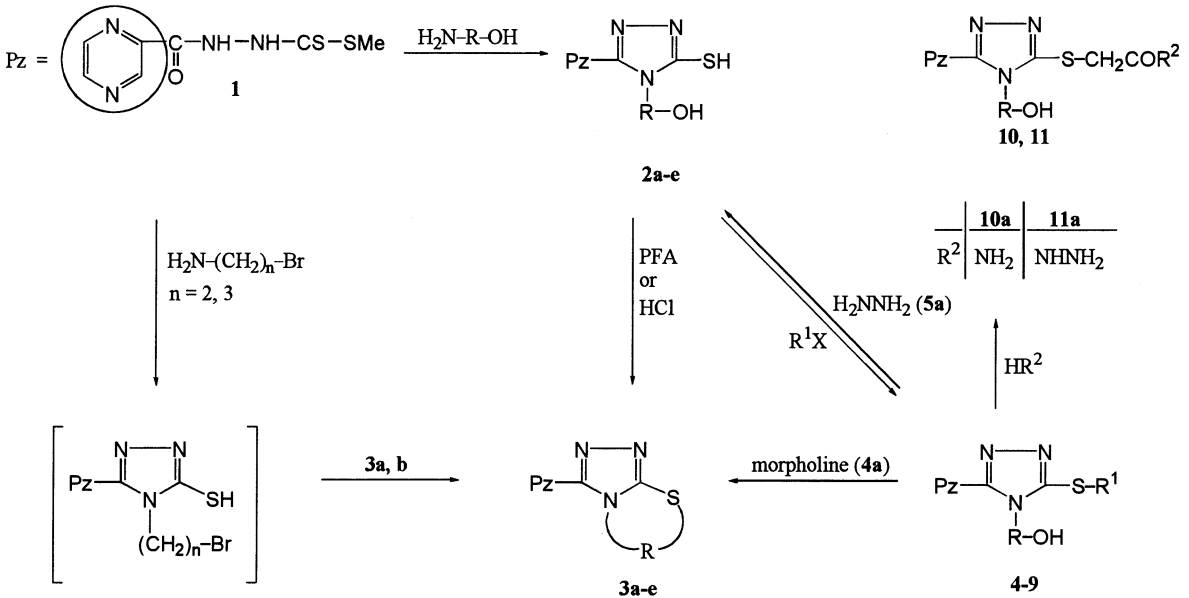
The corresponding compounds **2a–e** (5 mmole) was refluxed with concentrated HCl (10 ml) for 2 h. After cooling the mixture was treated with water (50 ml) and alkalified with ammonia. The products precipitated were filtered off and crystallized from water.

Method B

The reaction was carried on in similar way: compounds **2a–e** were heated to 100°C in polyphosphoric acid (15 g) (PEA).

Method C (for Compounds 3a,b)

To a solution of KOH (10 mmole) in dimethylformamide (DMF) (2 ml) and water (2 ml) either 2-bromoethylamine hydro-bromide (5 mmole) or 3-bromopropylamine hydrobromide (5 mmole), and then compound **1**, were added. The mixture was refluxed for 0.5 h. After cooling, water (5 ml) was added and alkalified with concentrated ammonia.



	10a	11a
R^2	NH_2	$NHNH_2$

2; 3	a	b	c	d	e
R	$(CH_2)_2$	$(CH_2)_3$	CH_2–CH(CH_3)–CH_3	$(CH_2)_4$	CH_2–CH(OH)–CH_2

	4a	5a	6a	7b	8b	9c
R^1	Me	COOEt	CH_2COOEt	Me	CH_2COOEt	Me

SCHEME 1

TABLE I Characteristics of the Newly Synthesized Pyrazinyl Compounds

Compound no.	m.p. (°C) and solvent for crystallization	Yield (%) and method	Formula	IR (cm^{-1}) MS (m/z (%))	^1H NMR δ (ppm)
2a	230–232 MeOH/H_2O	50	$C_8H_9N_5OS$	IR: 852, 954, 1043, 1243, 1295, 1344, 1392, 1463, 1504, 2904, 3150	d_6-DMSO: 3.75 and 4.7 (2t, 4H, $2CH_2$); 8.9 and 9.22 (2s, 3H, pyrazine)
2b	154–156 MeOH	85	$C_9H_{11}N_5OS$	IR: 752, 844, 1083, 1184, 1283, 1375, 1455, 1504, 2923	d_6-DMSO: 1.8–2.1; 3.4–3.5 and 4.4–4.8 (3m, 6H, $3CH_2$); 8.9 and 9.25 (2s, 3H, pyrazine)
2c	167–169 H_2O	81	$C_9H_{11}N_5OS$	IR: 415, 844, 1072, 1163, 1264, 1295, 1323, 1375, 1424, 1455, 2923, 3150	d_6-DMSO: 1.2 (d, 3H, CH_3); 3.9–4.4 (m, 2H, CH); 9.0 and 9.3 (2s, 3H, pyrazine)
2d	126–129 H_2O	91	$C_{10}H_{13}N_5OS$	IR: 415, 575, 752, 843, 1104, 1163, 1295, 1383, 1523, 1603, 3384	d_6-DMSO: 1.4–2.0 (m, 4H, $2CH_3$); 3.4–3.7 (m, 2H, CH_2O); 4.4–4.8 (m, 2H, CH_2N); 8.95 and 9.37 (2s, 3H, pyrazine)
2e	169–171 H_2O	60	$C_9H_8N_5O_2S$	IR: 656, 895, 975, 1095, 1264, 1295, 1375, 1504, 2912, 3312	d_6-DMSO: 3.3–3.7 (m, 2H, CH_2O); 3.8–4.2 (m, 1H, CH); 4.2–5.0 (m, 2H, CH_2N); 8.92 and 9.27 (2s, 3H, pyrazine)
3a	209–211 H_2O	A—50 B—64 C—53	$C_8H_7N_5S$	IR: 672, 864, 1024, 1152, 1264, 1440, 1483 MS: 207 (M^+2, 4.3), 206 (M^+1, 14.5), 205 (M^+, 100), 204 (32.9), 151 (5.6), 147 (15.2), 132 (14.6), 106 (25.3), 105 (6.5)	d_6-DMSO: 4.3–4.5 and 4.7–4.9 (2m, 4H, $2CH_2$); 8.55 and 9.42 (2s, 3H, pyrazine)

(Continued on next page)

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

Compound no.	m.p. (°C) and solvent for crystallization	Yield (%) and method	Formula	IR (cm^{-1}) MS (m/z (%))	^1H NMR δ (ppm)
3b	224–225 MeOH/H_2O	A–75 B–73 C–47	$C_9H_9N_5S$	IR: 864, 1072, 1123, 1152, 1403, 1563, 3472 MS: 221 (M^+2, 4.8), 220 (M^+1, 11.8), 219 (M^+, 100), 205 (6.6), 204 (35.1), 186 (11.7), 161 (7.7), 106 (25.8), 81 (6.0)	d_6-DMSO: 2.2–2.5; 3.2–3.5 and 4.5–4.7 (3m, 6H, $3CH_2$); 8.8 and 9.32 (2s, 3H, pyrazine)
3c	205–207 H_2O	A—42 B—50	$C_9H_9N_5S$	IR: 784, 1003, 1056, 1163, 1424, 1483, 1523, 1563, 2923 MS: 221 (M^+2, 4.1), 220 (M^+1, 10.7), 219 (M^+, 100), 218 (6.8), 205 (5.4), 204 (45.9), 186 (6.3), 165 (3.2), 161 (3.2), 146 (3.4), 105 (2.2), 81 (2.3)	d_6-DMSO: 1.7 (d, 3H, CH_3); 4.3–4.6 (m, 1H, CH); 4.7–5.2 (m, 2H, CH_2, pyrazine)
3d	185–187 H_2O	B—64	$C_{10}H_{11}N_5S$	IR: 723, 815, 992, 1043, 1136, 1152, 1412, 1563, 2944	d_6-DMSO: 1.8–2.4; 2.9–3.2 and 4.7–4.9 (3m, 8H, $4CH_2$); 8.9 and 9.4 (2s, 3H, pyrazine)
3e	203–205 H_2O	A—53	$C_9H_9N_5OS$	IR: 643, 752, 843, 1083, 1184, 1252, 1303, 1403, 1472, 1563, 3163	d_6-DMSO: 3.3–3.7 (m, 2H, CH_2O); 4.5–4.8 (m, 3H, CH_2CH); 5.9 (b.s, 1H, OH); 8.92 and 9.45 (2s, 3H, pyrazine)
4a	178–179 MeOH	68	$C_9H_{11}N_5OS$	IR: 723, 975, 1072, 1163, 1403, 1472, 2923, 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)

5a	89–91 C_6H_6	50	$C_{11}H_{13}N_5O_3S$	IR: 683, 1024, 1043, 1152, 1180, 1295, 1403, 1464, 1744, 2923, 3264	$CDCl_3$: 1.1 (t, 3H, CH_3); 3.9–4.3 (m, 4H, $2CH_2$); 4.5–4.8 (m, 2H, NCH_3); 8.5–8.7 (m, 2H, pyrazine); 9.2 (s, 1H, pyrazine)
6a	90–91 C_6H_6	46	$C_{12}H_{15}N_5O_3S$	IR: 1104, 1184, 1304, 1403, 1744, 2923, 3243	$CDCl_3$: 1.12 (t, 3H, CH_3); 3.85–4.25 (m, 6H, $3CH_2$); 4.45–4.7 (m, 2H, CH_2); 8.52 and 9.07 (2s, 3H, pyrazine)
7b	145–147 MeOH	80	$C_{10}H_{13}N_5OS$	IR: 672, 923, 1184, 1312, 1403, 2923, 3280	d_6-DMSO: 1.8–2.0 (m, 2H, CH); 2.82 (s, 3H, CH_3); 3.5 and 4.45 (2t, 4H, $2CH_2$); 3.82 (b.s, 1H, OH); 8.82 and 9.37 (2s, 3H, pyrazine)
8b	80–81 C_6H_6	50	$C_{11}H_{12}N_5O_3S$	IR: 864, 1024, 1040, 1184, 1295, 1403, 1744, 3456	$CDCl_3$: 1.15 (t, 3H, CH_3); 1.8–2.1 (m, 2H, CH_2); 3.7 (b.s, 1H, OH); 3.52 and 4.5 (2t, 4H, $2CH_2$); 4.15 (q, 2H, CH_2); 8.52 (d, 2H, pyrazine); 9.35 (s, 1H, pyrazine)
9c	147–149 H_2O	46	$C_{10}H_{13}N_5OS$	IR: 404, 483, 512, 569, 704, 864, 869, 975, 1056, 1151, 1215, 1323, 1403, 1472, 1535, 2963, 3203	d_6-DMSO: 1.2 (d, 3H, CH_3); 2.85 (s, 3H, SCH_3); 4.02 (t, 2H, CH_2); 8.87 and 9.47 (2s, 3H, pyrazine)
10a	182–184 EtOH	60	$C_{10}H_{12}N_6O_2S$	IR: 672, 1072, 1403, 1624, 1680, 3323	d_6-DMSO + TFA: 3.6–3.9 and 4.52–4.6 (2m, 4H, $2CH_2$); 4.12 (s, 2H, SCH_2); 8.75 and 9.37 (2s, 3H, pyrazine)
11a	189–191 H_2O	80	$C_{10}H_{13}N_7O_2S$	IR: 403, 583, 983, 1072, 1152, 1232, 1344, 1403, 1463, 1543, 1643, 3064, 3344, 3903	d_6-DMSO + TFA: 3.7–3.9 and 4.5–4.8 (2m, 2H, SCH_2); 8.80 and 9.42 (2s, 3H, pyrazine)

4-Hydroxyalkyl-3-mercaptomethyl-5-pyrazino-1,2,4-triazoles (4a, 7b, 9c)

To a solution of KOH (5 mmole) in ethanol (15 ml) the corresponding triazolothione (5 mmole) was introduced, and then methyl iodide (5 mmole) was added dropwise. The mixture was refluxed for 1 h. Then the solvent was evaporated, water (5 ml) was added, and the precipitates were filtered off.

4-Hydroxyalkyl-3-carboethylthio and 3-Carboxyethylomethylenthio-5-pyrazino-1,2,4-triazoles (5a, 6a, 8b)

To a solution of KOH (5 mmole) in ethanol (15 ml) compounds **2a** or **2b** (5 mmole) and the corresponding halogenoderivative, i.e., ethyl chloroformate or ethyl bromoacetate (5 mmole) were added and the mixture refluxed for 1 h. Then ethanol was evaporated, water (5 ml) was added, and the mixture alkalified with concentrated ammonia. Compound **6a** precipitated in crystalline form, and **5a** and **8b** were isolated by extraction with chloroform.

4-β-Hydroxyethyl-5-pyrazino-3-thioacetamido-1,2,4-triazole (10a)

Compound **6a** (5 mmole) and concentrated ammonia (20 ml), were placed in a closed vessel and stirred for 3 days. The mixture was then evaporated to dryness with a rotary vaporizer. The residue was purified by crystallization.

4-Hydroxyethyl-5-pyrazino-3-thioacetohydroxy-1,2,4-triazole (11a)

Compound **6a** (25 mmole), dioxane (5 ml), and 100%-hydrazine hydrate (1 ml) were refluxed for 0.5 h. On evaporating to dryness, the residue was treated with water (5 ml), cooled, and the precipitated compound **11a** filtered off.

REFERENCES

[1] H. Foks, J. Mieczkowska, and M. Sitarz, *Phosphorus, Sulfur, and Silicon*, **158,** 107 (2000).

[2] H. Foks, J. Mieczkowska, M. Janowiec, Z. Zwolska, and Z. Andrzejczyk, *Khim. Geterotsikl. Soedin.*, 918 (2002).

[3] D. Pancechowska-Ksepko, H. Foks, M. Janowiec, and Z. Zwolska-Kwiek, *Acta Polon. Pharm.*, **45,** 193 (1988).