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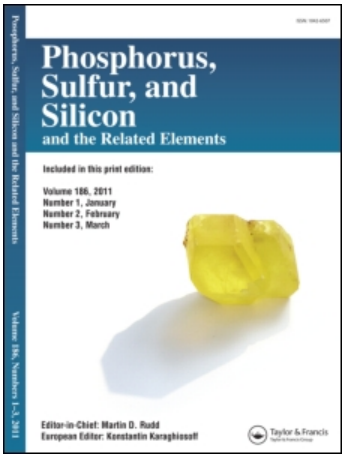

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Synthesis and Tuberculostatic Activity of Some 1,1-Bis-methylthio-2-nitro-ethene Derivatives

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Synthesis and Tuberculostatic Activity of Some 1,1-Bis-methylthio-2-nitro-ethene Derivatives

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1,1-bis-methylthio-2-nitro-ethene was used as a substrate to the syntheses of new heterocyclic compounds. In the reactions, with 1-phenylpiperazine—the corresponding diaminonitroethane ***1****, 1,3-diaminonitropropane, and 1,3-diaminonitropropanol—the nitromethylenotetrahydropyrimidine derivatives* ***2*** *and* ***3*** *were prepared, whereas, with o-phenylenediamine—2-nitromethyleno-benzimidazole* ***4*** *were obtained. In the condensation reactions of compounds* ***2****,* ***3****, and* ***4*** *with benzoyl isothiocyanate, the products* ***5****,* ***6****, and* ***7*** *were obtained, and afterwards two of them,* ***5*** *and* ***6****, were transformed into the isothiazolines* ***8*** *and* ***9****.*

*1,1-bis-(4-phenylpiperazino)-2-nitroethane (****1****) was exposed to the action of phenyl isothiocyanate and the derivative obtained (****10****) was transformed, in the reaction with phenacylbromide, in to benzoylonitrothiophene* ***11****. The diazo compounds* ***12****,* ***13****, and* ***14*** *were obtained in the reactions of nitromethylenotetrahydropyrimidines* ***2*** *and* ***3*** *and of 2-nitromethylenobenzimidazole* ***4*** *with benzenediazonium chloride. The derivatives obtained were tested in vitro for their tuberculostatic activity. The compounds* ***7*** *(MIC 8–32 μg/mL) and* ***14*** *(MIC 16–63 μg/mL) appeared to be the most active compounds.*

Keywords 1,1-Bis-methylthio-2-nitro-ethane; 1-phenylpiperazine; 1,3-diamines; 2-nitromethyleno-benzimidazoles; tuberculostatic

INTRODUCTION

The nitro ketene dithioacetals bearing different substituents have been utilized in the synthesis of many heterocyclic compounds, such as

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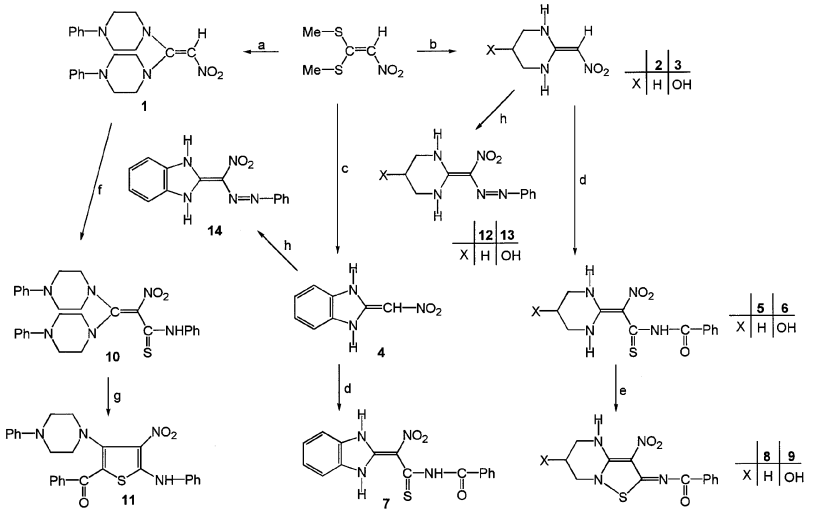
pyrrole, pyrimidine, pyridazine, triazole, thiazole, pyridine, thiophene, and isoxazole derivatives.[1] They also served as useful precursors for aminonitroethene derivatives which exhibited various biological activities, including gastroprotective[2] secretion and inhibition, antacid, antiulcer,[3] antifungal, and antibacterial,[4,5] inhibition of the histamine H2 receptor[6] activities.

CHEMISTRY

In the present work, an attempt at obtaining the new heterocyclic compounds of potentially tuberculostatic activity was made. 1,1-bis-methylthio-2-nitro-ethene, obtained from nitromethane and carbon disulphide according to the method described by Gomperer and Schaefer,[7] was used as a substrate. This compound reacted with 1-phenyl-piperazine and diphenylpiperazinonitroethen **1** was obtained in good yield (Scheme 1). The nitromethylenotetrahydropyrimidine derivatives **2** and **3** were produced from the starting compound and 1,3-diaminopropane as well as 1,3-diamino-2-propanol. Under the same conditions, upon heating the equimolar amounts of the substrates, 1,1-bis-methylthio-2-nitroethene and o-phenylenediamine in ethanol, 2-nitromethylenobenzimidazole **4** was produced.[8] The compounds **2**, **3**, and **4** reacted with benzoyl isothiocyanate to form, after several hours of heating in acetone, the benzoylthioamide derivatives **5**, **6**, and **7**. Two



SCHEME 1

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of them, **5** and **6**, were oxidized with hydrogen peroxide in an acidic medium to the isothiazoline derivatives **8** and **9** by analogy to the reactions reported earlier.[9–13]

1,1-bis-(4-phenylpiperazino)-2-nitro-ethene **1** reacted with phenyl isothiocyanate, while refluxing in dioxane, which gave compound **10**. It transformed in the next step into the benzoylnitrothiophene derivative **11**.

The nucleophilic character of the carbon atom next to the nitro group in compounds **2** and **3** was utilized in the reactions with benzenediazonium chloride, which produced diazo compounds **12** and **13**. The reaction with nitro-methylenobenzimidazole **4**, conducted analogically, gave the diazo derivative **14**.

PHARMACOLOGICAL TESTS

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The compounds obtained were tested for their tuberculostatic activity towards the mycobacterium tuberculosis $H_{37}Rv$ strain and two strains isolated from the tuberculotic patients: one was resistant to the Isonicotinic Acid Hydrazide (INH), Ethambutol (ETB), and Rifampycine (RFP); the other was fully susceptible to the drugs administered. Tuberculostatic activity was tested in vitro by the classical test tube method with Yoiman's liquid medium containing 10% of bovine serum.

The Minimum Inhibiting Concentration (MIC) values were within 8–500 μg/mL. The most active compounds **7** (MIC 8–32 μg/mL) and **14** (MIC 16–63 μg/mL) were tested in a complex way with the following standard strains (Table I): Myc. $H_{37}Rv$—human strain;

TABLE I Tuberculostatic Activity of Compounds 7 and 14

Mycobacterium strains	Compound	
	7 (MIC)	14 (MIC)
$H_{37}Rv$	8	16
An_5	32	250
Kansasii	63	32
Scrophulaceum	32	125
Intracellurae	63	63
Fortuitum	250	500
Kirchbarg	32	125
Wells	63	250
Smegmatis	500	250
607	250	500
Phlei	250	500

Myc. An_5—cattle strain; Myc. kansasii—photochromogenic strain; Myc. scrofulaceum—scotochromogenic strain; Myc. intracellulare—nonchromogenic strain; Myc. fortuitum—quick-growing strain from IV group according to Runyn; Myc. kirchberg—bird-strain; Myc. wells—rodents' strain; and from quick-growing saprophytic strains, Myc. smegmatic, Myc. 607 and Myc. phlei.

EXPERIMENTAL

Melting points were determined with the Reichert apparatus and are uncorrected. The ^{1}H NMR spectra were taken with a Varian Gemini 200 spectrometer. Reaction yields and the physical constants of the compounds obtained are given in Table II. The results of elemental analysis for C and H for all of the compounds that were obtained were in good agreement with the data calculated.

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1,1-Bis(4-phenyl-piperazin-1-yl)-2-nitro-ethene (1)

1,1-bis-methylthio-2-nitroethene (5 mmole) dissolved in ethanol (15 mL) was refluxed with 1-phenylpiperazine (10 mmole) for 1 h. On cooling down, the precipitate of compound **1** was filtered off.

2-(Nitromethylene)hexahydropyrimidine (2), 2-(Nitromethylene)hexahydropyrimidin-5-ol (3), and 2-Nitromethyl-1H-benzimidazole (4)

1,1-bis-methylthio-2-nitroethene (10 mmole) that was dissolved in ethanol (20 mL) was refluxed with 1,3-diaminopropane; 1,3-diamino-2-propanol; or o-phenylenodiamine, respectively, (10 mmole) for 1 h. Methyl mercaptan was evolved intensely when heating. On cooling down, the products precipitated and were filtered off.

N-[2-Nitro-2-(tetrahydro-pyrimidin-2-ylidene)-thioacetyl]-benzamide (5), N[2-(5-hy-droxy-tetrahydro-pyrimidin-2-ylidene)-2-nitro-thioacetyl]-benzamide (6), N-2-(1H-benzimidazol-2-yl)-2-nitro-thioacetylbenzamide (7)

Compound **2**, **3**, or **4** (5 mmole), respectively, dissolved in anhydrous acetone (10 mL) and was refluxed with benzoyl isothiocyanate (5 mmole) for 3 h. On cooling down, the coloured precipitates of compounds **5**, **6**, or **7** were filtered off.

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TABLE II Characteristics of the Synthesised Compounds (1–14)

Compound	Formula (molecular mass)	Yield [%]	M.P. [°C] solvent	^{1}H NMR solvent δ[ppm]
1	$C_{22}H_{27}N_5O_2$ 393,48	62	186–189 EtOH	(DMSO-d_6) 3.25(m, 16H, CH_2); 6.27(s, 1H, CH); 6.67–7.30(m, 10H, Ph)
2	$C_5H_9N_3O_2$ 143,15	70	209–210 EtOH	(DMSO-d_6+ D_2O) 2.0–2.27(m, 2H, CH_2); 3.60(m, 4H, CH_2); 6.65(s, 1H, CH); 9.15(s, 2H, NH)
3	$C_5H_9N_3O_3$ 159,15	63	230–232 R H_2O + dioksan	(DMSO-d_6) 3.48(m, 4H, CH_2); 3.62–3.75(m, 1H, OH); 4.25(m, 1H, CH); 6.52(s, 1H, CH); 9.12(s, 2H, NH)
4	$C_8H_7N_3O_2$ 177,16	83	178–180 EtOH	(DMSO-d_6) 6.86(s, 1H, CH); 7.22, 7.44(2m, 4H, CH, Ph); 12.76(s, 2H, NH)
5	$C_{13}H_{14}N_4O_sS$ 306,27	67	143–144 R DMF + H_2O	(DMSO-d_6) 2.10(m, 2H, CH_2); 3.37–3.62(m, 4H, CH_2); 5.35(s, 1H, OH); 7.90–8.10 (m, 5H, Ph); 9.97(s, 2H, NH)
6	$C_{13}H_{14}N_4O_4S$ 322,27	57	144–146 EtOH	(DMSO-d_6) 3.05–4.29(m, 5H, CH_2); 7.58, 8.44(3m, 5H, Ph); 8.80, 9.01(2s, 2H, NH)
7	$C_{16}H_{12}N_4O_3S$ 340,29	80	164–165 DMF + H_2O	(DMSO-d_6) 7.49–8.00(m, 9H, Ph); 14.04(s, 1H, NH); 14.56(s, 2H, NH)
8	$C_{13}H_{12}N_4O_3S$ 304,26	39	286–289 R DMF + H_2O	(DMSO-d_6) 2.01(m, 2H, CH_2); 3.41(m, 2H, CH_2); 3.74(m, 2H, CH_2); 7.58(m, 3H, Ph); 8.21(m, 2H, Ph); 9.00(s, 1H, NH)
9	$C_{13}H_{12}N_4O_4S$ 320,26	50	265–268 R DMF + H_2O	(DMSO-d_6) 3.47(s, 4H, CH_2); 3.82(m, 1H, CH); 5.65(m, 1H, OH); 6.70, 7.37(2m, 5H, Ph); 8.42(s, 1H, NH)
10	$C_{29}H_{32}N_6O_2S$ 528,59	76	115–117 EtOH	(DMSO-d_6) 3.20–4.0(m, 16H, CH_2); 6.80–8.00(m, 15H, Ph); 10.24(s, 1H, NH)
11	$C_{27}H_{24}N_4O_3S$ 484,49	99	94–95 EtOH	(DMSO-d_6) 3.25(m, 4H, CH_2); 3.50(m, 4H, CH_2); 7.0–7.75(m, 15H, Ph); 10.80(s, 1H, NH)
12	$C_{11}H_{13}N_5O_2$ 247,25	51	178–180 EtOH	($CDCl_3$) 1.95(m, 2H, CH_2); 3.41(m, 4H, CH_2); 7.25–7.70(m, 5H, Ph); 11.17(s, 2H, NH)
13	$C_{11}H_{13}N_5O_3$ 263,25	75	134–135 EtOH	(DMSO-d_6) 3.60(m, 4H, CH_2); 4.25(m, 1H, OH); 5.57(m, 1H, CH); 7.32–7.65(m, 5H, Ph); 10.80(s, 2H, NH)
14	$C_{14}H_{11}N_5O_2$ 281,27	40	189–191 DMF + H_2O	(DMSO-d_6) 7.18–7.85(m, 9H, Ph); 13.90(s, 2H, NH)

N-(3-Nitro-4,5,6,7-tetrahydro-isothiazolo[2,3-a]pyrimidin-2-ylidene)-benzamide (8), N-(6-hydroxy-3-nitro-4,5,6,7-tetrahydro-isothiazolo[2,3-a]pyrimidin-2-ylidene)-benzamide (9)

Compound **5** or **6** (2.5 mmole) that was dissolved in ethanol (20 mL) was treated with concentrated HCl (0.25 mL) and then treated with 30% H_2O_2 (0.6 mL) and refluxed 0.5 h. The solution was decolorized while heating and upon cooling down the compounds **8** or **9** precipitated.

3,3-Bis-(4-phenyl-piperazin-1-yl)-2-nitro-N-phenyl-thioacrylamide (10)

Compound **1** (2.5 mmole) dissolved in anhydrous dioxane (10 mL) was refluxed with phenyl isothiocyanate (2.5 mmole) for 2 h. The solvent was then evaporated, the oily residue was treated with ethyl ether, and the precipitated compound **10** was filtered off.

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[4-Nitro-5-phenylamino-3-(4-phenylpiperazin-1-yl)-thiophen-2-yl]-phenyl-methanone (11)

Compound **10** (2 mmole) and phenacylbromide (2 mmole) were dissolved in ethanol (15 mL) and refluxed for 2 h. On cooling down, the precipitated compound **11** was filtered off.

[Nitro-(tetrahydro-pyrimidin-2-ylidene)-methyl]-phenyl-diazene (12), 2-(Nitro-phenyl-azomethylene)-hexahydro-pyrimidin-5-ol (13), [(1H-benzoimidazol-2-yl)-nitro-methyl]-phenyl-diazene (14)

Compound **2**, **3**, or **4**, (10 mmole) respectively, that was dissolved in a solution of dimethylformamide (15 mL) and ethanol (30 mL) was treated with sodium acetate (1.25 g) and was dissolved in water (5 mL). The solution of a diazonium salt was prepared separately from aniline (0.91 mL), water (2.5 mL), concentrated HCl (2.5 mL), and $NaNO_2$ (1 g) in water (5 mL). This solution was added dropwise to the reaction mixture and stirred for 0.5 h at ambient temperature. The precipitate **12**, **13**, or **14** was filtered off.

REFERENCES

[1] Y. Tominaga and Y. J. Matsuda, *Heterocycl. Chem.*, **22,** 937 (1985).
[2] O. Sikiric, S. Seiwerth, and S. Deskovic, *Eur. J. Pharmacol.*, **364,** 23 (1999).

[3] O. V. Tan, B. Nyasse, T. Dimo, P. Wafo, and B. T. Akankuh, *Pharmazie*, **57,** 409 (2002).
[4] H. Kruszewska, T. Zaremba, and S. Tyski, *Acta Polon. Pharm.*, **59,** 436 (2002).
[5] S. Krakowka, K. A. Eaton, and R. D. Leunk, *Antimicrob. Agents and Chemother.*, **42,** 1549 (1988).
[6] J. M. Hoffman, A. M. Pietruszkiewicz, Ch. N. Kabecker, B. T. Philips, and W. A. Bolhofer, *J. Med. Chem.*, **26,** 140 (1983).
[7] R. Gomper and H. Schaefer, *Chem. Ber.*, **100,** 591 (1967).
[8] H. Schaefer and R. Gewald, *Z. Chem.*, **16,** 272 (1976).
[9] S. Rajappa, *Heterocycles*, **7,** 507 (1977).
[10] U. Aggarwal and H. Junjappa, *Synthesis*, 65 (1982).
[11] S. Rajappa, B. G. Advani, and R. Sreenivasan, *Indian J. Chem. Sect. B*, 886 (1977).
[12] S. Rajappa, B. G. Advani, and R. Sreenivasan, *Tetrahedron*, **33,** 1057 (1977).
[13] D. M. Argilagos, M. I. G. Trimino, A. M. Cabrera, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, **80,** 273 (1997).

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