ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LVIII, 9 SECTIO AA 2003

The synthesis and properties of N-substituted amides of 1-(5-methylthio-1,2,4-triazol-3-yl)-cyclohexane--2-carboxylic acid

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The synthesis of S-methyl-N^1-(cyclohexane-1,2-dicarbonyl)-isothiosemicarbazide and its reactions with primary aliphatic and aromatic amines were performed.
The direction and conditions of these reactions were examined.

1. INTRODUCTION

In the previous papers the synthesis of N^1-phthaloyl-thiosemicarbazides and N^1-(1,2,3,6-tetrahydrophthaloyl)-thiosemicarbazides have been reported [1,2].

As a continuation of the investigations on the properties of these compounds, the direction of the reaction with amines have been studied [1,3]. Reactions of N^1-(1,2,3,6-tetrahydrophthaloyl)-thiosemicarbazides with primary amines were possible in boiling acetic acid medium and the reactions path determined by elementary analysis, ^{1}H NMR spectrum and X-ray view of crystal structure showed that there was an elimination of water molecule and cyclization to the 1,2,4-triazole system lead to racemic mixture of chiral N-substituted amides of 1-(1,2,4-triazol-3-yl)-4-cyclohexene-2-carboxylic acid [3]. Quite different direction of this reaction has been stated than that described previously for N^1-phthaloylthiosemicarbazides, where the ring opening of succinimide system was not observed [1].

Derivatives of 1,2,4-triazole have been known as compounds stimulating activity of central nervous system. They show also hypotensive, anti-inflammatory, antimycotic, viral- and bacteriostatic, and diuretic actions. Some of them are approved as drugs, e.g. Triazolam (sedative, hypnotic) [4], Alprazolam (anxiolytic) [5], Virazole (antiviral) [6].

In the present paper we report the preparation of S-methyl-N^1-(cyclohexane-1,2-dicarbonyl)-isothiosemicarbazide (**II**) and behaviour of this compound towards the action of primary amines. (**II**) was obtained in the direct condensation of cyclohexane-1,2-dicarboxylic anhydride with S-methyl-isothiosemicarbazide hydroiodide in glacial acetic acid medium, as well as on alkylation reaction way of N^1-(cyclohexane-1,2-dicarbonyl)-thiosemicarbazide (**I**) by means of methyl iodide in methanol. (**I**) could be obtained in the reaction of anhydride with thiosemicarbazide in acetic acid, too.

The reaction of the compound (**II**) with aliphatic (propyl-, n-butyl-, sec-butyl-, benzyl-, 2-phenylethyl-, cyclohexyl-) and aromatic (phenyl-, o-chlorophenyl-, p-bromophenyl-, p-methoxyphenyl-, and α-naphtyl-) amines was effected by 5-6 hours heating of reagents in boiling glacial acetic acid (and in N,N-dimethylformamide, too).

In the spectrum of the selected (**IIIg**) compound there were observed proton signals at 2.43 ppm from $–SCH_3$ group as a singlet; signals for cyclohexane ring protons in a form of multiplets: $(2CH_2)$-1* at 1.58 ppm, $(2CH_2)$-2* at 1.82 ppm and (2CH) at 3.14 ppm; singlets from NH protons for amide group at 9.73 ppm, and for triazole ring proton at 13.46 ppm. In addition, the multiplet at 7.22 ppm was characteristic of aromatic protons.

Based on the spectral data and our previous investigations described in the literature, we have stated the formation of N-substituted amides of 1-(5-methylthio-1,2,4-triazol- 3-yl)-cyclohexane-2-carboxylic acid (**IIIa-k**).

The 5-methylthio-group of (**IIIa-k**) could be easily oxidized on the sulfur atom with the excess of hydrogen peroxide in glacial acetic acid at the room temperature for 24 hours yielded the corresponding sulfones (**IVa-k**).

The last compounds (**IVa-k**) with sulfone and amide group and also triazole ring are expected to be pharmacologically active. It is known from the literature that there are many sulfones with biological activity i.e. antibacterial-leprostatic, ophtalmic, antimalary, tuberculostatic, antiinflammatory, antirheumatic [7].

2. EXPERIMENTAL

Melting points were determined in Fischer-Johns block and presented without any corrections.

The ^1H NMR spectra were measured an the Tesla BS-677 A (100MHz) spectrometer in CD_3COCD_3 and DMSO-d_6 with TMS as internal standard.

The initial compounds – the cis-cyclohexane-1,2-dicarboxylic anhydride was a commercial product and S-methyl-isothiosemicarbazide hydroiodide was obtained by the method of Bayer and Liebenow [8].

N^1-(cyclohexane-1,2-dicarbonyl)-thiosemicarbazide (I)

0.91g (0.01 mole) of thiosemicarbazide and 1.54g (0.01 mole) of cyclohexane-1,2-dicarboxylic anhydride in 5 cm^3 of glacial acetic acid were refluxed for 1 hour. After cooling the precipitate crystallized was filtered off and recrystallized from mixture ethanol-water (1:2).
Yield: 2.2g (96.8%), m.p. 181-182°C.

Analysis for the formula $C_9H_{13}N_3O_2S$ (227.3)
Calcd.: 47.5% C, 5.8% H, 18.5% N
Found: 47.7% C, 5.6% H, 18.5% N

^{1}H NMR (DMSO-d_6):
1.36 [m,4H,$(CH_2)_2$-1*], 1.67 [m,4H,$(CH_2)_2$-2*], 3.05 [m,2H,$(CH)_2$], 8.00 [s,2H,NH_2], 9.58 [s,1H,NH].

S-methyl-N^1-(cyclohexane-1,2-dicarbonyl)-isothiosemicarbazide (II)

Method A

2.33g (0.01 mole) of S-methyl-isothiosemicarbazide hydroiodide and 1.54g (0.01 mole) of cyclohexane-1,2-dicarboxylic anhydride in 5 cm^3 of glacial acetic acid were refluxed for 1 hour. After cooling, the reaction mixture was neutralized with 25% aq. ammonia solution and left to crystallization for 2 hours. The crystalline precipitate was filtered off and recrystallized from water.
Yield: 1.3g (54%), m.p.174-175°C.

Method B

1.13g (0.005 mole) of N^1-(cyclohexane-1,2-dicarbonyl)-thiosemicarbazide (I) and 1 cm^3 of methyl iodide in 5 cm^3 of methanol were refluxed for 4 hours. The methanol was evaporated and the residue was neutralized with 25% aq. ammonia solution. The precipitate was filtered off and recrystallized from water.
Yield: 1.15g (95.8%), m.p. 174-175°C.

Analysis for the formula $C_{10}H_{15}N_3O_2S$ (241.3)
Calcd.: 49.7% C, 6.3% H, 17.4% N
Found: 49.0% C, 6.4% H, 17.2% N

^{1}H NMR (CD_3COCD_3):
1.35 [m,4H,$(CH_2)_2$-1*], 1.66 [m,4H,$(CH_2)_2$-2*], 2.92 [m,2H,$(CH)_2$], 2.35 [s,3H,CH_3 from $-SCH_3$], 6.98 [s,2H,NH_2].

N-substituted amides of 1-(5-methylthio-1,2,4-triazol-3-yl)-cyclohexane-2--carboxylic acid (III a-k)

General procedure:

1.2g (0.005 mole) of S-methyl-N^1-(cyclohexane-1,2-dicarbonyl)-isothiosemi-carbazide (II) and 0.005 mole of propyl-, n-butyl-, sec-butyl-, benzyl-, 2-phenylethyl-, cyclohexyl-, phenyl-, o-chlorophenyl-, p-bromophenyl-p-methoxyphenyl-, and α-naphtyl- amine in 5 cm^3 of glacial acetic acid were refluxed for 5-6 hours. After cooling and standing a few hours the precipitate was filtered off and recrystallized from ethanol or ethanol-water.

The detailed data relating to the products of the reaction are listed in the Table 1.

N-substituted amides of 1-(5-methylsulfonyl-1,2,4-triazol-3-yl)-cyclohex-ane-2-carboxylic acid (IV a-k)

General procedure:

One drop of 10% sulphuric acid and 2 cm^3 of 30% hydrogen peroxide solution were added to the solution of 0.001 mole of (III a-k) in 5 cm^3 of glacial acetic acid and allowed to stand overnight at room temperature. The solvent was evaparated under reduced pressure and the residue crystallized from ethanol.
Yield 90-100%.

^{1}H NMR (DMSO-d_6) for (IVg) :
1.53 [m,4H,$(CH_2)_2$-1*], 1.83 [m,4H,$(CH_2)_2$-2*], 3.09 [m,2H,$(CH)_2$], 3.21 [s,3H,CH_3 from SO_2CH_3], 7.21 [m,5H,Ph], 9.77 [s,1H,NH amide], 14.46 [s,1H,NH triazole].

The detailed data are listed in Table 2.

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[1] Galewicz-Walesa K.: Acta Polon. Pharm., 48, No. 3-4, 43 (1991).
[2] Galewicz-Walesa K.: Acta Polon. Pharm., 52, No. 6, 501 (1995).
[3] Galewicz-Walesa K.: Annales UMCS, sectio AA, vol. LII/LIII, 2, 23-28, (1997/1998).
[4] Brucato A., Coppola A.: Boll-Soc. Ital. Biol. Sper., 54, 1051 (1978).
[5] Coffen D. L., Fryer R.: US Patent No. 3849434 (1974).
[6] Witkowski J. T., Robins R. K.: J. Med. Chem. 16, 935 (1973).
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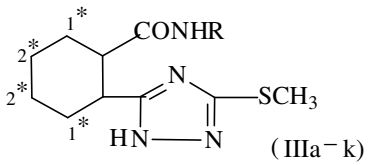
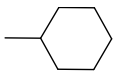
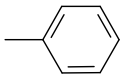
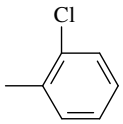
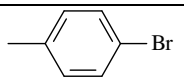
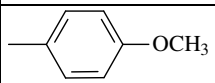
[8] Beyer H., Liebenow W.: Chem. Ber., 190, 1742 (1957).

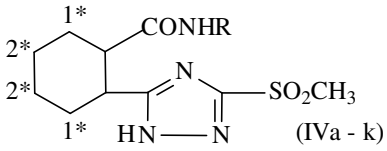
Tab. 1. Physical-chemical data of reaction conditions and obtained compounds



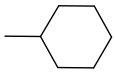
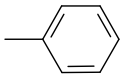
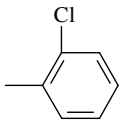
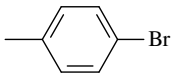
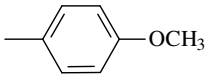
(IIIa – k)

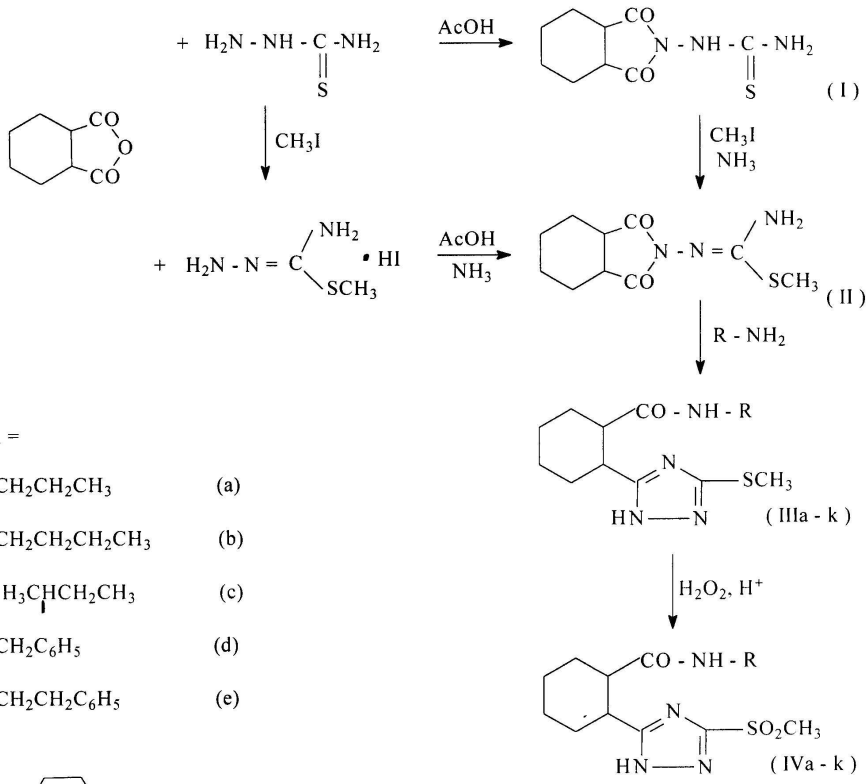
Comp. No.	R	Formula Molecular weight	Yield [%]	M.p. [°C]	Analysis Calculated/Found %C	%H	%N
III a	-$CH_2CH_2CH_3$	$C_{13}H_{22}N_4OS$ 282.4	85.2	191-192	55.3 54.8	7.8 7.6	19.8 20.3
III b	-$CH_2CH_2CH_2CH_3$	$C_{14}H_{24}N_4OS$ 296.4	84.4	184-185	56.7 56.5	8.1 7.8	18.9 18.8
III c	$CH_3C\overset{H}{\underset{|}{}}CH_2CH_3$	$C_{14}H_{24}N_4OS$ 296.4	81.4	211-212	56.7 56.2	8.1 7.8	18.9 19.6
III d	-$CH_2C_6H_5$	$C_{17}H_{22}N_4OS$ 330.4	99.5	223-224	61.8 62.6	6.7 6.8	17.0 17.0
III e	-$CH_2CH_2C_6H_5$	$C_{18}H_{24}N_4OS$ 344.8	90.7	134-135	62.7 62.0	7.0 6.9	16.3 16.3
III f		$C_{16}H_{26}N_4OS$ 322.5	78.3	236-237	59.6 59.0	8.1 7.9	17.4 17.0
III g		$C_{16}H_{20}N_4OS$ 316.4	87.2	215-216	60.7 59.9	6.4 6.8	17.7 18.1
III h		$C_{16}H_{19}N_4OSCl$ 350.9	77.1	198-199	54.8 53.9	5.5 5.5	16.0 16.0
III i		$C_{16}H_{19}N_4OSBr$ 395.3	89.8	204-205	48.6 48.2	4.8 4.7	14.2 14.2
III j		$C_{18}H_{24}N_4O_2S$ 360.5	88.8	173-174	60.0 59.6	6.7 6.2	15.5 15.6
III k	-α-$C_{10}H_7$	$C_{20}H_{22}N_4OS$ 366.5	92.3	236-237	65.5 64.8	6.0 5.8	15.3 15.1

Tab. 2. Physical-chemical data of reaction conditions and obtained compounds



(IVa - k)

Comp. No.	R	Formula Molecular weight	Yield [%]	M.p. [°C]	Analysis Calculated/Found %N
IV a	-$CH_2CH_2CH_3$	$C_{13}H_{22}N_4O_3S$ 314.4	81.0	185-186	17.8 18.0
IV b	-$CH_2CH_2CH_2CH_3$	$C_{14}H_{24}N_4O_3S$ 328.4	80.6	159-160	17.1 17.3
IV c	$CH_3CHCH_2CH_3$	$C_{14}H_{24}N_4O_3S$ 328.4	76.5	205-206	17.1 16.7
IV d	-$CH_2C_6H_5$	$C_{17}H_{22}N_4O_3S$ 362.4	87.5	204-205	15.5 15.2
IV e	-$CH_2CH_2C_6H_5$	$C_{18}H_{24}N_4O_3S$ 376.8	81.3	141-142	14.9 15.4
IV f		$C_{16}H_{26}N_4O_3S$ 354.5	80.9	217-218	15.8 15.2
IV g		$C_{16}H_{20}N_4O_3S$ 348.4	82.3	221-222	16.1 16.3
IV h		$C_{16}H_{19}N_4O_3SCl$ 382.9	84.5	214-215	14.6 14.2
IV i		$C_{16}H_{19}N_4O_3SBr$ 427.3	86.7	229-230	13.1 13.6
IV j		$C_{18}H_{24}N_4O_4S$ 392.5	77.5	180-181	14.3 14.3
IV k	-α-$C_{10}H_7$	$C_{20}H_{22}N_4O_3S$ 398.5	89.7	225-226	14.1 14.3



R =

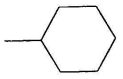
-$CH_2CH_2CH_3$ (a)

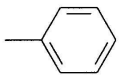
-$CH_2CH_2CH_2CH_3$ (b)

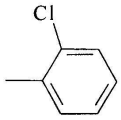
$CH_3CHCH_2CH_3$ (c)

-$CH_2C_6H_5$ (d)

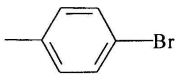
-$CH_2CH_2C_6H_5$ (e)

 (f)

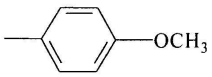
 (g)



(h)



(i)



(j)

-α-$C_{10}H_7$ (k)

Scheme

CURRICULA VITAE

Dr Krystyna Galewicz-Walesa. Born in Poland in 1947. Graduated from Maria Curie-Skłodowska University in Lublin. Since 1971 employed in Department of Organic Chemistry, Faculty of Pharmacy of Medical University in Lublin. Ph.D. degree received in 1978.
She published 17 papers from the field of synthesis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives. She took part in 10 Polish and 2 international symposia.

Dr Anna Pachuta-Stec. Born in Poland in 1963. Graduated from Maria Curie-Skłodowska University in Lublin. Since 1987 employed in Department of Organic Chemistry, Faculty of Pharmacy of Medical University in Lublin. Ph.D. degree received in 1993.
She published 11 papers and 3 patents from the field of synthesis of 1,2,4-triazole and 1,3,4-thiadiazole derivatives. She took part in 14 Polish and 7 international symposia.