

Medical Academy in Lublin

KRYSTYNA GALEWICZ-WALESA\*

*The synthesis and structure of N-substituted amides of  
2-(5-ethyltio-1,2,4-triazol-3-yl)-4-cyclohexene-  
carboxylic acid*

---

Synteza i struktura N-podstawionych amidów kwasu  
2-(5-etylotio-1,2,4-triazol-3-ilo)-4-cykloheksenokarboksyłowego

## 1. INTRODUCTION

The S-alkyl-isothiosemicarbazides and S-alkyl-isothiosemicarbazones are the group of the useful compounds to the synthesis of heterocyclic systems, first of all 1,2,4-triazole and 1,2,4-triazine; the biological activity different derivatives of them is well known in the literature.

During our studies on the reaction of dicarboxylic acid anhydrides with the compounds containing hydrazine moiety, the reaction conditions of the selected anhydrides with S-alkyl-isothiosemicarbazides were found.

The synthesis of S-ethyl-N<sup>1</sup>-phthaloyl-isothiosemicarbazide and S-ethyl-N<sup>1</sup>(1,2,3,6-tetrahydrophthaloyl)-isothiosemicarbazide were described [1,2]. The last compound was obtained in the direct condensation of tetrahydrophthalic anhydride with S-ethyl-isothiosemicarbazide hydrobromide in glacial acetic acid medium, as well as on alkylation reaction way of 1,2,3,6-tetrahydrophthaloyl thiosemicarbazide by means of ethyl bromide in methanol. The necessary 1,2,3,6-tetrahydrophthaloyl-thiosemicarbazide could be obtained in the reaction of anhydride with thiosemicarbazide in acetic acid, too.

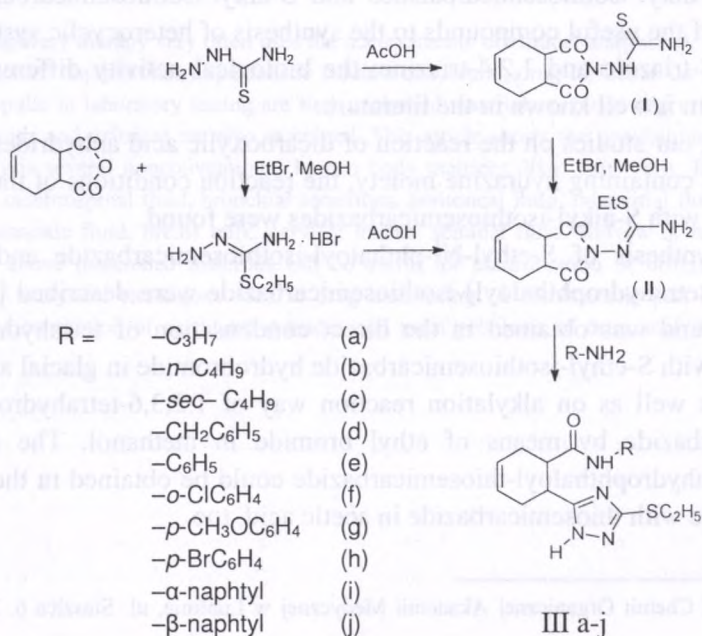
---

\* Zakład Chemii Organicznej Akademii Medycznej w Lublinie, ul. Staszica 6, 20-081 Lublin, Poland.

In the present paper we report the behavior of S-ethyl-N<sup>1</sup>(1,2,3,6-tetrahydro-phthaloyl)-isothiosemicarbazide (II) toward the action of primary and secondary amines.

The reaction of compound (II) with aliphatic (propyl, n-butyl, sec-butyl, benzyl) and aromatic (phenyl, *o*-chlorophenyl, *p*-bromophenyl, *p*-methoxyphenyl,  $\alpha$ -naphthyl and  $\beta$ -naphthyl)-amines was affected by 5–8 hours' heating of reagents in boiling glacial acetic acid, but secondary amines (piperidine, morpholine, pyrrolidine and diethylamine) failed to react under the above given conditions. When the drastic reaction conditions were applied polymerization and decomposition of the initial compound took place. The reaction path was determined by elementary analysis, <sup>1</sup>H-NMR spectrum and X-ray view of crystal structure showed that there was an elimination of molecule of water and cyclization to 1,2,4-triazole system to afford N-substituted amides of 2-(5-ethylthio-1,2,4-triazol-3-yl)-4-cyclohexene carboxylic acid (III a-j).

In the spectrum of the selected (IIIe) compound there were observed proton signals at 1.29 and 3.05 ppm from –SCH<sub>2</sub>CH<sub>3</sub> group as a triplet and a quartet, signals from tetrahydrophthalic ring protons in a form of multiplets: 2CH<sub>2</sub> at 2.46ppm, C<sup>5</sup>–H at 3.27ppm, C<sup>10</sup>–H at 3.60ppm, 2 CH= at 5.72ppm; singlets from NH protons – for amide group at 9.35ppm and for triazole ring proton at 12.74ppm. In addition, the multiplet at 7.30ppm was characteristic of aromatic protons.





## 2. EXPERIMENTAL

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

The  $^1\text{H-NMR}$  spectra were measured on the Tesla BS-677 A (100MHz) spectrometer in  $\text{CD}_3\text{COCD}_3$  with TMS as internal standard.

X-ray analysis for crystal of (IIIe) compound was carried out on four-circle automated Euraf-Nonius MACH 3 diffractometer (Institute of Organic Chemistry, PAN, Warsaw). Numbering scheme and general view of molecule are showed in Figure 1.

The initial compound – the 1,2,3,6-tetrahydrophthalic anhydride was a commercial product and S-ethyl-isothiosemicarbazide hydrobromide was obtained by the method of Beyer and Liebenow [3].

### *S-ethyl-N<sup>1</sup>(1,2,3,6-tetrahydrophthaloyl)-isothiosemicarbazide (II)*

#### *Method A*

2g (0.01 mole) of S-ethyl-isothiosemicarbazide hydrobromide and 1.52g (0.01 mole) of 1,2,3,6-tetrahydrophthalic anhydride in  $4\text{cm}^3$  of glacial acetic acid were refluxed for 1/2 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: 1.54g (61%), m.p. 124–125°C.

#### *Method B*

1.1g (0.005 mole) of  $\text{N}^1(1,2,3,6\text{-tetrahydrophthaloyl})\text{-thiosemicarbazide}$  and  $1\text{cm}^3$  of ethyl bromide in  $5\text{cm}^3$  of methanol were refluxed for 6 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: 0.87g (69%), m.p. 124–125°C.

Analysis for the formula  $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$  (253.3):

Calcd.: 52.1% C, 6.0% H, 16.6% N;

Found: 52.1% C, 5.8% H, 16.4% N.

$^1\text{H-NMR}$  ( $\text{CD}_3\text{COCD}_3$ ):

1.37 (t, 3H,  $\text{CH}_3$  from  $-\text{SCH}_2\text{CH}_3$ ), 3.05 (q, 2H,  $\text{CH}_2$  from  $-\text{SCH}_2\text{CH}_3$ ), 2.40 /m, 4H,  $(\text{CH}_2)_2$ /, 3.20 /m, 2H,  $(\text{CH}-)_2$ /, 5.97 /m, 2H,  $(\text{CH}=\)_2$ /, 6.30 (s, 2H,  $-\text{NH}_2$ ).

*N*-substituted amides of 2-(5-ethylthio-1,2,4-triazol-3-yl)-4-cyclohexene-carboxylic acid (III a-j)

General procedure :

1.2g (0.005 mole) of S-ethyl-N<sup>1</sup>(1,2,3,6-tetrahydrophthaloyl)-isothiosemicarbazide (II) and 0.005 mole of propyl-, n-butyl-, sec-butyl-, benzyl-, phenyl-, *o*-chlorophenyl-, *p*-methoxyphenyl-, *p*-bromophenyl-,  $\alpha$ -naphthyl- and  $\beta$ -naphthyl-amine in 5cm<sup>3</sup> of glacial acetic acid were refluxed for 5 hours (aliphatic amines) and 8 hours (aromatic amines). 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.

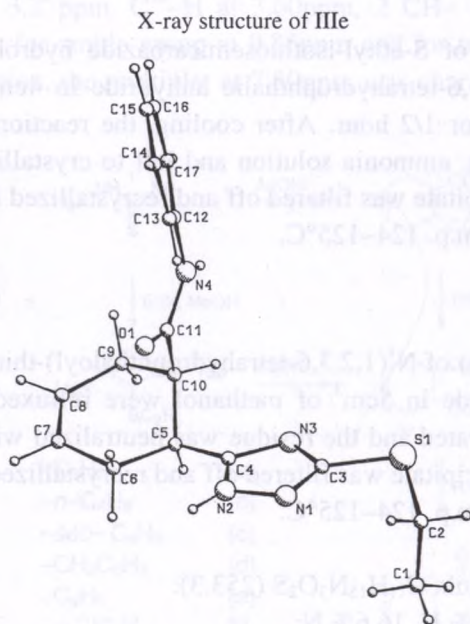
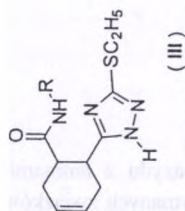


Fig. 1. Numbering scheme and general view of molecule of (IIIe) in the solid state  
Schemat numeracji i ogólny wygląd cząsteczki związku IIIe w stanie stałym

Ac-derivative of (III d) – m.p. 128–129°C, (III e) – m.p. 113–114°C.



Table 1. Physical-chemical data of reaction conditions and obtained compounds  
Dane fizykochemiczne warunków reakcji i otrzymanych związków



Comp. No.	R	Formula Molecular weight	Yield [%]	M.p. [°C]	Analysis					
					%C		%H		%N	
					Calc.	Found	Calc.	Found	Calc.	Found
IIIa	C <sub>3</sub> H <sub>7</sub>	C <sub>14</sub> H <sub>22</sub> N <sub>4</sub> O 294.4	81.6	127–128	57.1	57.6	7.5	7.5	19.0	18.8
IIIb	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	C <sub>15</sub> H <sub>24</sub> N <sub>4</sub> O 308.4	87.3	110–111	58.4	58.2	7.8	7.5	18.2	18.4
IIIc	<i>sec</i> -C <sub>4</sub> H <sub>9</sub>	C <sub>15</sub> H <sub>24</sub> N <sub>4</sub> O 308.4	90.2	150–151	58.4	58.0	7.8	7.6	18.2	17.9
III d	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>18</sub> H <sub>22</sub> N <sub>4</sub> O 342.4	97.0	178–179	63.1	62.8	6.5	6.4	16.4	16.0
III e	C <sub>6</sub> H <sub>5</sub>	C <sub>17</sub> H <sub>20</sub> N <sub>4</sub> O 328.4	90.2	163–164	62.2	61.6	6.1	6.3	17.1	17.2
III f	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>17</sub> H <sub>19</sub> N <sub>4</sub> O 362.9	99.4	176–177	56.3	56.4	5.3	5.1	15.4	15.2
III g	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	C <sub>18</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> S 358.4	96.6	174–175	60.3	59.9	6.2	5.8	15.6	15.7
III h	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	C <sub>17</sub> H <sub>19</sub> N <sub>4</sub> O 407.3	96.0	180–181	50.1	50.4	4.7	4.9	13.7	13.6
III i	$\alpha$ -C <sub>10</sub> H <sub>7</sub>	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O 378.5	99.5	195–196	66.6	66.8	5.8	5.3	14.8	14.5
III j	$\beta$ -C <sub>10</sub> H <sub>7</sub>	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O 378.5	99.5	156–157	66.6	66.3	5.8	6.0	14.8	14.9

## REFERENCES

- [1] K. Galewicz-Walesa: *Acta Polon. Pharm.*, 48, No. 3-4, 43 (1991).
- [2] K. Galewicz-Walesa: *Acta Polon. Pharm.*, 52, No. 6, 501 (1995).
- [3] H. Beyer, W. Liebenow: *Chem. Ber.*, 190, 1742 (1957).

## STRESZCZENIE

Przebadano reakcję S-etylo-N<sup>1</sup>(1,2,3,6-tetrahydroftaloilo)-izotiosemikarbazydu z aminami. Ustalono warunki oraz kierunek reakcji z aminami I-rzędowymi. Strukturę otrzymanych związków określono w oparciu o analizę widma <sup>1</sup>H-NMR oraz analizę rentgenostrukturalną kryształu wybranego związku.