NEW SYNTHESIS OF AMINORHODANIN AND CONDENSED DERIVATIVES

MOHAMMAD ALI JALILI AND KAMRAN MOUSAVI HOSSEINI*

Iranian Blood Transfusion Organization, Research Center, Tehran, Iran

ABSTRACT

Aminorhodanins are heterocyclic compounds of dithiocarbazoyl which include sulphur and nitrogen in their structures. Different research studies have been performed on rhodanin and it's condensed derivatives and several reports have been issued indicating their antimicrobial properties. In the present work, first a new method has been developed for production of aminorhodanin, which include one more nitrogen atom in third position compare to rhodanins molecule, then condensed reactions with aldehydes have been investigated. The probable biological properties of produced compounds will be investigated in another research study.

Keywords: Hydrazine, thiocarbamoylthioacetic acid, aminorhodanine and it's condensed derivatives.

INTRODUCTION

There has been extensive investigation concerning rhodanins. For these group of compounds, several biological properties such as: antibacterial and antifungal (Gualtieri *et al*., 2006; Orchard *et al*., 2004; Janowic *et al*., 1957) antiviral (Eggers *et al*., 1970), antihelmentic (Mackie *et al*., 1954), pesticide (Bashour 1956), analgesic, sedative and antiepilepsy (Jones *et al*., 1946; Von Bruening 1955; Zepaknyok 1966) and antioxidant (Ellis 1958) have been reported. There have been few investigation performed for aminorhodanins with one amine group substituded on third position and there have been reported that antimicrobial effect has been observed for N, N-dimethylaminorhodanin (Hanefeld and Hinz 1980; Hanefeld 1975; Latussek 2004). Regarding to the approximate similarity between rhodanins and aminorhodanins and extensive scope of biological properties of rhodanins, we carried out the new aminorhodanin synthesis and then condensed reaction with aldehydes. Their probable biological properties will be investigated separately.

MATERIAL AND METHODS

All chemical and solvents including ether, acetic acid, sodium chloride, acetic anhydride, hydrazine and its derivatives, triethylamine and carbon disulfide were obtained from Merck company (Germany).

Melting point determination has been done by Linstroem. Analytical method was performed by Autoanalyser 185-CHN.

The IR spectra were recorded on Perkin-Elmer 398PE spectrophotometer.

The ^{1}H-NMR spectra were recorded on Varian apparatus (60MHz).

The ^{13}C-NMR spectra were run on Firma-Bruker (400MHz).

The mass spectra were run on a Varian MAT III and mass data given is EIMS.

2-(3-Methyl-3-phenyl-thiocarbazoylthio)-acetic acid(a)

N-Methyl-N-phenyl hydrazine (15g, 0.12M) and triethylamine (12.2 g, 0.12 M) was dissolved in 100 ml of dry ether, and carbondisulfide (9.2 g, 0.12 M) and nartium chloroacetate solution with the amount of (1:1) was added to the obtained salt and it was stirred for 30 min at room temperature. Then at the temperature between 5 to 10°C, diluted hydrochloric acid (25%) was added with the equal amount while stirring. Then the achieved acid was separated with the help of crystallized acetonytril (82%).

m.p.=134°C	Anal. for $C_{10}H_{12}N_2O_2S_2$			
Cal.	C, 46.86	H, 4.72	N, 10.93	S, 25.02
Found	C, 47.0	H, 4.75	N, 10.71	S, 24.83

IR(KBr): 3150 (NH), 2990-2700 (COOH), 1680 (C=O).
^{1}H-NMR (DMSO-d_6): δ,10.2(s,COOH), 7.0 (s,C_6H_5), 6.8(s,NH), 3.5(s,CH_2), 3.1(s,CH_3).
M.S.: m/z(%), 238,(0.5) (M^+-H_2O), 164 (53 C_6H_5-CH_3-N-N=C=S), 106(66 C_6H_5-N-CH_3).

2-(N-Azepano-thiocarbamoylthio)-acetic acid (b)

This compound was prepared as same as compound (a). Other data are as the following:
N-aminohomopiperidine (25g, 0.12 M)
Triethylamine (21g, 0.21 M), carbondisulfide (16g, 0.021 M), ether (200 m1).
Crystallization: toluen, petroliumether. Yield: 90%.

m.p.: 119°C	Anal. for $C_9H_{16}N_2O_2S_2$			
Cal.	C, 43.52	H, 6.48	N, 11.27	S, 25.68
Found	C, 43.31	H, 6.23	N, 11.21	S, 25.65

**Corresponding author:* Tel: 0218205216, e-mail: mkmousavi@yahoo.com

IR(KBr): 3100 (NH), 3000-2600 (COOH).
^{1}H-NMR(DMSO-d_6):11.7(s,COOH), 10.9(s,NH), 4.0(s,CH_2), 3.0-2.8(m,CH_2-N-CH_2), 1.7-1.5(m,$(CH_2)4$) (related to four CH_2 on homopiperidine ring).
M.S.: m/z (%), 248,(0.9) (M^+), 159(65), 42(100).

3-(N-methyl-N-phenyl-amino)-2-thioxo-thiazolidin-4-one (c)

N-methyl-N-phenylthio-carbazoyl-thio acetic acid (2g, 0.01 M) was dissolved in anhydride acetic (50 ml) and add 3 drops of concentrated sulphuric acid prefilled with ice-cube and it was stirred thoroughly. The achieved precipitate color was yellow, and it should be separated and with the help of toluene it was crystalized. The yield was 60%.

m.p.: 163°C	Anal. for $C_{10}H_{10}N_2OS_2$			
Cal.	C, 50.40	H, 4.23	N, 11.75	S, 26.91
Found	C, 50.71	H, 4.25	N, 11.64	S, 26.88

IR(KBr): 1750 (C=O), 1600, 1550, 1390.
^{1}H-NMR($CDCl_3$): 7.9-7.4(m,C_6H_5), 4.7(s,CH_2), 4.1(s,CH_3).
^{13}C-NMR($CDCl_3$):196.7(C=S), 170.5(C=O), 146.6, 129.9, 112.3(C_6H_5), 37.9(CH_2), 32.6(CH_3).
M.S.: m/z (%), 238,(27) (M^+), 164(2 N-methyl-N-phenyl=C=S), 91(4 C_6H_5-N).

3-Azepano-2-thioxo-thiazolidin-4-one (d)

The method for preparation was as same as compound (c).
2-(N-azepano-thiocarbamoylthio)-acetic acid (40 g, 0.16M)
Anhydrid acetic (50ml)
Concentrated H_2S0_4
It was heated for 15 minutes, and it was crystallized by toluene. Yield: 54%.

m.p.=54°C	Anal. for $C_9H_{14}N_2OS_2$			
Cal.	C, 46.93	H, 6.13	N, 12.16	S, 27.84
Found	C, 47.18	H, 5.94	N, 11.96	S, 27.45

IR (KBr): 1795 (C=O), 1445, 1390, 1300.
^{1}H- NMR ($CDCl_3$): 3.8(s,CH_2C), 3.3-3.1(m,CH_2-N-CH_2), 2.0-1.8(m,$(CH_2)_4$).
M.S.: m/z (%), 230,(0.7) (M^+), 113(3 azepano-NH), 98(58 azepanyl), 97(100).

5-Benzyliden-3-(N-methyl-N-phenyl-amino)-2-thioxo-thiazolidino-4-one (e)

3-(N-Metyl-N-phenyl-amino)-2-thioxothiazolidin-4-one (1.0g, 0.04 M) was dissolved in dry ethanol, and fresh distilled benzaldhyde (0.46g, 0.04 M) was added with 3 drops of piperidine, then it was heated for 30 min.

After cooling at room temperature, yellow precipitate was separated and crystallized with ethanol. Yield: 95%.

m.p.=137°C	Anal. for $C_{17}H_{14}N_2OS_2$			
Cal.	C, 62.55	H, 4.32	N, 8.58	S, 19.64
Found	C, 62.28	H, 4.37	N, 8.03	S, 19.59

IR (KBr): 1720 (C=O), 1590 (C=C), 1450, 1250.
^{1}H-NMR($CDCl_3$): 7.8 (s,=CH), 7.5(s,C_6H_5-CH), 7.6-6.6(m,C_6H_5N-), 3.4(s,CH_3).
^{13}C-NMR(CDCl3):189.3(C=S), 164.8(C=O), 145.5, 134.2, 132.5, 130.8, 130.6, 125.8(C_6H_5=CH), 120.5(C_5), 38.1(CH_3).
M.S.: m/z (%), 326,(100) (M^+), 221(13M^+ - C_6H_5N=CH_2), 134(20 C_6H_5-CH=C=S), 106 (40 C_6H_5N-CH_3).

3-Piperidino-5-(p-dimethylamino-benzyliden)-2-thioxo-thiazolidin-4-one (f)

The method for the preparation was as same as compound (e).
3-Piperidino-2-thioxo-thizaolidin-4-one (2.0 g, 0.09 M)
P-Dimethyl amino benzaldehyde (4.0 g, 0.09 M)
Ethanol (50 ml) and piperidine (2 drops).
It was heated for 20 minutes at 80°C, and it was crystallized by ethanol.
The color was yellow. Yield: 74%.

m.p.=203°C	Anal. for $C_{17}H_{21}N_3OS_2$			
Cal.	C, 58.76	H, 6.09	N, 12.09	S, 18.45
Found	C, 58.53	H, 5.88	N, 12.31	S, 18.49

IR (KBr): 1675(C=O), 1600.
^{1}H-NMR ($CDCl_3$): 7.9-7.2(m,C_6H_4 and =CH), 3.6-3.4(m,$(CH_2)_2$), 3.2(s,$(CH_3)_2$, 1.9-1.7(m,$(CH_2)_3$).
M.S.: m/z (%), 347,(7) (M^+), 84(4 piperidyl), 43(2 CH=N-CH_3).

5-(*p*-Dimethylamino-benzyliden)-3-dimethylamino-2-thioxo-thiazolidin-4-one (g)

Preparation method was as same as compound (e).
3-Dimethylamino-2-thioxo-thiazolidin-4-one (2g, 0.01 M)
p-Dimethyl amino benzaldehyde (8.2 g, 0.05 M)
2 to 3 drops piperidine was added.
It was heated for 10 to 15 minutes.
The color of the precipitate was yellow.
Crystallization has been done by ethanol. Yield: 60%.

m.p.= 163°C	Anal. for $C_{14}H_{17}N_3OS_2$			
Cal.	C, 46.59	H, 3.58	N, 13.58	S, 20.73
Found	C, 46.53	H, 3.57	N, 13.45	S, 20.76

IR (KBr): 1675 (C=O), 1600, 1500.
^{1}H-NMR ($CDCl_3$): 7.9-7.6(m,C_6H_5 and =CH), 3.2(s,$(CH_3)_4$).
M.S.: m/z (%), 307,(22) (M^+), 177(100), 133(3$(CH_3)_2$N – C_6H_4=CH), 101(2$(CH_3)_2$-N-N=C=S-H).

3-Dimethylamino-5-(p-nitrobenzyliden)-2-thioxo-thiazolidin-4-one (h)

The method for preparation was as same as for the compound (e).

3-Dimethylamino-2-thioxo-thiazolidin-4-one (2.0 g, 0.01 M)
p-nitrobenzaldehyde (8.3 g, 0.05 M), ethanol 50 ml
It was heated for 30 minutes.
Obtained yellow precipitate was crystallized by ethanol. Yield: 83%.

m.p.= 215°C		Anal. for $C_{12}H_{11}N_3O_3S_2$		
Cal.	C, 46.59	H, 3.58	N, 13.58	S, 20.73
Found	C, 46.53	H, 3.57	N, 13.45	S, 20.76

IR (KBr): 1700 (C=O), 1610, 155, 1335, 1250.
^{1}H-NMR ($CDCl_3$): 8.2-7.6 (q,C_6H_5 and =CH), 3.1(s,$(CH_3)_2$.
M.S.: m/z (%), 309(5) (M^+), 134(10 ON_2-C_6H_5-CH), 102(49$(CH_3)_2N$ –N =C=S), 86(8(CH_3)-N-N=C=O), 43(100CH_2=N-CH_3).

5-Benzyliden-3-dimethylamino-2-thioxo-thiazolidin-4-one (i)
The method of preparation was as same as compound (e).
3-Dimethylmino-2- thioxo-4-thiazolidine (3.5 g, 0.02 M), Benzaldehyde (2.3 g, 0.02 M), ethanol 50ml
The yellow precipitate was crystallized by ethanol. Yield: 97%.

m.p.= 130°C		Anal. for $C_{12}H_{12}N_2OS_2$		
Cal.	C, 54.52	H, 4.58	N, 10.60	S, 24.26
Found	C, 54.54	H, 4.55	N, 10.47	S, 24.27

IR (KBr): 1650 (C=O), 1560 (C=C), 1310, 1250, 1150, 1120.
^{1}H-NMR ($CDCl_3$): 7.8(s =CH), 7.5(s,(C_6H_5), 3.2(s,$(CH_3)_2N$).
^{13}C-NMR ($CDCl_3$): 189.3(C=S), 165.5(C=O), 136.3, 132.5, 130.7, 127.8, 125, 5(C_6H_5) and=CH), 120.3(C_4), 40.7$(CH_3)_2N$.
M.S.: m/z (%), 254,(3) (M^+), 222(24 C_2H_4N), 134(C_6H_5-CH=C=S 100).

5-(*p*-Nitrobenzyliden)-3-piperidino-2-thioxo–thiazolidin–4–one (j)
The method for preparation was as same as compound (e).
3-Piperdino–2–thioxo–thiazolidin–4–one (2.0 g, 0.09 M)
p-nitrobenzaldehyde (4.2 g, 0.03 M), ethanol 50 ml.
It was heated for 20 min.
The yellow precipitate was crystallized by ethanol. Yield: 77%.

m.p.= 214°C		Anal. for $C_{15}H_{15}N_3O_3S_2$		
Cal.	C, 51.56	H, 4.33	N, 12.03	S, 18.35
Found	C, 51.57	H, 4.34	N, 12.27	S, 18.37

IR (KBr): 1700 (C=O), 1590, 1500, 1340.
^{1}H-NMR ($CDCl_3$): 8.2–7.6(2d, C_6H_4), 7.6(s,=CH), 3.8–3.2(m,$(CH_2)_2$-N), 2-1.8(m, $(CH_2)_3$).
M.S. : m/z (%), 349,(1) (M^+), 142(3-piperidino–N=C=S), 84(42 piperidyl) 83 (100).

3-Morpholino-5-(*p*-dimethylamino-benzyliden)2-thioxo-thiazolidin-4-one (k)
The preparation method was as same as compound (e).

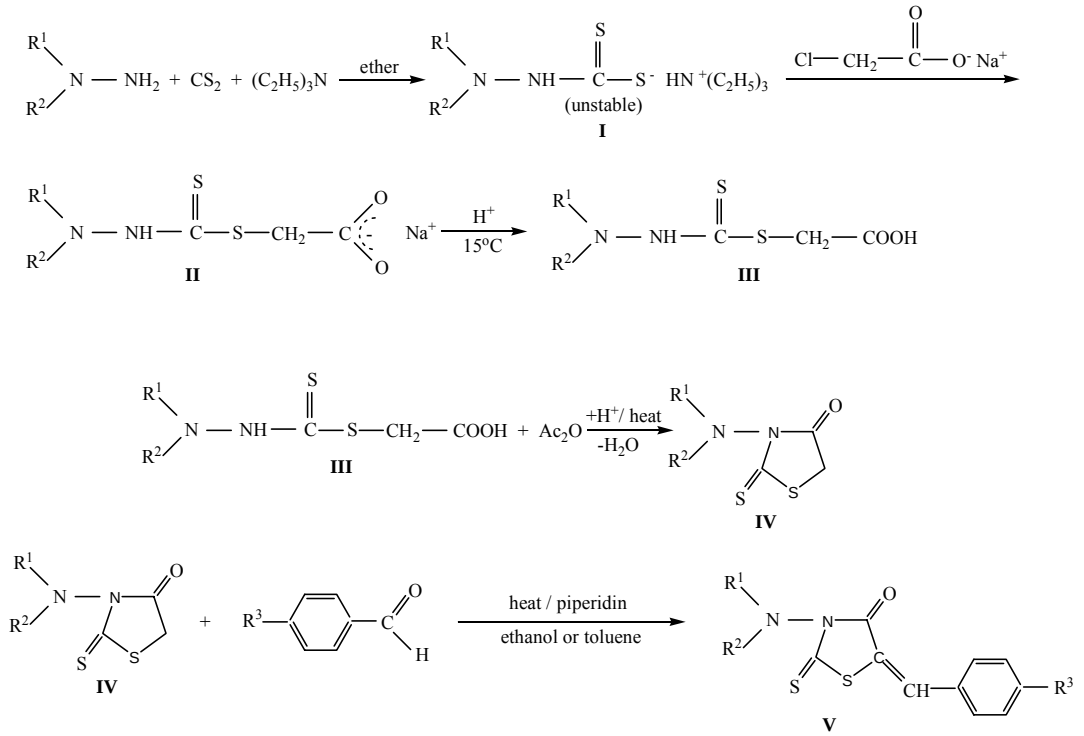

Fig. 1: Preparation of aminorhodanines and it's condensed derivatives

3-Morpholino-2-thioxo-thiazolidin-4-one (2.0 g, 0.08 M)
p-Dimethylamiobenzaldehyde (5.4 g, 0.03 M)
Ethanol (50 ml), piperidine (3 drops)
It was heated for 30 minutes.
The yellow precipitate was crystallized by ethanol. Yield: 65%.

m.p.= 235°C		Anal. for $C_{16}H_{19}N_3O_2S_2$		
Cal.	C, 54.99	H, 5.48	N, 12.02	S, 18.35
Found	C, 54.88	H, 5.45	N, 12.12	S, 18.09

IR (KBr): 1670 (C=O), 1600, 1550, 1430.
^{1}H-NMR ($CDCl_3$): 7.6–7.0(m,C_6H_4 and =CH), 4.1-3.8(m,(CH_2-O-CH_2), 3.2(s,$(CH_3)_2$), 3.1-3.0(m,$(CH_2)_2$-N).
M.S.: m/z (%), 349,(14) (M^+), 264(31), 177(100), 144(3 morpholino-N=C=S).

3-Azepano-5-benzyliden-2-thioxo-thiazolidin-4-one (l)
The method for the preparation was as same as compound (e).
3-Azepano-2-thioxo-thiazolidin-4-one (2.3 g, 0.01 M)
Benzaldehyde (1.3 g, 0.01 M)
Ethanol (50 ml), piperidine (3 drops)
The yellow precipitate was crystallized by ether. Yield: 47%.

m.p.= 155°C		Anal. for $C_{16}H_{18}N_2OS_2$		
Cal.	C, 60.35	H, 5.70	N, 8.80	S, 20.14
Found	C, 60.22	H, 5.54	N, 8.65	S, 20.03

IR (KBr): 1690 (C=O), 1560 (C=C), 1445, 1325, 1250.
^{1}H-NMR ($CDCl_3$): 7.7(s=CH), 7.5(s,C_6H_5), 3.4-3.2(m,CH_2–N–CH_2), 1.8-1.6(m,$(CH_2)_4$).
^{13}C-NMR ($CDCL_3$): 190.5(C=S), 165.9(C=O), 133.3, 132.5, 129.2(C_6H_5 and =CH), 110.7 (C5), 53.9(CH_2-N-CH_2), 28.7, 27.4($(CH_2)_2$).
M.S.: m/z (%), 318,(1) (M^+), 134(41 C_6H_5-CH=C=S), 99(14 azepan), 98(100 azepanyl).

RESULTS AND DISCUSSION

For synthesis of aminorhodanins, first, hydrazine or one of it's derivatives plus triethylamine were dissolved in dry ether and then carbondisulfide is added at 5-10°C while mixing.

The Produced salt (I) is dissolved in sodium chloroacetate which form salt (II), concentrated hydrochloric acid was added at 15°C to the water dissolved salt (II) solution, while mixing. The obtained acid solution (III) is changed to aminorhodanin (IV) using acetic andhydride and in the presence of sulphuric acid. For condensation of compound (IV), it dissolved in suitable solvent and reacted with aldehyde in the presence of piperidine to obtain compound (V).

Fig. 1 shows the preparation pathway of aminorhodanine derivatives and table 1,2,3 show some of synthesized aminorhodanine derivatives in this study.

Table 1: Compounds with the structure of III

No.	R1	R2	%	m.p.°C
(a)	-CH3	-C_6H_5	82	134
(b)	C_6H_{12}N-	C_6H_{12}N-	90	118

Table 2: Compounds with the structure of IV

No.	R1	R2	%	m.p.°C
(c)	-CH3	-C_6H_5	82	134
(d)	C_6H_{12}N-	C_6H_{12}N-	81	54

The effort has been taken to produce aminorhodanins, considering the minimum needed equipment and choosing the most convenient way for short reaction time, low cost with high yield. In comparison with other works we used triethylamine instead of ammonia and we have made the five member ring in one step by using acetic anhydride, which make the whole process shorter.

REFERENCES

Bashour J T (1956). Rhodanine and their use as pesticiedes. (To Stauffer Chemical Co.). U.S. 1956, **24**: 2, 743, 211. via C.A. 50 11598 (1956).

Eggers H J, Koch M A, Furst A, Doyle G, and Wilczynski J (1970). Rhodanine: selective inhibitor of the multiplication of Echovirus. 12. *Science,* **167**(3916): 294-7. Via C.A. 72, 76057f (1970).

Ellis W C, Antioxidants, Jr. (To Stauffer Chem. Co.). U.S. 1957, **23**: 2, 800, 491. Via C.A. 52, 500 7a (1958).

Table 3: Compounds with the structure of V

No.	R^1	R^2	R^3	%	m.p.°C
(e)	-CH3	-C_6H_5	-H	95	137
(f)	C_5H_{10}N-	C_5H_{10}N-	-$(CH_3)_2$	74	203
(g)	-CH3	-CH3	-$(CH_3)_2$	60	163
(h)	-CH3	-CH3	-NO_2	83	215
(i)	-CH3	-CH3	-H	97	130
(j)	C_5H_{10}N-	C_5H_{10}N-	-NO_2	77	214
(k)	O(CH_2CH_2)N-	O(CH_2CH_2)N-	-$(CH3)_2$	65	235
(l)	C_6H_{12}N-	C_6H_{12}N-	-H	67	155

Gualtieri M, Bastide L, Villain-Guillot P, Michaux-Charachon S, Latouche J, and Leonetti, J P (2006). *In vitro* activity of a new antibacterial rhodanine derivative against Staphylococcus epidermidis biofilms. J. Antimicrob. Chemotrap., **58**(44): 778-783.

Hanefeld W, Hinz W (1980). 1,3-Thiazines, X: Attempted synthesis of fungitoxoic hydrochloric 2-thiotetrahydro-1,3-thiazin-4-ones. Arch. Pharm (Weinheim), No. **313**(1): 20-26.

Hanefeld W (1975). 1,3-Thiazines, IV. The constitution of the reaction products of 2-thioxo-4-oxo- and 2,4-dioxotetrahydro-1,3-thiazines with alkoxides. Arch Pharm (Weinheim). **308**(6):450-455.

Janowic M, Venulet and wieniak W (1957). Antibacterial action of some rhodanine derivatives. Bull. Acad. Pol. Sci. sersc. Biol., **5**: 201-206.

Jones E R H, Robinson F A, and Strachan M N (1946). Some 5-spirothiazolidiones. *J. Chem. Soc.*, page 91.

Latussek E (2004). Dissertation, Universitaet Marburg, Marburg, Germany.

Mackie A, and Misra A L (1954). Rhodanine derivativesas possible antihelmintics. J. Chem. Soc., 3919-22, Via C, A., 49, 13973 f (1955).

Orchard M G, Neuss J C, Galley C M, Carr A, Porter D W, Smith P, Scopes D I, Haydon D, Vousden K, Stubberfield C R, Young K, and Page M (2004). Rhodanine-3-acetic acid derivatives as inhibitors of fungal protein mannosyl transferase 1 (PMT 1). Bioorg. Med. Chem. Lett., **14**(15):3975-3978.

Von Bruening L (1955). Farbwerke Hoechst A.G., Germany Pat. 924,630 (7, Marth 1955), C.A. 52, 4694 (1958).

Zepaknyok V H (1966). Anticonvulsive drugs, their classification and mechanisms of action. Vrach, Delo., **10**: 71-75, Via. C.A. Vo 166, 1967.