SYNTHESIS OF NEW 2-HYDRAZONO-4-OXO-5-THIAZOLIDINEACETIC ACIDS AND THEIR ALKYLAMIDES

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The direct two step synthesis of three new 2-hydrazono-4-oxo-5-thiazolidineacetic acids from thiosemicarbazide, the appropriate ketones (acetophenone, cyclopentanone, cyclohexanone) and maleic anhydride is described. The prepared acids were transformed, via their mixed anhydrides with ethyl carbonate, into their alkylamides in a one-pot procedure.
Key words: 2-Hydrazono-4-oxo-5-thiazolidine; Effect on chlorophyll production.

Several 2-hydrazono- and 2-aza-4-oxo-5-thiazolidineacetic acids possess the antiviral properties[1–3]. The fungicidal properties of the compounds with similar structure were described also[4]. It is of interest that no attention has been paid to the investigation of the biological activity of their amides.

The main goal of this work was to prepare new 2-hydrazono-4-oxo-5-thiazolidineacetic acids and their amides and to investigate their biological activity[5].

Synthesis of 2-hydrazono-4-oxo-5-thiazolidineacetic acids[1,6] **2a**–**2c** from the corresponding thiosemicarbazones **1** (refs[7–10]) was performed by a two step procedure depicted in Scheme 1. Thiosemicarbazones **1a–1c**, which were isolated in 80–90% yields, were allowed to react with maleic anhydride in chloroform. After several hours heating at reflux temperature and usual work-up reasonable yields (50–90%) of the acids **2a**–**2c** as good crystallizing solids were achieved. The conversion of 2-hydrazono-4-oxo-5-thiazolidineacetic acids **2** into their alkylamides **3** was performed as described in Scheme 1. The characteristic data of the compounds **3** are given in Table I.

The biological activity of the prepared compounds was briefly evaluated by their effect on the chlorophyll production. No special effect of their addition on the chlorophyll production has been found. Their biological activity is under screening.

EXPERIMENTAL

^{1}H NMR spectra (δ, ppm; *J*, Hz) were recorded in $(CD_3)_2SO$ on a Tesla BS 487 apparatus (80 MHz) with tetramethylsilane as internal standard. The effect of compounds **2a–2c** and **3a–3o** on chlorophyll synthesis in stationary-cultivated *Chlorella vulgaris algae* (7 days, 16 h light/8 h dark period) was

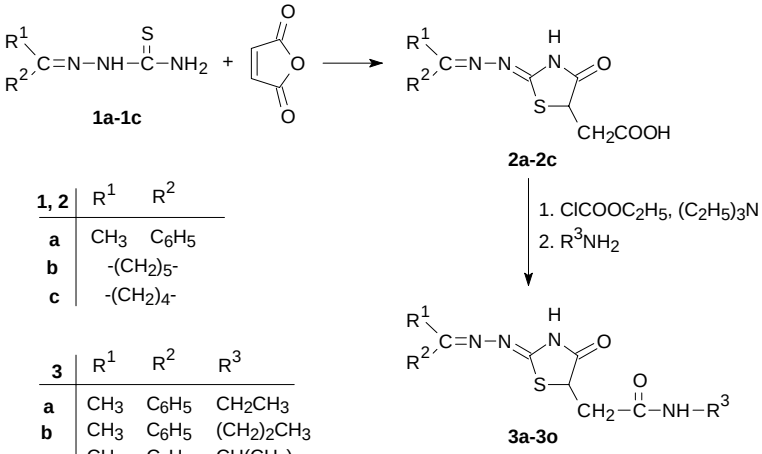
TABLE I
Characteristic data of compounds **2** and **3**

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found			
			% C	% H	% N	% S
2a[a]	246–247 89	$C_{13}H_{13}N_3O_3S$ 291.3	53.61 53.16	4.50 4.56	14.43 14.22	10.98 10.65
2b	181–184 70	$C_{11}H_{15}N_3O_3S$ 269.3	49.06 49.40	5.61 5.68	15.60 15.95	11.91 12.26
2c	210–212 48	$C_{10}H_{13}N_3O_3S$ 255.3	47.05 46.95	5.13 5.05	16.46 16.42	12.56 12.75
3a	204–207 19	$C_{15}H_{18}N_4O_2S$ 318.4	56.58 56.50	5.70 5.70	17.60 17.48	10.07 10.14
3b	163–165 20	$C_{16}H_{20}N_4O_2S$ 332.4	57.81 56.72	6.06 6.16	16.85 17.06	9.65 9.62
3c	227–229 42	$C_{16}H_{20}N_4O_2S$ 332.4	57.81 57.49	6.06 6.08	16.85 16.77	9.65 9.38
3d	168–173 47	$C_{17}H_{22}N_4O_2S$ 363.4	58.94 59.24	6.40 6.63	16.17 16.22	9.26 9.06
3e	194–196 5	$C_{20}H_{20}N_4O_2S$ 380.5	63.14 62.91	5.30 5.40	14.73 14.76	8.43 8.37
3f	183–185 25	$C_{13}H_{20}N_4O_2S$ 296.4	52.68 52.60	6.80 6.77	18.90 18.88	10.82 10.84
3g	164–167 8	$C_{14}H_{22}N_4O_2S$ 310.4	54.17 54.35	7.14 7.13	18.05 18.10	10.33 10.20
3h	210–214 32	$C_{14}H_{22}N_4O_2S$ 310.4	54.17 54.52	7.14 7.15	18.05 17.91	10.33 10.57
3i	165–167 22	$C_{15}H_{24}N_4O_2S$ 324.4	55.53 55.41	7.46 7.37	17.27 17.15	9.88 10.30
3j	170–175 49	$C_{18}H_{22}N_4O_2S$ 358.5	60.31 60.32	6.19 6.08	15.63 16.09	8.94 9.14
3k	188–190 16	$C_{12}H_{18}N_4O_2S$ 282.4	51.04 51.26	6.42 6.51	19.84 19.64	11.36 11.19
3l	209–211 11	$C_{13}H_{20}N_4O_2S$ 296.4	52.68 52.40	6.80 6.80	18.90 18.78	10.82 10.56

TABLE I
(*Continued*)

Compound	M.p., °C Yield, %	Formula M.w.	Calculated/Found			
			% C	% H	% N	% S
3m	234–237	$C_{13}H_{20}N_4O_2S$	52.68	6.80	18.90	10.82
	41	296.4	52.56	6.84	18.91	10.56
3n	164–167	$C_{14}H_{22}N_4O_2S$	54.15	7.17	18.04	10.33
	13	310.5	54.27	7.32	17.94	10.36
3o	194–198	$C_{17}H_{20}N_4O_2S$	59.28	5.85	16.27	9.31
	32	344.4	58.89	5.75	16.17	9.22

[a] Ref.[1] gives m.p. 248–249 °C, yield 80%.



1, 2	R^1	R^2
a	CH_3	C_6H_5
b	-$(CH_2)_5$-	
c	-$(CH_2)_4$-	

3	R^1	R^2	R^3
a	CH_3	C_6H_5	CH_2CH_3
b	CH_3	C_6H_5	$(CH_2)_2CH_3$
c	CH_3	C_6H_5	$CH(CH_3)_2$
d	CH_3	C_6H_5	$(CH_2)_3CH_3$
e	CH_3	C_6H_5	$CH_2C_6H_5$
f	-$(CH_2)_5$-		CH_2CH_3
g	-$(CH_2)_5$-		$(CH_2)_2CH_3$
h	-$(CH_2)_5$-		$CH(CH_3)_2$
i	-$(CH_2)_5$-		$(CH_2)_3CH_3$
j	-$(CH_2)_5$-		$CH_2C_6H_5$
k	-$(CH_2)_4$-		CH_2CH_3
l	-$(CH_2)_4$-		$(CH_2)_2CH_3$
m	-$(CH_2)_4$-		$CH(CH_3)_2$
n	-$(CH_2)_4$-		$(CH_2)_3CH_3$
o	-$(CH_2)_4$-		$CH_2C_6H_5$

SCHEME 1

TABLE II
^{1}H NMR parameters of compounds **2** and **3**

Compound	^{1}H NMR spectrum
2a	2.39 s, 3 H (CH_3); 2.84 d, 2 H, J = 3.4 (CH_2); 4.37 dd, 1 H, J = 9.5, 4.0 (CH); 7.44–7.91 m, 5 H (arom); 12.10 s, 1 H (COOH)
2b	1.59 s, 6 H (3 × CH_2); 2.26 s, 4 H (2 × CH_2); 2.87 d, 2 H, J = 3.4 (CH_2); 4.23 dd, 1 H, J = 9.5, 4.0 (CH); 12.10 s, 1 H (COOH)
2c	1.73 m, 4 H (2 × CH_2); 2.33 m, 4 H (2 × CH_2) 2.92 d, 2 H, J = 3.4 (CH_2); 4.25 dd, 1 H, J = 9.5, 4.0 (CH); 12.03 s, 1 H (COOH)
3a	1.02 t, 3 H, J = 7.3 (CH_3); 2.38 s, 3 H (CH_3); 2.76–3.20 m, 4 H (2 × CH_2); 4.18 dd, 1 H, J = 9.5, 4.0 (CH); 7.40–7.91 m, 6 H (arom, NH); 11.89 s, 1 H (NH)
3b	0.85 t, 3 H, J = 7.2 (CH_3); 1.37 m, 2 H (CH_2); 2.39 s, 3 H (CH_3); 2.70–3.19 m, 4 H (2 × CH_2); 4.32 dd, 1 H, J = 9.5, 4.0 (CH); 7.39–7.91 m, 6 H (arom, NH); 11.92 s, 1 H (NH)
3c	1.05 d, 6 H, J = 6.4 (2 × CH_3); 2.38 s, 3 H (CH_3); 2.85 d, 2 H, J = 4.0 (CH_2); 3.73 m, 1 H (CH); 4.29 dd, 1 H, J = 9.5, 4.0 (CH); 7.39–7.96 m, 6 H (arom, NH); 11.89 s, 1 H (NH)
3d	0.87–1.37 m, 7 H (CH_3, 2 × CH_2); 2.38 s, 3 H (CH_3); 2.66–3.12 m, 4 H (2 × CH_2); 4.30 dd, 1 H, J = 9.5, 4.0 (CH); 7.40–8.10 m, 6 H (arom, NH); 11.73 s, 1 H (NH)
3e	2.38 s, 3 H (CH_3); 2.76–3.00 m, 4 H (2 × CH_2); 4.30 dd, 1 H, J = 9.5, 4.0 (CH); 7.28 s, 5 H (arom); 7.40–7.93 m, 5 H (arom); 8.52 t, 1 H, J = 6.0 (NH); 11.7 s, 1 H (NH)
3f	1.04 t, 3 H, J = 7.3 (CH_3); 1.58 s, 6 H (3 × CH_2); 2.49 s, 4 H (2 × CH_2); 2.55–3.16 m, 4 H (2 × CH_2); 4.19 dd, 1 H, J = 9.5, 4.0 (CH); 8.07 t, 1 H, J = 6.0 (NH); 11.63 s, 1 H (NH)
3g	0.87 t, 3 H, J = 7.2 (CH_3); 1.27–1.45 m, 2 H (CH_2); 1.58 s, 6 H (3 × CH_2); 2.50 s, 4 H (2 × CH_2); 2.70–3.14 m, 4 H (2 × CH_2); 4.21 dd, 1 H, J = 9.5, 4.0 (CH); 7.96 t, 1 H, J = 6.0 (NH); 11.59 s, 1 H (NH)
3h	1.05 d, 6 H, J = 6.4 (2 × CH_3); 1.59 s, 6 H (3 × CH_2); 2.25 s, 4 H (2 × CH_2); 2.79 d, 2 H, J = 4.0 (CH_2); 3.71–3.87 m, 1 H (CH); 4.20 dd, 1 H, J = 9.5, 4.0 (CH); 7.87 d, 1 H, J = 7.3 (NH); 11.52 s, 1 H (NH)
3i	0.34–1.36 m, 7 H (CH_3, 2 × CH_2); 1.59 s, 6 H (3 × CH_2); 2.25 s, 4 H (2 × CH_2); 2.69–3.30 m, 4 H (2 × CH_2); 4.20 dd, 1 H, J = 9.5, 4.0 (CH); 7.95 t, 1 H, J = 6.0 (NH); 11.58 s, 1 H (NH)
3j	1.59 s, 6 H (3 × CH_2); 2.27 s, 4 H (2 × CH_2); 2.92 d, 2 H, J = 4.0 (CH_2); 4.20 dd, 1 H, J = 9.5, 4.0 (CH); 7.28 s, 5 H (arom); 8.61 t, 1 H, J = 6.0 (NH); 11.67 s, 1 H (NH)
3k	1.02 t, 3 H, J = 7.2 (CH_3); 1.71 m, 4 H (2 × CH_2); 2.36 m, 4 H (2 × CH_2); 2.68–3.16 m, 4 H (2 × CH_2); 4.21 dd, 1 H, J = 9.5, 4.0 (CH); 8.10 t, 1 H, J = 6.0 (NH); 11.66 s, 1 H (NH)
3l	0.84 t, 3 H, J = 7.2 (CH_3); 1.41 m, 2 H (2 × CH_2); 2.37 m, 4 H (2 × CH_2); 2.69–3.05 m, 4 H (2 × CH_2); 4.22 dd, 1 H, J = 9.5, 4.0 (CH); 7.96 t, 1 H, J = 6.0 (NH); 11.65 s, 1 H (NH)

TABLE II
(*Continued*)

Compound	^{1}H NMR spectrum
3m	1.05 d, 6 H, J = 6.4 (2 × CH_3); 1.70 m, 4 H (2 × CH_2); 2.36 m, 4 H (2 × CH_2); 2.79 d, 2 H, J = 4.0 (CH_2); 3.82 m, 1 H (CH); 4.21 dd, 1 H, J = 9.5, 4.0 (CH); 7.88 d, 1 H, J = 7.3 (NH); 11.65 s, 1 H (NH)
3n	0.87–1.71 m, 7 H (CH_3, 2 × CH_2); 2.36 m, 4 H (2 × CH_2); 2.53–2.83 m, 4 H (2 × CH_2); 4.22 dd, 1 H, J = 9.5, 4.0 (CH); 7.99 t, 1 H, J = 6.0 (NH); 11.66 s, 1 H (NH)
3o	1.71 m, 4 H (2 × CH_2); 2.48 m, 4 H (2 × CH_2); 2.68–2.93 m, 4 H (2 × CH_2); 4.20 dd, 1 H, J = 9.5, 4.0 (CH); 7.28 s, 5 H (arom); 8.58 t, 1 H, J = 6.0 (NH); 11.62 s, 1 H (NH)

investigated according to the ref.[5]. Thiosemicarbazones **1a–1c** were prepared according to general procedures[7–10] with minor modifications in their purification. Thiosemicarbazone **1a** was recrystallized from aqueous 50% (v/v) methanol. Thiosemicarbazones **1b** and **1c** were recrystallized from aqueous 30% (v/v) ethanol.

2-Hydrazono-4-oxo-5-thiazolidineacetic Acids[1,6] **2**. General Procedure

Maleic anhydride (0.15 mol, 14.7 g) was dissolved in chloroform (500 ml) and then added eqiumolar amount of corresponding thiosemicarbazone **1**. The reaction mixture was stirred under reflux for 4 h and then left overnight at room temperature. Crystalline product was filtered off and crystallized from aqueous 30% (v/v) ethanol. Yields, melting points and elemental analyses of compounds **2** are given in Table I, their ^{1}H NMR spectra in Table II.

2-Hydrazono-4-oxo-5-thiazolidineacetic Acids Alkylamides[11] **3**. General Procedure

To a stirred solution containing 0.01 mol of corresponding acid **2a**–**2c**, triethylamine (1.0 g, 0.01 mol) and anhydrous dichloromethane (60 ml) was added dropwise ethyl chloroformate (1.1 g, 0.01 mol) in dichloromethane (15 ml). The reaction mixture was stirred at 0 °C for 15 min, then corresponding amide (0.01 mol) dissolved in dichloromethane (15 ml) was added and the mixture was stirred for further 20 min at 0 °C. The reaction mixture was left for 4 h at room temperature, then refluxed for 2 h, cooled and washed with water (2 × 50 ml), saturated solution of sodium hydrogen carbonate (2 × 50 ml) and water (2 × 50 ml). The organic phase was dried with anhydrous sodium sulfate, the solvent was evaporated under reduced pressure and the crude product was crystallized from aqueous 30% (v/v) ethanol. The characteristic data for compounds **3** are given in Table I, their ^{1}H NMR spectra in Table II.

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