Studies on Chemotherapeutics III. Synthesis and Cyclisation of 5-Substituted-4-oxo-1,4-dihydro-3-pyridinecarbonyl-semicarbazide and- thiosemicarbazide

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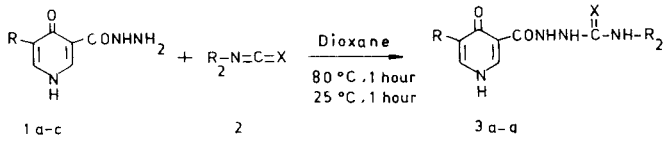
1,4-Disubstituted-semicarbazide and thiosemicarbazide derivatives were synthetized from 5-substituted-4-oxo-1,4-dihydro-3-pyridinecarbohydrazides and cyclized to 3-mercapto-4*H*-1,2,4-triazoles. The obtained compounds could be *S*-methylated with methyl iodide in methanol. The new compounds were tested for antibacterial and antifungal activities.

J. Heterocyclic Chem., **17**, 175 (1980).

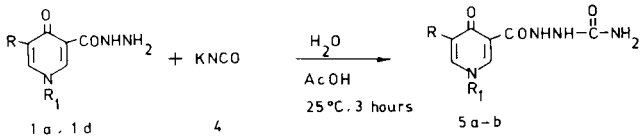
In our earlier papers the synthesis and antimicrobial testing of 1-alkyl-5-substituted-4-oxo-1,4-dihydro-3-pyridinecarboxylic acids (1), further of the corresponding carbohydrazides and their condensation products (2) had been described. In the present paper we report on the synthesis of γ-pyridone derivatives wearing a 1,2,4-triazolyl group in position 3 *via* semicarbazide and thiosemicarbazide derivatives.

4-Oxo-1,4-dihydro-3-pyridinecarbohydrazides (**1a-c**) (2) react with isocyanates and isothiocyanates (**2**) in dioxane under mild conditions to afford 1,4-disubstituted semicarbazide and thiosemicarbazide derivatives (**3a-g**) in 80-90% yields.



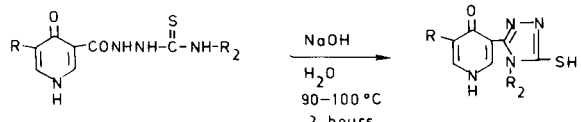
1 a-c 2 3 a-g

The reaction of the carbohydrazides (**1a,1d**) with potassium cyanate (**4**) in aqueous acetic acid at room temperature leads to 1-substituted semicarbazides (**5a-b**) with excellent yields.



1 a, 1 d 4 5 a-b

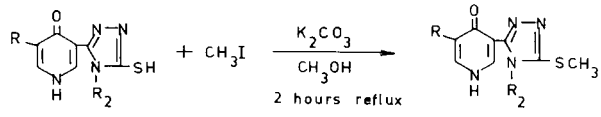
As it is known from the literature, 1-acyl-4-substituted thiosemicarbazides can be cyclized with base-catalysts to give 3-mercapto-4*H*-1,2,4-triazoles (3).



3c, 3f, 3g 6 a-c

The 4-substituted-1-/5-substituted-4-oxo-1,4-dihydro-3-pyridinecarbonyl/-thiosemicarbazides (**3c,3f,3g**) were transformed into compounds **6a-c** by heating with dilute sodium hydroxide solution at 90-95° for 2 hours. In all cases the yield was 80-90%.

The 5-*R*-3-(4-R_2-3-mercapto-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridines (**6a-c**) could be *S*-methylated with methyl iodide in methanol, in the presence of anhydrous potassium carbonate.



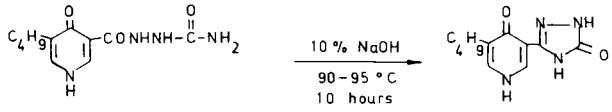
6a-c 7 a-c

The *S*-methylation is confirmed by the singlet at δ = 2.66 ppm in the nmr spectra of compounds **7a-c**.

The tautomerism of compounds **6a-c** can be studied by spectroscopic methods. In solid state compounds **6a** and **6b** exist predominantly in the thioxo form as it is shown by the ν C=S band at 1250 cm^{-1} in the ir spectra of these compounds. As for 5-heptyl-3-(3-mercapto-4-methyl-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridine (**6c**) the thiol form is present even in solid state (ν SH = 2605 cm^{-1}).

In 96% ethanolic solutions all the three compounds (**6a-c**) can be characterized by the thiol form, their uv spectra resemble to those of the S-methyl derivatives (**7a-c**).

1-(5-Butyl-4-oxo-1,4-dihydro-3-pyridinecarbonyl)-semicarbazide (**5a**) was cyclized by heating with a 10% sodium hydroxide solution for 10 hours to 5-butyl-4-oxo-3-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-1,4-dihydropyridine (**8**) with 85.5% yield.

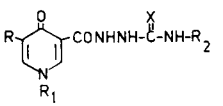


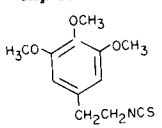
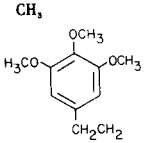
5 a 8

0022-152X/80/010175-05$02.25

Table 1

1,4-Disubstituted-Semicarbazide and Thiosemicarbazide Derivatives and their Uv and Ir Data

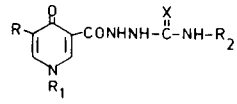


Starting Material	RNCO or RNCS	Product	R	R_1	X	R_2	Yield %	M.p. °C	Appearance, Solvent of Recrystallization	Formula M.W.	Analysis Calcd./Found % C	H	N	S	λ max nm log ε		Ir (Potassium bromide) cm^{-1} ν C=O amide	ν C=O ring	ν C=O NHCONH	ν C=S
1a	C_6H_5NCO	**3a**	C_4H_9	H	O	C_6H_5	95.9	236-237	white	$C_{17}H_{20}N_4O_3$	62.18	6.14	17.07		284	241	1700 i	1635	1660 i	
									DMF	328.373	62.11	6.13	17.05		3.88	4.29				
1a	C_4H_9NCO	**3b**	C_4H_9	H	O	C_4H_9	89.2	218	white	$C_{15}H_{24}N_4O_3$	58.42	7.84	18.17		286	254	1700		1640	
									Ethanol	308.383	58.57	7.47	18.00		3.78	3.91				
1a	C_6H_5NCS	**3c**	C_4H_9	H	S	C_6H_5	91.5	226-227 dec.	white	$C_{17}H_{20}N_4O_2S$	59.28	5.85	16.27	9.31		258	1695	1635		1280
									Ethanol	344.437	59.14	5.76	16.36	9.31		4.26				
1a	CH_3NCS	**3d**	C_4H_9	H	S	CH_3	95.7	190-191	white	$C_{12}H_{16}N_4O_2S$	51.05	6.43	19.84	11.35	287	245	1680	1650		1280
									Ethanol	282.366	51.03	6.33	19.99	11.31	3.85	4.20				
1a		**3e**	C_4H_9	H	S		76.5	195-196	white	$C_{21}H_{28}N_4O_4S$	58.31	6.52	12.95	7.41	281	250	1680	1645		1270
									Ethanol	432.546	58.25	6.82	12.87	7.53	3.97	4.25				
1b	C_6H_5NCS	**3f**	C_6H_{13}	H	S	C_6H_5	80.6	222-224 dec.	white	$C_{19}H_{24}N_4O_2S$	61.27	6.49	15.04	8.61		257	1670	1650 i		1270
									Methanol	372.492	61.05	6.71	15.07	8.62		4.07				
1c	CH_3NCS	**3g**	C_7H_{15}	H	S	CH_3	96.0	193 dec.	pale yellow	$C_{15}H_{24}N_4O_2S$	55.53	7.46	17.27	9.88	288	245	1680	1650		1280
									Ethanol	324.447	55.16	7.51	17.23	9.74	3.85	4.24				
1a	KNCO	**5a**	C_4H_9	H	O	H	78.2	230-231	white	$C_{11}H_{16}N_4O_3$	52.37	6.39	22.21		287	254	1680	1650 i	1670	
									Water	252.275	52.17	6.56	21.96		3.79	3.93				
1d	KNCO	**5b**	H_2NCONH-NHCO	CH_2=CH-CH_2	O	H	97.9	283 dec.	white	$C_{12}H_{15}N_7O_3$	42.73	4.48	29.07			(a)	1700		1650	
											42.64	4.54	29.17							

i = inflexion. (a) **5b** insoluble in Ethanol.

Table 2

Nmr Data for 1,4- Disubstituted Semicarbazide and Thiosemicarbazide Derivatives



Compound No.	Solvent	C_2-H	C_6-H	C_5-$(CH_2)_3$-CH_3	C_5-CH_2-$(CH_2)_2$-CH_3		δ ppm
3a	Trifluoroacetic acid	9.21 s	8.43 s	0.80-1.25 m	1.25-2.10 m	C_5-CH_2-$(CH_2)_2$-CH_3	2.65-3.20 m
						-NH-C_6H_5	7.41 s
3b	Trifluoroacetic acid	9.28 s	8.51 s	0.80-1.17 m	1.20-2.00 m	-NH-$(CH_2)_3$-CH_3	0.80-1.17 m
						-NH-CH_2-$(CH_2)_2$-CH_3	1.20-2.00 m
						C_5-CH_2-$(CH_2)_2$-CH_3	2.60-3.10 m
						-NH-CH_2-$(CH_2)_2$-CH_3	3.20-3.65 m
3c	DMSO-d_6	8.59 d J = 2 Hz	7.20-7.90 m	0.80-1.20 m	1.20-1.90 m	C_5-CH_2-$(CH_2)_2$-CH_3	2.30-2.80 m
						CSN*H*C_6H_5	3.20-3.70 bs
						CSNHC$_6$*H*$_5$	7.20-7.90 m
						CONHN*H*CS	10.08 s
						CON*H*NHCS	12.85 s
3d	Trifluoroacetic acid	9.30 s	8.50 s	0.75-1.15 m	1.25-2.00 m	C_5-CH_2-$(CH_2)_2$-CH_3	2.88 t J = 7 Hz
						-NH-CH_3	3.30 s
3e	DMSO-d_6	8.53 bs	7.84 bs	0.75-1.10 m	1.20-1.80 m	C_5-CH_2-$(CH_2)_2$-CH_3	} 2.30-3.10 m
						-NH-CH_2-CH_2	
						3,4-$(CH_3O)_2$-C_6H_3	3.77 s
							3.80 s
						3,4-$(CH_3O)_2$-C_6H_3	6.89 s
						CSN*H*-CH_2-CH_2-	8.05 bs
						CONH*NH*CS	9.68 bs
						CO*NH*NHCS	12.22 bs
3f	Trifluoroacetic acid	9.32 s	8.48 s			C_5-$(CH_2)_5$-CH_3	0.70-1.10 m
						C_5-CH_2-$(CH_2)_4$-CH_3	1.20-2.10 m
						C_5-CH_2-$(CH_2)_4$-CH_3	2.70-3.30 m
						-NH-C_6H_5	7.30-7.80 m
3g	DMSO-d_6	8.48 bs	7.80 bs			C_5-$(CH_2)_6$-CH_3	0.70-1.05 m
						C_5-CH_2-$(CH_2)_5$-CH_3	1.10-2.70 m
						C_5-CH_2-$(CH_2)_5$-CH_3	2.33-2.60 m
						-NH-CH_3	2.92 d J = 5 Hz
						CSN*H*CH_3	7.99 d J = 5 Hz
						CONHN*H*CS	9.45 bs
						CON*H*NHCS	12.35 s
5a	Trifluoroacetic acid	9.30 bs	8.52 bs			C_5-$(CH_2)_3$-CH_3	0.80-1.16 m
						C_5-CH_2-$(CH_2)_2$-CH_3	1.25-2.00 m
						C_5-CH_2-$(CH_2)_2$-CH_3	2.91 t J = 7 Hz
5b	Trifluoroacetic acid	9.01 s (a)				N-CH_2-CH=CH_2	4.75-5.05 m
						N-CH_2-CH=CH_2	5.30-5.80 m
						N-CH_2-CH=CH_2	5.80-6.45 m

s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet. (a) C_2-H and C_6-H appears at the same chemical shift.

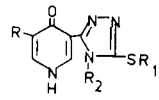
The obtained new compounds (**3a-g, 5a-b, 6a-c, 7a-c, 8**) were tested for antibacterial and antifungal activities. Only compounds **5a** and **8** exhibited a weak activity against microspores, while the rest of the compounds showed no significant activity.

EXPERIMENTAL

All melting points are uncorrected. The uv spectra were taken in ethanol with a Unicam SP 800 spectrophotometer, the ir spectra were recorded on a Zeiss UR 20 spectrophotometer, nmr spectra were measured with a Perkin-Elmer R-12 spectrometer using tetramethyl silane as an internal standard.

Table 3

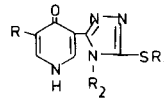
5-*R*-3-(4-R_2-3-SR_1-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridines and their Uv and Ir Data



Starting Material	Product	R	R_1	R_2	Yield %	M.p. °C	Appearance, Solvent of Recrystallization	Formula M.W.	Analysis Calcd./Found % C	H	N	S	λ max nm log ε	Ir (Potassium bromide) cm^{-1} ν C=O ring	ν C=S	ν SH
3c	**6a**	C_4H_9	H	C_6H_5	89.9	315	white	$C_{17}H_{18}N_4OS$	62.55	5.56	17.16	9.82	261	1650	1250	
							DMF	326.422	62.36	5.79	17.25	10.04	4.23			
3f	**6b**	C_6H_{13}	H	C_6H_5	90.5	315 dec.	white	$C_{19}H_{22}N_4OS$	64.38	6.26	15.81	9.04	260	1650	1250	
							Methanol	354.477	63.96	6.01	15.75	8.96	4.23			
3g	**6c**	C_7H_{15}	H	CH_3	82.8	264	white	$C_{15}H_{22}N_4OS$	58.80	7.24	18.28	10.46	254	1660		2605
							Methanol	306.432	59.02	7.35	18.33	10.59	3.31			
6a	**7a**	C_4H_9	CH_3	C_6H_5	70.3	114-115	white	$C_{18}H_{20}N_4OS \cdot H_2O$	60.31	6.19	15.63	8.94	260	1660		
							Ethanol-water	358.465	60.28	6.25	15.48	8.85	4.00			
6b	**7b**	C_6H_{13}	CH_3	C_6H_5	79.7	164	white	$C_{20}H_{24}N_4OS$	65.19	6.56	15.20	8.70	260	1655		
							Benzene-ethyl acetate	368.504	65.42	6.80	15.22	8.58	4.02			
6c	**7c**	C_7H_{15}	CH_3	CH_3	50.1	125	white	$C_{16}H_{24}N_4OS$	59.97	7.55	17.48	10.01	264	1660		
							Ethyl acetate	320.459	59.70	7.75	17.09	9.82	3.99			

Table 4

Nmr Data for 5-*R*-3-(4-R_2-3-SR_1-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridines



Compound No.	Solvent	C_2-H	C_6-H	N-C_6H_5	N-CH_3	S-CH_3	δ ppm	
6a	Trifluoroacetic acid	8.40 bs	7.40-8.00 (a) m		—	—	C_5-$(CH_2)_3$-CH_3	0.80-1.20 m
							C_5-CH_2-$(CH_2)_2$-CH_3	1.20-2.00 m
							C_5-CH_2-$(CH_2)_2$-CH_3	2.92 t J = 7 Hz
7a	Deuteriochloroform	7.78 s	7.25-7.65 (a) m		—	2.66 s	C_5-$(CH_2)_3$-CH_3	0.70-1.05 m
							C_5-CH_2-$(CH_2)_2$-CH_3	1.15-1.60 m
							C_5-CH_2-$(CH_2)_2$-CH_3	2.30-2.70 m
6b	DMSO-d_6	8.05 s	7.61 s	7.46 s	—	—	C_5-$(CH_2)_5$-CH_3	0.75-1.05 m
							C_5-CH_2-$(CH_2)_4$-CH_3	1.05-1.45 m
							C_5-CH_2-$(CH_2)_4$-CH_3	2.00-2.40 m
7b	Deuteriochloroform	7.81 s	7.25-7.70 (a) m		—	2.66 s	C_5-$(CH_2)_5$-CH_3	0.70-1.04 m
							C_5-CH_2-$(CH_2)_4$-CH_3	1.10-1.65 m
							C_5-CH_2-$(CH_2)_4$-CH_3	2.15-2.65 m
							ring-N*H*	10.95 bs
6c	DMSO-d_6	8.10 d J = 2.7 Hz	7.82 s	—	3.40 s	—	C_5-$(CH_2)_6$-CH_3	0.75-1.10 m
							C_5-CH_2-$(CH_2)_5$-CH_3	1.15-1.75 m
							C_5-CH_2-$(CH_2)_5$-CH_3	2.48 t J = 7.5 Hz
7c	Deuteriochloroform	7.93 s	7.59 s	—	3.57 s	2.64 s	C_5-$(CH_2)_6$-CH_3	0.65-1.05 m
							C_5-CH_2-$(CH_2)_5$-CH_3	1.10-1.80 m
							C_5-CH_2-$(CH_2)_5$-CH_3	2.30-2.80 m
							ring-N*H*	8.82 s

(a) The C_6-H and N-C_6H_5 protons appear together.

General Procedure for the Synthesis of 1-(5-Alkyl-4-oxo-1,4-dihydro-3-pyridinecarbonyl)-4-substituted-semicarbazides and Thiosemicarbazides (**3a-g**).

To a suspension of the 5-alkyl-4-oxo-1,4-dihydro-3-pyridinecarbohydrazide (**1a-c**) (2) (0.01 mole in dioxane (50 ml.)) the appropriate isocyanate or isothiocyanate (0.01 mole) was added at 80°. The reaction mixture was stirred at 80° for one hour (after a few minutes crystals began to separate) and then at 25° for one hour. After a few hours the separated crystals were filtered off, and washed with dioxane and ethanol. For the yields, m.p., solvents used for recrystallization and analytical data of compounds **3a-g** see Table 1, and for their spectroscopic characteristics Tables 1 and 2.

General Procedure for the Synthesis of 1-(5-Butyl-4-oxo-1,4-dihydro-3-pyridinecarbonyl)-semicarbazide (**5a**) and 1,1'-(1-Allyl-4-oxo-1,4-dihydro-3,5-pyridinedicarbonyl)-disemicarbazide (**5b**).

A solution of potassium cyanate (0.022 mole) in water (10 ml.) was added dropwise, within 15 minutes, under stirring, at 0° to a solution of the carbohydrazide (**1a,1d**) (0.02 mole) in a mixture of acetic acid (40 ml.) and water (40 ml.). After about 10 minutes white crystals began to separate from the solution. The reaction mixture was stirred at 20-25° for 3 hours, chilled and the precipitate was filtered off, and washed with water and ethanol.

For the physical data and analytical results of the semicarbazides **5a** and **5b** see Table 1, for their spectroscopic data Tables 1 and 2.

Cyclization of the Thiosemicarbazide Derivatives in Alkaline Medium. Preparation of 5-Alkyl-3-(4-substituted-3-mercapto-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridines (**6a-c**).

A solution of 1-(5-alkyl-4-oxo-1,4-dihydro-3-pyridinecarbonyl)-4-substituted thiosemicarbazide (**3c,3f,3g**) (0.01 mole) and sodium hydroxide (0.012 mole) in water (50 ml.) was stirred at 90-95° for two hours, then the light yellow solution was filtered and acidified with 1:1 hydrochloric acid to *p*H = 4-5. After chilling the separated white crystalline material was filtered and washed with water.

For the physical data of the obtained compounds (**6a-c**) see Table 3, for their spectroscopic data Tables 3 and 4.

Preparation of 5-Alkyl-3-(4-substituted-3-methylmercapto-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridines (**7a-c**).

A mixture of 5-alkyl-3-(4-substituted-3-mercapto-4*H*-1,2,4-triazol-5-yl)-4-oxo-1,4-dihydropyridine (**6a-c**) (0.01 mole), methyl iodide (0.011 mole), anhydrous potassium carbonate (0.011 mole) and methanol (100 ml.) was stirred on a steam bath for two hours. The solution was filtered and evaporated to dryness under vacuum. The residue was dissolved in water (100 ml.), and extracted with three 50 ml. portions of methylene chloride. The organic extracts were dried over sodium sulfate, and evaporated. The viscous, resinous, colourless residue was crystallized from the solvent given in Table 3. For the yields, m.p. and analytical data of the *S*-methyl derivatives (**7a-c**) see Table 4.

The results of the uv, ir and nmr studies are summarized in Tables 5 and 6.

Preparation of 5-Butyl-4-oxo-3-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-1,4-dihydropyridine (**8**).

A mixture of 1-(5-butyl-4-oxo-1,4-dihydro-3-pyridinecarbonyl)-semicarbazide (**5a**) (0.01 mole) and 10% sodium hydroxide solution (40 ml.) was stirred at 90-95° for 10 hours. The yellow solution was filtered and acidified with 1:1 hydrochloric acid under cooling to *p*H = 3. After dilution with water (60 ml.) the mixture was allowed to stand at 4° overnight, then the separated yellow crystals were filtered off and washed with water. In this manner 2.0 g. (yield, 85.5%) of the cyclized product (**8**) melting above 300° was obtained, and recrystallized from dimethyl formamide; uv (96% ethanol): λ max (log ε) 303 (3.89) 231 (4.02); ir (potassium bromide): ν C=O (ring) 1750, 1655 cm^{-1}; nmr (trifluoroacetic acid): 9.13 (C_2-H, bs), 8.54 (C_6-H, bs), 0.75-1.20 (C_5-$(CH_2)_3$-CH_3, m), 1.25-2.05 (C_5-CH_2-$(CH_2)_2$-CH_3, m), 2.95 (C_5-$CH_2(CH_2)_2$-CH_3, t, J = 7.5 Hz).

Anal. Calcd. for $C_{11}H_{14}N_4O_2$ (234.259): C, 56.40; H, 6.02; N, 23.92. Found: C, 56.25; H, 5.98; N, 23.73.

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