

SYNTHESIS OF SOME 1,2,4-TRIAZOLO[4,3-*c*]QUINAZOLINES BASED ON 4-QUINAZOLYLTHIOSEMICARBAZIDES

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The paper describes the cyclization reactions of substituted 1-(4'-quinazolyl)-4-phenylthiosemicarbazides (*Ia – Ie*). The thermal intramolecular cyclization gives 2*H*-1,2,4-triazolo[4,3-*c*]quinazoline-3-thiones (*Ila – Ild*). Heating of *I* with HgO gives 3-anilino-1,2,4-triazolo[4,3-*c*]quinazolines (*Illa – Illle*). The IR and ¹H NMR spectra of the compounds synthesized are presented.

Derivatives of triazole and quinazoline exhibit a number of interesting biological effects^{1,2}. With the aim of combining these properties, we described^{3 – 5} syntheses of series of 1,2,4-triazolo[4,3-*c*]quinazolines substituted in both the pyrimidine and benzene nuclei.

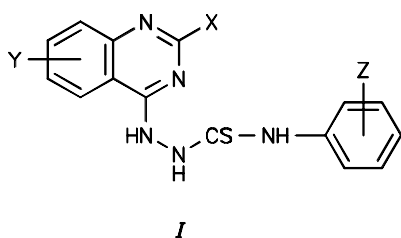
In order to extend the spectrum of these compounds, the present communication describes syntheses of some 1,2,4-triazolo[4,3-*c*]quinazoline-3-thiones *II* and 3-anilino derivatives *III*.

The syntheses of both types of compounds started from the chosen 1-(4'-quinazolyl)-4-phenylthiosemicarbazides *Ia – Ie* obtained by the reaction of the corresponding 4-hydrazinoquinazolines with phenyl isothiocyanate. Similar thiosemicarbazides with a methyl or aryl group in 2-position are described in ref.⁶ where also their antituberculo-static properties are mentioned.

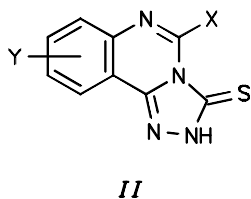
The final thiones *Ila – Ille* were obtained by the method described by Marckwald⁷ for quinoline derivatives. The heating of thiosemicarbazides at their melting points without solvent results in the condensation with simultaneous splitting off of aniline. Two similar compounds, viz. 5-phenyl- and 5-(4-pyridyl)-1,2,4-triazolo[4,3-*c*]quinazoline-3-thiones were described in the above-mentioned communication⁶ and their structure was confirmed by independent synthesis – the reaction of corresponding 4-hydrazinoquinazolines with carbon disulfide. The heating of the thiosemicarbazides *Ia – Ie* with the yellow mercury(II) oxide gave products identified as the corresponding 2*H*-3-anilino-1,2,4-triazolo[4,3-*c*]quinazolines *Illa – Illle*. Their formation can be described in the following way: in actual fact, the dehydrosulfurization takes place with the imidoylthiourea – one of the tautomeric forms of thiosemicarbazide *I*.

The treatment with HgO gives the corresponding imidoylcarbodiimide with exocyclic C=N bond. Such compounds are little stable and easily cyclize, giving (in a 6π -electrocyclic reaction) the above-mentioned triazole skeleton condensed to quinazoline. Similar cyclizations were described also for other imidoylheterocumulenes^{8,9}.

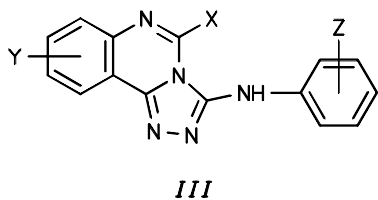
The IR spectra of these compounds show skeletal vibrations as well as the absorption bands at $3\ 300\text{ cm}^{-1}$ characteristic of secondary amines. The corresponding characteristic peak appears in $^1\text{H NMR}$ at 8.9 ppm. Interesting is the position of the H-10 proton at 8.2 ppm (i.e. outside the aromatic multiplet at 6.6 – 7.7). A similar phenomenon is observed also with other quinazoline derivatives having an extended conjugated system, e.g. with compounds *Ia* – *Ie*.



I	X	Y	Z
a	piperidyl	6-Cl	H
b	morpholinyl	6-Cl	H
c	4-phenylpiperazinyl	6-Cl	H
d	phenyl	8-CH ₃	H
e	phenyl	8-CH ₃	4-NO ₂



II	X	Y
a	piperidyl	9-Cl
b	morpholinyl	9-Cl
c	4-phenylpiperazinyl	9-Cl
d	phenyl	7-CH ₃



III	X	Y	Z
a	piperidyl	9-Cl	H
b	morpholinyl	9-Cl	H
c	4-phenylpiperazinyl	9-Cl	H
d	phenyl	7-CH ₃	H
e	phenyl	7-CH ₃	4-NO ₂

TABLE I
Characteristic data of synthesized compounds I – III

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
<i>Ia</i>	C ₂₀ H ₂₁ ClN ₆ S (412.9)	228 – 229	58.17	5.12	20.35	7.76
		85	57.92	5.08	20.19	7.90
<i>Ib</i>	C ₁₉ H ₁₉ ClN ₆ OS (414.9)	219 – 221	55.00	4.61	20.25	7.72
		84	54.78	4.53	20.17	7.84
<i>Ic</i>	C ₂₅ H ₂₄ ClN ₇ S (490.1)	223 – 225	61.27	4.93	20.00	6.54
		92	61.03	4.79	19.87	6.39
<i>Id</i>	C ₂₂ H ₁₉ N ₅ S (385.5)	212 – 215	68.54	4.97	18.16	8.31
		87	68.27	4.91	18.03	8.23
<i>Ie</i>	C ₂₂ H ₁₈ N ₆ O ₂ S (430.5)	207 – 209	61.38	4.21	19.52	7.45
		89	61.19	4.07	19.37	7.33
<i>IIa</i>	C ₁₄ H ₁₄ ClN ₅ S (319.8)	124 – 126	52.58	4.41	21.89	10.02
		69	52.40	4.35	21.72	9.86
<i>IIb</i>	C ₁₃ H ₁₂ ClN ₅ OS (321.9)	130 – 133	48.51	3.76	21.75	9.96
		98	48.33	3.63	21.63	9.83
<i>IIc</i>	C ₁₉ H ₁₇ ClN ₆ S (396.9)	147 – 149	57.50	4.32	21.17	8.08
		64	57.38	4.28	21.03	7.91
<i>IIId</i>	C ₁₆ H ₁₂ N ₄ S (292.4)	223 – 226	65.73	4.14	19.16	10.96
		79	65.61	4.01	19.02	10.82
<i>IIIa</i>	C ₂₀ H ₁₉ ClN ₆ (378.9)	252 – 253	63.40	5.05	22.18	–
		65	63.27	4.89	22.00	–
<i>IIIb</i>	C ₁₉ H ₁₇ ClN ₆ O (380.9)	248 – 250	59.92	4.50	22.06	–
		44	59.78	4.44	21.83	–
<i>IIIc</i>	C ₂₅ H ₂₂ ClN ₇ (455.8)	253 – 255	65.88	4.83	21.51	–
		64	65.69	4.72	21.39	–
<i>IIId</i>	C ₂₂ H ₁₇ N ₅ (351.4)	234 – 236	75.19	4.88	19.92	–
		44	74.98	4.77	19.78	–
<i>IIIe</i>	C ₂₂ H ₁₆ N ₆ O ₂ (396.4)	287 – 290	66.66	4.06	21.20	–
		51	66.42	4.01	20.98	–

TABLE II
Spectral properties of synthesized compounds *I – III*

Compound	IR spectra, cm^{-1}			^1H NMR, δ ppm			
	$\nu(\text{NH})$	$\nu(\text{C}=\text{N})$	$\nu(\text{C}-\text{N})$	NH	H-5, resp. H-10	H-Ar	H-Het
<i>Ia</i>	3 338 3 280 3 210	1 615	1 380	10.13 bs 9.86 s 9.66 s	8.28 d	7.00 – 7.57 m	3.62 m 1.57 m
<i>Ib</i>	3 350 3 295 3 190	1 620	1 370	10.22 bs 9.87 s 9.67 s	8.29 d	7.00 – 7.56 m	3.65 m
<i>Ic</i>	3 331 3 294 3 111	1 616	1 388	10.20 bs 9.87 s 9.70 s	8.29 d	7.00 – 7.58 m	3.81 m 3.24 m
<i>Id</i>	3 360 3 350 3 320	1 620	1 385	10.27 bs 9.87 s 9.70 s	–	6.90 – 8.70 m	2.65 s^c
<i>Ie</i>	3 336 3 296 3 272	1 620	1 388 1 510 ^a 1 310 ^b	10.62 bs 10.20 bs	–	7.20 – 8.60 m	2.65 s^c
<i>IIa</i>	–	1 628	1 384	10.50 bs	–	6.90 – 8.40 m	1.54 m 3.50 m
<i>IIb</i>	–	1 635	1 380	10.00 bs	–	6.44 – 8.30 m	3.71 m 3.78 m
<i>IIc</i>	–	1 628	1 381	9.91 bs	–	6.20 – 8.10 m	3.40 m 3.85 m
<i>IId</i>	–	1 630	1 361	10.01 bs	–	7.20 – 8.60 m	2.60 s^c
<i>IIIa</i>	3 304	1 620	1 350	8.86 bs	8.15 m	6.65 – 7.76 m	3.70 m 1.58 m
<i>IIIb</i>	3 315	1 612	1 365	8.88 bs	8.16 m	6.70 – 7.76 m	3.68 m
<i>IIIc</i>	3 280	1 624	1 360	8.88 bs	8.18 m	6.60 – 7.70 m	3.85 m 3.34 m
<i>IIId</i>	3 416	1 616	1 388	8.89 bs	8.25 m	6.50 – 7.75 m	2.58 s^c
<i>IIIe</i>	3 364	1 620	1 384 1 570 ^a 1 345 ^b	9.04 bs	8.31 m	7.10 – 7.75 m	2.59 s^c

^a $\nu(\text{as}) \text{NO}_2$; ^b $\nu(\text{s}) \text{NO}_2$; ^c (CH_3) .

EXPERIMENTAL

The IR absorption spectra of synthesized compounds were measured with a Specord M 80 apparatus (Zeiss, Jena) using the KBr technique. The ^1H NMR spectra were measured with a BS 587 A Tesla spectrometer at the working frequency of 80 MHz using hexadeuteriodimethyl sulfoxide as solvent and tetramethylsilane as internal reference.

The syntheses of starting 4-hydrazinoquinazolines are described elsewhere³⁻⁵.

Substituted 1-(4'-Quinazolyl)-4-phenylthiosemicarbazides *Ia - Ie*

The respective substituted 4-hydrazinoquinazoline (0.01 mol) was suspended in 100 ml ethanol at boiling temperature, and a solution of 1.4 g (0.01 mol) phenyl isothiocyanate in 20 ml ethanol was added through the condenser. After 1 h refluxing, the solution was cooled, and the precipitated crystalline solid was collected by filtration and recrystallized from ethanol. Characterization of compounds is given in Tables I and II.

Substituted 2*H*-1,2,4-Triazolo[4,3-*c*]quinazoline-3-thiones *Ila - Ild*

The respective substituted 1-(4'-quinazolyl)-4-phenylthiosemicarbazide (0.01 mol) was heated at its melting temperature without solvent on an oil bath. The obtained melt was dissolved in dioxane, boiled with charcoal, filtered, and left to stand. The precipitated crystalline solid was purified by recrystallization from hexane. Characterization of compounds is given in Tables I and II.

Substituted 3-Anilino-1,2,4-triazolo[4,3-*c*]quinazolines *IIla - IIle*

A mixture of the respective substituted 1-(4'-quinazolyl)-4-phenylthiosemicarbazide (0.01 mol), 4.4 g yellow HgO, and 20 ml dry dichloroethane was stirred at boiling temperature 1 h, whereafter another portion of 2.2 g HgO was added and the stirring was continued for another 5 h. The colloidal HgS precipitated on cooling was separated by filtration, the filtrate was boiled with charcoal, filtered, and evaporated in vacuum until dry. The evaporation residue was recrystallized from ethyl acetate. Characterization of compounds is given in Tables I and II.

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