SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF S-SUBSTITUTED 2-THIOQUINAZOLIN-4(3H)-ONES

A. N. Krasovskii,[1] A. K. Bulgakov,[1] L. Yu. Chumakova,[1] I. A. Krasovskii,[1] A. M. Dyachenko,[2] A. A. Bokun,[3] N. A. Kravchenko,[1] and A. M. Demchenko[1]

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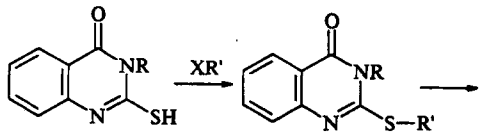
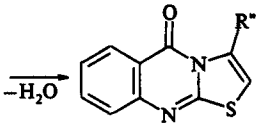
It was repeatedly reported that quinazolin-4(3H)-one derivatives exhibit antimicrobial, antimycotic, antimalarial, antituberculous, and antihypertensive effects, as well as anticonvulsant and sedative (calming) action [1 – 5].

In order to obtain new potential antibacterial and tuberculostatic agents, we have studied the interaction of 2-thio-3-R-quinazolin-4(3H)-ones (Ia – Ic) with 2,4-dinitrochlorobenzene and aromatic α-halogenoketones and characterized the corresponding S-substituted derivatives (IIa – IIh).

These reactions proceeded when equimolar amounts of the initial reagents were boiled for 4 h in 2-propanol or kept at 18 – 20°C in the presence of an alkaline agent (KOH) [6]. Subsequent treatment of 4(3H)-quinazolinones IIc and IIh with concentrated H_2SO_4 led to compounds IIIc and IIIh.



Ia – Ic IIa – IIh



IIIc, IIIh

I: R = H (a), R = allyl (b), R = C_6H_5 (c);
II: R = allyl, R′ = 2,4-$(O_2N)_2$-C_6H_3; (a), R = H, R′ = 4-$BrC_6H_4COCH_2$ (b); R = H, R′ = 4-$CH_4OC_6H_4COCH_2$ (c); R = allyl, R′ = $C_6H_5COCH_2$ (d); R = allyl, R′ = 4-$ClC_6H_4COCH_2$ (e); R = allyl, R′ = 4′-$CH_3C_6H_4COCH_2$ (f); R = C_6H_5, R′ = 4-$BrC_6H_4COCH_2$ (g);
R = H, R′ = $C_6H_5COCH_2$ (h);
III: R″ = 4-$CH_3C_6H_4$ (c), R″ = C_6H_5 (h).

Purity of the synthesized compounds was checked and the proposed structures were confirmed by elemental analyses and ^1H NMR spectroscopic measurements (Table 1).

EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were recorded on a Bruker-300 (300 MHz) spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard.

2-Thioquinazolin-4(3H)-one (Ia) and 2-thio-3-phenylquinazolin-4(3H)-one (Ic) were synthesized as described in [2]; 2-phenacylthioquinazolin-4(3H)-one (IIh) and 3-phenyl-5-oxo-5H-thiazolo[2,3-b]quinazoline (IIIh) were obtained according to [5]; 2-thio-3-allylquinazolin-4(3H)-one (Ib), 2-(*p*-methoxyphenacylthio)quinazolin-4(3H)-one (IIc) and 3-(*p*-methoxyphenyl)-5-oxo-5H-thiazolo[2, 3-b]quinazoline (IIIc) were synthesized as described in [6].

2-(2′,4′-Dinitrophenylthio)-3-allylquinazolin-4(3H)-one hydrochloride (IIa). To a solution of 2.18 g (0.01 mole) of compound Ib in 15 ml of ethanol was added 2.02 g (0.01 mole) of 2,4-dinitrochlorobenzene. The mixture was boiled for 2 h and cooled. The precipitate of compound IIa was filtered.

2-(Phenacylthio)-3-R-quinazolin-4(3H)-ones (IIb – IIh).

Method A. To a solution of 0.01 mole of compound Ia or Ib in 15 ml of ethanol 0,5 g KOH was added 0.01 mole of the corresponding α-bromoketone. The mixture was kept for 24 h and the precipitate was filtered (compounds IIb – IId, IIh).

Method B. To a solution of 0.01 mole of compound Ib or Ic in 15 ml of 2-propanol was added 0.01 mole of the corresponding α-bromoketone and the mixture was boiled for 4 h. Upon cooling, the precipitate was filtered (compounds IIe – IIg).

[1] Technological Institute, Chernigov, Ukraine.
[2] Bashkir State Medical University, Ufa, Bashkortostan, Russian Federation.
[3] Institute of Agricultural Microbiology, Ukrainian Academy of Agricultural Sciences, Chernigov, Ukraine.

TABLE 1. Yields and Physicochemical Characteristics of Compounds IIa – IIh

Compound	Yield, %	M.p., °C	Empirical formula	Proton chemical shift, δ, ppm		
				S-CH_2 (s)	R	H_{arom} (m)
IIa	95	186 – 187	$C_{17}H_{12}N_4O_5S \cdot HCl$	...	4.7 (d, 2H, CH_2); 5.2 (q, 2H, CH_2); 6.1 (m, 1H, CH)	7.19 – 8.01
IIb	78	197 – 198	$C_{16}H_{11}BrN_2O_2S$	4.84	12.3 (s, 1H, NH)	7.14 – 8.05
IIc*	90	194 – 195	$C_{17}H_{14}N_2O_3S$	4.82	12.7 (s, IH, NH)	7.11 – 8.09
IId	73	115 – 116	$C_{19}H_{16}N_2O_2S$	4.84	4.5 (d, 2H, CH_2); 5.13 (q, 2H, CH_2); 5.83 (m, 1H, CH)	7.2 – 8.02
IIe	55	132 – 133	$C_{19}H_{15}ClN_2O_2S \cdot HBr$	4.85	4.77 (d, 2H, CH_2); 5.2 (q, 2H, CH_2); 5.96 (m, 1H, CH)	6.98 – 8.18
IIf**	65	135 – 136	$C_{20}H_{18}N_2O_2S \cdot HBr$	4.83	4.72 (d, 2H, CH_2); 5.16 (q, 2H, CH_2); 5.91 (m, 1H, CH)	6.87 – 8.08
IIg	94	201 – 202	$C_{22}H_{15}BrN_2O_2S \cdot HBr$	4.7	7.48...7.67 (m, 5H, C_6H_5)	7.05 – 8.11
IIh	52	196 – 197	$C_{16}H_{12}N_2O_2S$	4.81	12.5 (s, 1H, NH)	7.15 – 8.01

* Signal of OCH_3 protons, 3.88 ppm (s).
** Signal of CH_3 protons, 2.45 ppm (s).

Compounds IIa – IIh, IIIc, and IIIh appear as crystalline colorless (IIb – IIh, IIIc, IIIh) or light-yellow (IIa) substances insoluble in water and soluble in most organic solvents (DMF, acetic acid, ethanol) recrystallized from ethanol (IIe, IIh), 2-propanol (IId, IIf), acetic acid (IIa, IIc) methanol (IIIc, IIIh), and DMF – water mixture, 1:1 (IIg).

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of compounds IIa, IIb, IId – IIg was determined by the conventional method of double serial dilutions in a meat-extract broth. The stock solutions, prepared by dissolving 100 or 200 μg of each compound in 1 ml of the plain broth, were diluted to an initial working concentration of 12.5 μg/ml. Then, sequential half-diluted solutions were placed into tubes and test microbe cultures were added to a load of 2.5×10^5 CFU/ml. The tests were performed with clinical strains of *E. coli, P. vulgaris, Anthracoides, St. aureus, Citrobacter, Enterobacter,* and *Ps. aeruginosa*. The cultures were incubated for 72 h at 37°C and for 48 h at 25°C. The antimicrobial activity was judged by inhibition of the test culture growth after incubation for 1, 2, 3, or 5 days. The bactericidal activity was determined by additional tests, whereby the media with no visible growth were inoculated onto dishes with a meat-extract agar and into tubes with the meat-extract broth. These samples were incubated for one, two, or three days and the results were evaluated after 24, 48, or 72 h [7].

The tuberculostatic activity of compounds Ib, IIa, IIc, IIh, IIIc, and IIIh *in vitro* was studied by the method of serial dilutions using the Levenstein – Jensen dense egg culture medium. Prior to coagulation of the medium, the test compounds were added to a concentration of 25 (series I), 5 (II), 1 (III), and 0.2 μg/ml (IV) [8]. The tests were performed with the following *Mycobacterium tuberculosis* cultures: *M. tuberculosis* (strain 192), *M. bovinus* (strain Vallce), and *M. Avium* (strain 14141). The initial culture suspensions were referenced to the bacterial turbidity standard corresponding to 500×10^6 BCG microbial bodies per ml, diluted 1 : 10 with a physiological solution, and introduced (0.2 ml) into each test tube containing the culture medium with substances studied. The samples were incubated at 37°C for a time period corresponding to the optimum incubation time for each culture studied (7 to 30 days).

It was found that not one of the compounds studied exhibited antibacterial activity.

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