Synthesis of 1-(4-oxo-3,4-dihydro-2-quinazolinecarbonyl)-4-substituted thiosemicarbazides and their cyclization to 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones

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4-Oxo-3,4-dihydro-2-quinazolincarbohydrazide reacted with isothiocyanates in the mixture of acetonitrile-butanol at reflux to form 1-(4-oxo-3,4-dihydro-2-quinazolinecarbonyl)-4-substituted thiosemicarbazides. The latter under treatment of 20% KOH were cyclized to 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones, which exist as thiones according to the data of IR spectra.

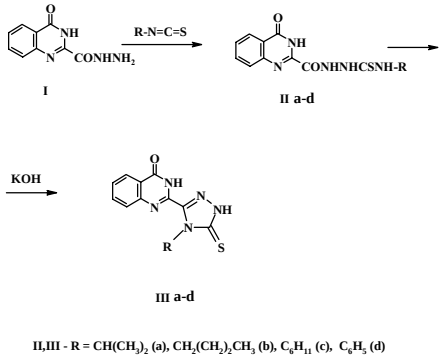
Key words: 1-(4-oxo-3,4-dihydro-2-quinazolincarbonyl)-4-substituted thiosemicarbazide, 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinone, synthesis, IR-, ^{1}H NMR-spectra

INTRODUCTION

Pyrimidine carboxylic acid thiosemicarbazides are known for their practical importance [1, 2]. On the other hand, they are used as precursors in the synthesis of physiologically active pyrimidinylazoles [2, 3]. Some of 4-quinazolone-2-carboxylic acid nitrogen derivatives are known to be pharmacologically active [4]. The synthesis and properties of 1-(4-oxo-3,4-dihydro-2-quinazolincarbonyl)-4-substituted thiosemicarbazides have been not reported. In view of these observations, it seems actual to synthesize and test this kind of compounds.

RESULTS AND DISCUSSION

As a precursor, in this work the readily synthesized 4-oxo-3,4-dihydro-2-quinazolincarbohydrazide **(I)** was used.



I II a-d III a-d

II,III - R = $CH(CH_3)_2$ (a), $CH_2(CH_2)_2CH_3$ (b), C_6H_{11} (c), C_6H_5 (d)

It was converted into acylthiosemicarbazides **II a-d** under reflux with the appropriate isothiocyanates in good yields (63–86%) in an acetonitrile–butanol solution. The latter compounds undergo cyclization to 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones **(III a-d)** when treated at reflux with 20% KOH solution.

The structure assignments of the synthesized compounds were based on their elemental analysis (Table 1), IR (Table 2) and ^{1}H NMR (Table 3) spectral data.

The IR spectra of all the compounds show absorption bands around 1603–1630 (C=N, C=C) and 1673–1682 cm^{-1} (C=O lactone) due to the atom vibrations of the 4-quinazolone ring. The acylthiosemicarbazides **II a-d** give infrared absorption peaks of NCS vibrations at 1533–1556 cm^{-1}, 1439–1447 cm^{-1}, 1144–1160 cm^{-1} and C=O (amide) in the 1688–1734 cm^{-1} region. The latter band is not observed in the IR spectra of 1,2,4-triazolin-3-thiones **III a-d**. The absence of SH band around 2500–2600 cm^{-1} and the presence of two absorption peaks in the 1496–1510 cm^{-1} regions characteristic of C=S vibrations of 1,2,4-triazolin-3-thiones [6] allow to suggest assign compounds **III a-d** to exist in the thione tautomeric form. Thiones **III a-d** also show 3 absorption bands in the 1418–1433 cm^{-1} , 1236–1258 cm^{-1} and 1138–1163 cm^{-1} regions arising from 1,2,4-triazole ring vibrations [7]. The main difference in the ^{1}H NMR spectra of acylthiosemicarbazides

Table 1. **Characteristics of synthesized thiosemicarbazides II a-d and triazoles III a-d**

Com-pound	Yield, %	M.p., °C, solvent	Brutto-formula	Found/Calculated, %			
				C	H	N	S
IIa	73	216–217	$C_{13}H_{15}N_5O_2S$	51.31	4.45	23.15	10.25
		butanol		51.13	4.95	22.93	10.50
IIb	71	223–224	$C_{14}H_{17}N_5O_2S$	52.73	5.59	22.12	9.59
		dioxane		52.65	5.36	21.93	10.04
IIc	76	200–202	$C_{16}H_{19}N_5O_2S$	55.67	5.54	20.63	9.13
		butanol		55.64	5.54	20.27	9.28
IId	63	250 (dec.)	$C_{16}H_{13}N_5O_2S$	56.22	4.09	21.08	9.34
		butanol		56.63	3.86	20.64	9.45
IIIa	71	302–303	$C_{13}H_{13}N_5OS$	54.73	4.72	24.45	11.35
		butanol		54.34	4.56	24.37	11.16
IIIb	75	307–308	$C_{14}H_{15}N_5OS$	55.94	4.97	23.51	10.19
		butanol		55.80	5.02	23.24	10.64
IIIc	71	>330	$C_{16}H_{17}N_5OS$	58.38	5.31	21.65	9.64
		butanol		58.70	5.23	21.39	9.79
IIId	78	300–301	$C_{16}H_{11}N_5OS$	59.40	3.36	21.91	9.75
		butanol		59.80	3.45	21.79	9.98

Table 2. **Data of IR spectra of thiosemicarbazides II a-d and triazoles III a-d**

Compound	NH	C=O	C=O (lact.)	C=N, C=C	NCS	1,2,4-triazolering
IIa	3348 3303 3196	1718	1676	1603	1537, 1446, 1148	–
IIb	3134	1710	1678	1606	1548, 1443, 1144	–
IIc	3312	1734	1673	1604	1533, 1447, 1147	–
IId	3484 3286	1710	1682	1604	1556, 1439, 1160	–
IIIa	3257	–	1677	1625 1607	1506, 1337	1420, 1258, 1151
IIIb	3257	–	1682	1628 1603	1510, 1340	1433, 1236, 1138
IIIc	3254	–	1677	1626 1604	1506, 1336, 1311	1423, 1238, 1145
IIId	3239	–	1674 1605	1630	1496, 1336, 1320	1418, 1244, 1163

Table 3. **The data of ^{1}H NMR spectra of thiosemicarbazides II a-d and triazoles III a-d**

Compound	Chemical shifts, δ, ppm
IIa	1.13 (6H, d, J=7 Hz, CH_3), 4.45 (1H, m, CH), 7.38–8.24 (4H, m, arom. proton), 9.39 (1H, s, CONH), 10.77 (1H, s, NHCH), 12.50 (1H, s, NH quinazol.)
IIb	0.87 (3H, t, CH_3), 1.42 [4H, m, $(CH_2)_2$], 3.97 (2H, m, CH_2), 7.62–8.23 (4H, m, arom. proton), 9.4 (1H, s, CONH), 10.82 (1H, s, NHCH_2), 12.47 (1H, s, NH quinazol.)
IIc	1.16–1.74 [10H,m, $(CH_2)_5$], 4.17(1H, m, CH cyclohex.), 7.50–8.26 (4H, m, arom. proton), 9.42 (1H, s, CONH)
IId	7.2–8.26 (9H, m, arom. proton), 9.83 (2H, s, CONHNH), 11.10 (1H, s, NH-Ph), 12.58 (1H, s, quinazol.)
IIIa	1.56 (6H, d, J=7 Hz, CH_3), 5.27 (1H, m, CH), 7.50–8.28 (4H, m, arom. proton), 12.9 (1H, s, NH quinazol.), 14.2 (1H, s, NH triazole)
IIIb	0.95 (3H, t, CH_3), 1.15–1.81 [4H, m, $(CH_2)_2$], 4.51 (2H, m, CH_2), 7.50–8.26 (4H, m, arom. proton)
IIIc	1.14–1.85 [10H, m, $(CH_2)_5$], 4.92 (1H, m, CH cyclohex.), 7.60–8.26 (4H, m, arom. proton)
IIId	7.04–8.16 (9H, m, arom. proton), 13.4 (2H, br. s, NH quinazol., triazole)

II and 1,2,4-triazolin-3-thiones **III** appears in the resonanse of protons of the substituents of the 4th position. The signals of protons of the substituents of the 4th position of 1,2,4-triazolin-3-thiones **III** occur about 2 ppm downfield if compared to those of acylthiosemicarbazides **II.** This may be caused by magnetic anisotropy.

EXPERIMENTAL

The melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in nujol mulls on a IR FT PERKIN ELMER spectrometer. The ^{1}H NMR spectra of newly synthesized compounds were recorded on a Tesla BS 487 C (80 MHz) NMR spectrometer in DMSO.

4-Oxo-3,4-dihydro-2-quinazolincarbohydrazide (I) was synthesized according to the literature [5] under treatment of ethyl 4-oxo-3,4-dihydro-2-quinazolinecarboxylate with hydrazine hydrate.

1-(4-Oxo-3,4-dihydro-2-quinazolincarbonyl)-4-substituted thiosemicarbazides (II a-d). Hydrazide **I** (2 g, 0.0098 mol) was dissolved at reflux in a mixture of 100 ml dry butanol and 10 ml dry acetonitrile. To the solution, an appropriate isothiocyanate (0.0196 mol) was added. The reaction mixture then was stirred and refluxed for 11 h. When cooled to room temperature, the precipitate formed was filtered off, dried and purified.

2-(4-Substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones (III a-d). The appropriate thiosemicarbazide **II** (0.005 mol) was dissolved in 70 ml of 20% KOH and refluxed for 6 h. After cooling to room temperature, the content was diluted with 50 ml of H_2O and acidified with conc. HCl to pH 5–6. The solid formed was filtered off, washed with water, dried and purified.

Characteristics of the synthesized compounds are given in Table 1, the data of IR and ^{1}H NMR are presented in Tables 2 and 3.

CONCLUSIONS

1. 4-Oxo-3,4-dihydro-2-quinazolincarbohydrazide reacted with isothiocyanates to give 1-(4-oxo-3,4-dihydro-2-quinazolincarbonyl)-4-substituted thiosemicarbazides.

2. 1-(4-Oxo-3,4-dihydro-2-quinazolincarbonyl)-4-substituted thiosemicarbazides under treatment with 20% KOH undergo cyclization to 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones.

3. By the data of IR spectra (show C=S absorption peaks, no absorption of S-H), the 2-(4-substituted-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-3,4-dihydro-4-quinazolinones exist in the thione tautomeric form.

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1-(4-OKSO-3,4-DIHIDRO-2-CHINAZOLINKARBONIL)-4-PAKEISTŲ TIOSEMIKARBAZIDŲ SINTEZĖ IR JŲ CIKLIZACIJA Į 2-(4-PAKEISTUS-5-TIOKSO-4,5-DIHIDRO-1H-1,2,4-TRIAZOL-3-IL)-3,4-DIHIDRO-4-CHINAZOLINONUS

S a n t r a u k a

4-Okso-3,4-dihidro-2-chinazolinkarbohidrazidą virinant su izotiocianatais butanolio ir acetonitrilo mišinyje susidaro 1-(4-okso-3,4-dihidro-2-chinazolinkarbonil)-4-pakeisti tiosemikarbazidai, kurie dėl 20% KOH poveikio ciklizuojasi į 2-(4-pakeistus-5-tiokso-4,5-dihidro-1H-1,2,4-triazol-3-il)-3,4-dihidro-4-chinazolinonus. IR spektrų duomenimis, jie egzistuoja tioninės formos.

Г. Мякушкене, М. М. Бурбулене, П. Вайнилавичюс

СИНТЕЗ 1-(4-ОКСО-3,4-ДИГИДРО-2-ХИНАЗОЛИНКАРБОНИЛ)-4-ЗАМЕЩЕННЫХ ТИОСЕМИКАРБАЗИДОВ И ИХ ЦИКЛИЗАЦИЯ В 2-(4-ЗАМЕЩЕННЫЕ-5-ТИОКСО-4,5-ДИГИДРО-1Н-1,2,4-ТРИАЗОЛ-3-ИЛ)-3,4-ДИГИДРО-4-ХИНАЗОЛИНОНЫ

Р е з ю м е

При кипячении 4-оксо-3,4-дигидро-2-хиназолинкарбогидразида с изотиоцианатами в смеси бутанола-ацетонитрила получены 1-(4-оксо-3,4-дигидро-2-хиназолинкарбонил)-4-замещенные тиосемикарбазиды, которые под воздействием 20% КОН циклизуются в соответствующие 2-(4-замещенные-5-тиоксо-4,5-дигидро-1Н-1,2,4-триазол-3-ил)-3,4-дигидро-4-хиназолиноны.