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SYNTHESIS OF THIAZINO- AND THIAZOLO-QUINAZOLINONES BY CYCLIZATION OF S-(2-PROPENYL) DERIVATIVES OF 2-THIOXO-2,3-DIHYDRO-4(1H)-QUINAZOLINONE

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Interaction of potassium salts of quinazolin-2-thiol-4-one with γ-substituted allyl halides gave thiazoloquinazolinones with linear or angular structures depending on the structure of the carbonyl radical. S-Allyl substituted quinazolin-2-thiol-4-one reacted with halogens to give iminium salts of thiazinoquinazolinone with an angular structure. The conversion of these salts to the corresponding bases and thiazoloquinazolinones has been studied.

Keywords: thiazinoquinazolinones, thiazoloquinazolinones, cyclization, rearrangement.

Condensed derivatives of pyrimidine play a major role in metabolic processes and their synthetic analogs possess a wide spectrum of physiological activities [1, 2] and consequently they have been much studied.

However, tricyclic systems in which the pyrimidine ring is condensed with a benzene and a thiazole (or thiazine) ring have not been adequately studied. A method for the synthesis of linear tricyclic systems containing benzene, pyrimidine, and thiazole rings by the cyclization of 2-mercapto-3-(2-propenyl)-4(1H)-quinazolinones reacting with bromine has been described [3].

Cyclization of derivatives of S-allylquinazolin-2-thion-4-one to produce tricyclic compounds containing the thiazino(thiazolo)quinazolinones fragments with linear and angular structures is described in this paper.

It is known that alkylation of salts of quinazolin-2-thiol-4-ones with alkyl halides occurs with the formation of 2-S-alkyl derivatives [4]. We have established that alkylation of the potassium salt of quinazolin-2-thiol-4-one (**1**) with cinnamyl chloride gave analogously the S-alkenyl derivative **2**. However, when an attempt was made to alkylate salt **1** with ethyl 4-bromocrotonate (**3**), instead of the expected 2-(3-carboethoxy-2-propenylthio)-4(3H)quinazolinone (**4**) we obtained the products of its cyclization, compounds **5** and **6** (Scheme 1).

The formation of these products is explained as follows. The presence of the electron accepting carboethoxy group on the double bond increases the electrophilicity of the β-carbon atom of the butenyl unit to a considerable extent which, in its turn, facilitates nucleophilic attack of the equally distant nitrogen atoms N(1) and N(3) at the stage of intramolecular cyclization of the intermediate **4**.

It should be noted that when the reaction was carried out in boiling ethanol only the angular compound **6** was formed, while when the reaction was carried out at a lower temperature (10-15 °C) a mixture of the linear and angular cyclization products was obtained.

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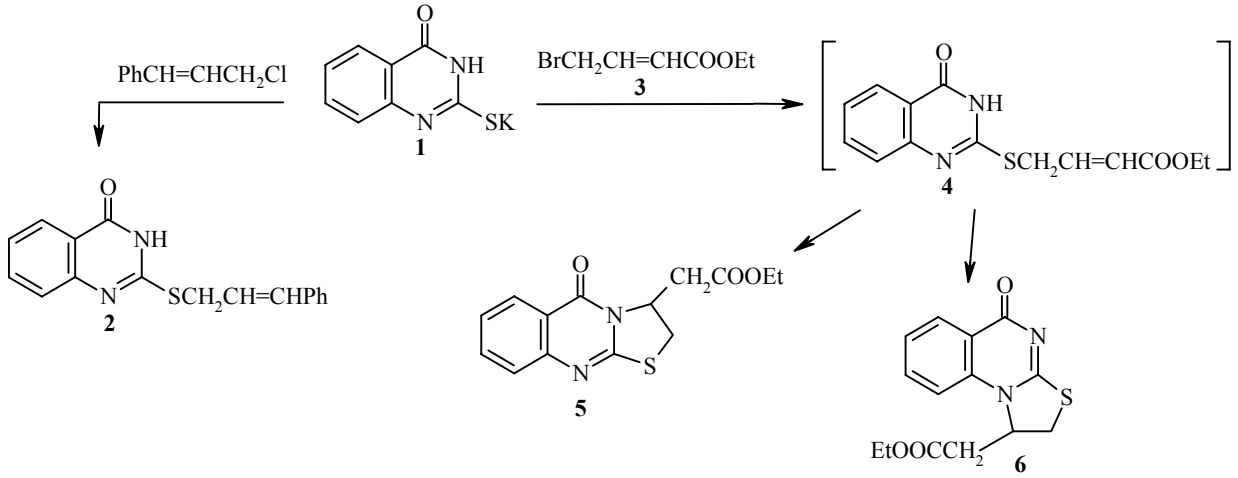
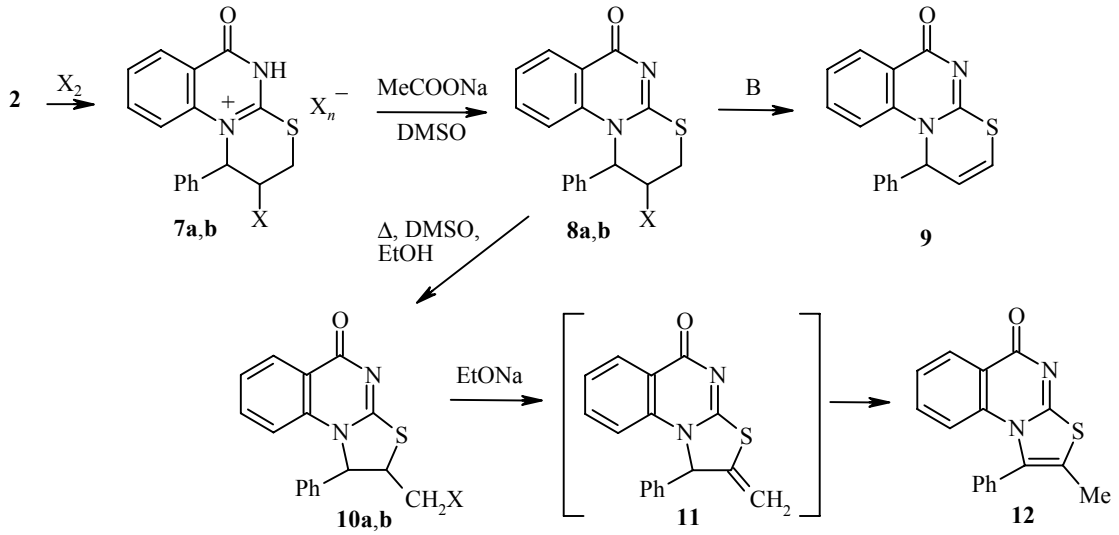
Scheme 1



Thiazinoquinazolinones of angular structure, **7a,b**, were formed in almost quantitative yield from the action of bromine or iodine on a solution of compound **2** in acetic acid at 15-20°C. When the reaction was carried out at a higher temperature or in chloroform slight resin formation occurred with the formation of a mixture of derivatives of thiazino- and thiazoloquinazolinone.

The yield of compounds **7a,b** depends on the amount of halogen used. For example, with a 1:1 molar ratio of halogen to compound **2** the yield of products **7a,b** was 30%. When the ratio was increased to 2:1 for bromine or 3:1 for iodine compounds **7a,b** may be obtained in almost quantitative yield. The bromine derivative **7a** is orange yellow, while the iodine derivative **7b** is dark brown.

Treatment of the salts **7a,b** with sodium acetate gave the corresponding bases **8a,b** which lost a hydrogen halide on treatment with organic bases (morpholine or piperidine) to give compound **9**. The thiazinoquinazolinones **8a,b** underwent rearrangement when heated in an ethanol–DMSO mixture to give the thiazoloquinazolinones **10a,b**. The latter, when treated with sodium ethoxide, lost a molecule of hydrogen halide to give the intermediate **11**, which underwent intramolecular rearrangement, accompanied by migration of the exocyclic double bond into the thiazole ring, to give compound **12** as the final product.



7, **8**, **10 a** X = Br, *n* = 3; **b** X = I, *n* = 5; B = morpholine, piperidine

The composition and structures of the products synthesized were confirmed by elemental analysis and IR and ^{1}H NMR spectroscopy (Tables 1 and 2). It should be noted that the positions of the absorption bands of the carbonyl groups in the quinazolone unit in the IR spectra of the thiazino- and thiazoloquinazolinones with linear and angular structures differ considerably. For example, in the spectra of compounds with an angular structure this band appears in the 1665-1650 cm^{-1} range, whereas in the spectra of the linear heterocyclic systems it appears at 1695-1670 cm^{-1} [5,6]. We used this observation to confirm the structures of the compounds synthesized.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, %
		C	H	Hal	N	S		
2	$C_{17}H_{14}N_2OS$	69.61 / 69.36	4.77 / 4.79	—	9.75 / 9.52	10.36 / 10.89	191-193	90
5	$C_{14}H_{14}N_2O_3S$	58.08 / 57.92	4.87 / 4.86	—	9.73 / 9.65	11.03 / 11.04	108-109	42
6	$C_{14}H_{14}N_2O_3S$	57.89 / 57.92	5.00 / 4.86	—	9.70 / 9.65	11.00 / 11.04	158-159	84
7a	$C_{17}H_{14}Br_4N_2OS$	33.09 / 33.26	2.10 / 2.30	52.71 / 52.06	4.42 / 4.56	5.12 / 5.22	202-205	95
7b	$C_{17}H_{14}I_6N_2OS$	19.08 / 19.34	1.15 / 1.34	70.90 / 72.12	2.46 / 2.65	2.89 / 3.04	136-137	97
8a	$C_{17}H_{13}BrN_2OS$	54.59 / 54.70	3.40 / 3.51	21.38 / 21.41	7.42 / 7.50	8.49 / 8.59	194-195	88
8b	$C_{17}H_{13}IN_2OS$	48.50 / 48.58	3.04 / 3.12	30.19 / 30.20	6.40 / 6.67	7.51 / 7.63	187-188	75
9	$C_{17}H_{12}N_2OS$	69.82 / 69.84	4.02 / 4.14	—	9.51 / 9.58	10.89 / 10.96	198-200	95
10a	$C_{17}H_{13}BrN_2OS$	54.64 / 54.70	3.47 / 3.51	21.42 / 21.41	7.43 / 7.50	8.51 / 8.59	182-183	82
10b	$C_{17}H_{13}IN_2OS$	48.55 / 48.58	3.07 / 3.12	30.23 / 30.20	6.51 / 6.67	7.54 / 7.63	196-197	74
12	$C_{17}H_{12}N_2OS$	69.84 / 69.84	4.09 / 4.14	—	9.54 / 9.58	10.91 / 10.96	292-293	67

TABLE 2. Spectroscopic Characteristics of the Compounds Synthesized

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	IR spectrum, ν(C=O), cm^{-1}
1	2	3
2	4.10 (2H, d, *J* = 7.2, CH_2); 6.42 (1H, dt, *J* = 7.2 and *J* = 15.9, C<u>H</u>=CH–C_6H_5); 6.76 (1H, d, *J* = 15.9, CH=C<u>H</u>–C_6H_5); 7.23-7.34 (3H, m, ArH); 7.41-7.44 (3H, m, ArH); 7.60-7.63 (1H, m, ArH); 7.76-7.81 (1H, m, ArH); 8.03-8.06 (1H, m, ArH); 12.59 (1H, s, NH)	1685*
5	1.15 (3H, t, *J* = 7.2, CH_3); 2.82 (dd) and 2.95 (dd) (2H, *J* = 15.8 and *J* = 3.6, *J* = 15.8 and *J* = 8.7, SCH_2); 3.32 (m) and 3.90 (m) (2H, CH_2COO); 4.08 (2H, q, *J* = 7.2, $COOC\underline{H}_2CH_3$); 5.31 (1H, m, CH); 7.42-7.52 (2H, m, ArH); 7.77 (1H, m, ArH); 8.06 (1H, m, ArH)	1690* 1730*[2]
6	1.16 (3H, t, *J* = 7.0, CH_3); 2.70 (dd) and 2.95 (dd) (2H, *J* = 16.0 and *J* = 3.2, *J* = 16.0 and *J* = 9.2, SCH_2); 3.46 (m) and 3.96 (m) (2H, CH_2COO); 4.07 (2H, q, *J* = 7.0, $COOC\underline{H}_2CH_3$); 5.58 (1H, m, CH); 7.43-7.54 (2H, m, ArH); 7.80 (1H, m, ArH); 8.04 (1H, m, ArH)	1655* 1735*[2]
7a	3.30 (2H, m, CH_2); 5.63 (1H, m, $SCH_2C\underline{H}$); 6.54 (1H, m, CH); 7.47 (7H, m, ArH); 7.74 (1H, m, ArH); 8.14 (1H, m, ArH)	1720*

TABLE 2 (continued)

1	2	3
7b	3.10 (2H, m, CH_2); 5.58 (1H, m, $SCH_2C\underline{H}$); 6.46 (1H, m, CH); 7.44 (7H, m, ArH); 7.74 (1H, m, ArH); 8.16 (1H, m, ArH)	1710*
8a	3.26 (2H, m, CH_2); 5.59 (1H, m, $SCH_2C\underline{H}$); 6.44 (1H, m, CH): 7.44 (7H, m, ArH); 7.67 (1H, m, ArH); 8.09 (1H, m, ArH)	1660*
8b	3.04 (2H, m, CH_2); 5.56 (1H, m, $SCH_2C\underline{H}$); 6.38 (1H, m, CH); 7.46 (7H, m, ArH); 7.68 (1H, m, ArH); 8.09 (1H, m, ArH)	1650*
9	6.49 (1H, dd, J = 6.6 and J = 9.7, SCH=C$\underline{H}$); 6,71 (1H, d, J = 9.7, S$C\underline{H}$=CH); 6.90 (1H, d, J = 6.6, CH); 7.28-7.35 (5H, m, ArH); 7.50 (1H, m, ArH); 7.72-7.81 (2H, m, ArH); 8.09 (1H, m, ArH)	1655*
10a	4.07 (3H, m, CH_2–CH); 6.24 (1H, m, CH); 7.22-7.45 (7H, m, ArH); 7.61-7.69 (1H, m, ArH); 8.07 (1H, m, ArH)	1650*
10b	3.93 (3H, m, CH_2–CH); 6.13 (1H, m, CH); 7.23-7.44 (7H, m, ArH); 7.65 (1H, m, ArH); 8.07 (1H, m, ArH)	1650*
12	2.14 (3H, s, CH_3); 6.62 (1H, m, ArH); 7.35 (1H, m, ArH); 7.45 (1H, m, ArH); 7.56-7.64 (5H, m, ArH); 8.17 (1H, m, ArH)	1650*

* (C=O of the quinazoline unit).

*[2] (C=O of the carbethoxy unit).

EXPERIMENTAL

IR spectra of KBr tablets were recorded with a UR-10 instrument. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Varian VXR (300 MHz) machine.

2-(3-Phenyl-2-propenylthio)-4(3H)-quinazolinone (2). Cinnamyl chloride (3.1 g, 20 mmol) was added to a solution of compound **1** (4.32 g, 20 mmol) in a mixture of ethanol (80 ml) and water (20 ml) and the mixture was boiled for 60-70 min. The quinazolinone **2** which crystallized was filtered off, washed with water heated to 35-40°C (40 ml), and then with ethanol and ether. It was recrystallized from a 4:1 mixture of ethanol and dioxane.

Reaction of Compound 1 with Ethyl 4-Bromocrotonate 3. A. Compound **1** (1.08 g, 5 mmol) was added to a mixture of ethanol (30 ml) and water (2 ml) and heated with stirring until the solid dissolved. The solution was cooled to 10-15°C and kept at that temperature while compound **3** (1.0 g, 6 mmol) was added dropwise with vigorous stirring. After 20 h the precipitate was filtered off and washed with water and ethanol to give a white microcrystalline substance (1.33 g) which consisted (from the data of ^{1}H NMR spectroscopy) of 45% of compound **6** and 55% of 3-carboethoxymethyl-2,3-dihydro-5H-thiazolo[2,3-*b*]quinazolin-5-one (**5**). Both compounds were obtained pure by fractional crystallization from ethanol.

B. **1-Carboethoxymethyl-1,2-dihydrothiazolo[3,2-*a*]quinazol-5-one (6).** Compound **1** (1.08 g, 5 mmol) was dissolved in a mixture of ethanol (20 ml) and water (10 ml). Compound **3** (1.0 ml, 6 mmol) was then added. The mixture was boiled for 1 h, the precipitate which formed was filtered off, washed with water heated to 30-40°C, and then with ethanol and ether. It was crystallized from ethanol.

2-Bromo-6-oxo-1-phenyl-1,2-dihydro-3H,5H-[1,3]thiazino[3,2-*a*]quinazolinium Tribromide (7a). A solution of bromine (0.16 ml, 3 mmol) in acetic acid (15 ml) was added dropwise over 30-40 min with intermittent stirring to a suspension of compound **2** (0.441 g, 1.5 mmol) in glacial acetic acid (35 ml). The reaction temperature remained at 15-18°C. The orange microcrystalline precipitate which separated over 8-10 h was filtered off, washed with acetic acid and ether, and dried in a vacuum desiccator over P_2O_5.

2-Iodo-6-oxo-1-phenyl-1,2-dihydro-3H,5H-[1,3]thiazino[3,2-*a*]quinazolinium Pentaiodide (7b). Compound **2** (0.441 g, 1.5 mmol) was dissolved on heating in glacial acetic acid (40 ml). The solution was cooled to 20°C and iodine (1.14 g, 4.5 mmol) in acetic acid (100 ml) was added dropwise over 1 h with

intermittent stirring. Stirring was continued for 20-25 h, the brown precipitate was filtered off, washed with acetic acid and ether, and dried in a vacuum desiccator over P_2O_5.

2-Bromo-1-phenyl-1,2-dihydro-3H-[1,3]thiazino[3,2-*a*]quinazolin-6-one (8a) and 2-Iodo-1-phenyl-1,2-dihydro-3H-[1,3]thiazino[3,2-*a*]quinazolin-6-one (8b). The corresponding salts **7a** and **7b** (2 mmol) were dissolved in DMSO (25 ml). After solution was complete 20% aqueous sodium acetate (15 ml) was added to the stirred solution in a water bath (15°C). The precipitate which formed after 1.5-2 h was filtered off and washed with water. Compound **8b** was partially resinified so it was triturated with acetone (30-40 ml) and filtered again. Both substances were dried in a vacuum desiccator over P_2O_5.

1-Phenyl-1H-[1,3]thiazino[3,2-*a*]quinazolin-6-one (9). Compound **8a** or **8b** (3 mmol) was dissolved in morpholine (or piperidine) (10 ml) at 10-15°C.The solution was kept at room temperature for 20 h, then water (20 ml) was added. The precipitate was filtered off, washed with ethanol and ether, and was then dried in a vacuum desiccator over P_2O_5.

2-Bromomethyl-1-phenyl-1,2-dihydrothiazolo[3,2-*a*]quinazolin-5-one (10a) and 2-Iodomethyl-1-phenyl-1,2-dihydrothiazolo[3,2-*a*]quinazolin-5-one (10b). Compounds **8a** or **8b** (3 mmol) was added to a 1:1 mixture of ethanol–DMSO (20 ml), the reaction mixture was boiled for 1.5 h, after which it was cooled and water (30 ml) was added. After 10-15 h, the precipitate was filtered off and washed with ethanol and ether. Both products were crystallized from ethanol.

2-Methyl-1-phenylthiazolo[3,2-*a*]quinazolin-5-one (12). Compound **10a** or **10b** (3 mmol) was added to a 5% solution of sodium ethoxide (10 ml) and the mixture was kept for 4-5 h, after which water (20 ml) was added. The precipitate produced over 20 h was filtered off and washed with ethanol and ether. The products were crystallized from DMF and were then boiled in ethanol to remove DMF.

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