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REACTION OF α,α-, α,α'- DIHALOTHIONES WITH 8-MERCAPTO-QUINOLINIUM HALIDES AS A ROUTE TO TETRAHYDRO-1,4-THIAZINOQUINOLINIUM HALIDES

L. G. Shagun, I. A. Dorofeev, I. A. Mikhailova, V. A. Shagun, and M. G. Voronkov

The reaction of 8-mercaptoquinolinium bromide with 1,3-dibromopropane-2-thione or 3,3-dibromo-butane-2-thione in methanol gave the 2-bromomethyl-2-mercaptotetrahydro-1,4-thiazino[2,3,3,4-i,j]quinolinium and 3-bromo-2-mercapto-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-i,j]quinolinium bromides which readily exchanged the Br^- anion for ClO_4^- upon treatment with sodium perchlorate in methanol. Oxidation of the 3-bromo-2-mercapto-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-i,j]-quinolinium bromide by selenium dioxide gave 2,2-dithiobis(3-bromo-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-i,j]quinolinium) bromide.

Keywords: 2,2-dibromobutane-3-thione, 1,3-dibromopropane-2-thione, 2-bromomethyl-2-mercapto-tetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium, 3-bromo-2-mercapto-2,3-dimethyltetrahydro-1,4-thiazino-[2,3,3,4-*i,j*]quinolinium and 2,2-dithiobis(3-bromo-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-*i,j*]-quinolinium) bromides.

Quinoline and thiazine heterocyclic fragments occur in the composition of many medicinal compounds and have anti-inflammatory, antidepressant, and bactericidal properties together with other forms of pharmacological activity [1]. In this connection, there is special interest in biologically active compounds having both of these heterocycles simultaneously. Amongst these, in particular, are tetrahydro-1,4-thiazinoquinolinium salts.

A known route for their synthesis is based on three consecutive reactions [2]:

1. S-Alkylation of potassium 8-mercaptoquinolinate using 2-chloroethanol;
2. C-Halogenation of the S-alkyl substituent using thionyl chloride;
3. Intramolecular quaternization of the quinoline nitrogen atom.

We have previously developed [3-6] a novel route for the synthesis of tetrahydro-1,4-thiazinoquinolinium salts based on the reaction of 8-mercaptoquinolinium halides with monohalo-substituted thioacetones in ethanol or DMF at -40°C in the presence of the corresponding hydrohalide. Extending this investigation we have studied the possibility of constructing the condensed system, including the quinoline and tetrahydrothiazine heterocycles, *via* the reaction of 8-mercaptoquinolinium halides with the α,α'- (**1**) and α,α-dihalothiones **2**, which we have recently been able to prepare [7].

The reaction of 1,3-dibromopropane-2-thione (**1**) with 8-mercaptoquinolinium bromide (equimolar ratio of reagents, -40°C, 12 h) in methanolic HCl solution gave the previously unknown 2-bromomethyl-2-mercaptotetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium bromide (**3**) in a single preparative stage and in 69% yield.

A. E. Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Irkutsk 664033; e-mail: shag@irioch.irk.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1720-1723, November, 2006. Original article submitted July 13, 2006.

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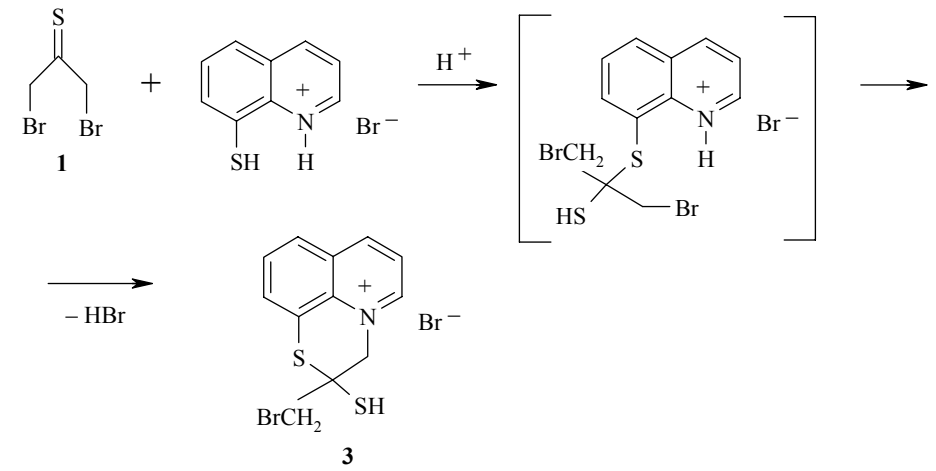
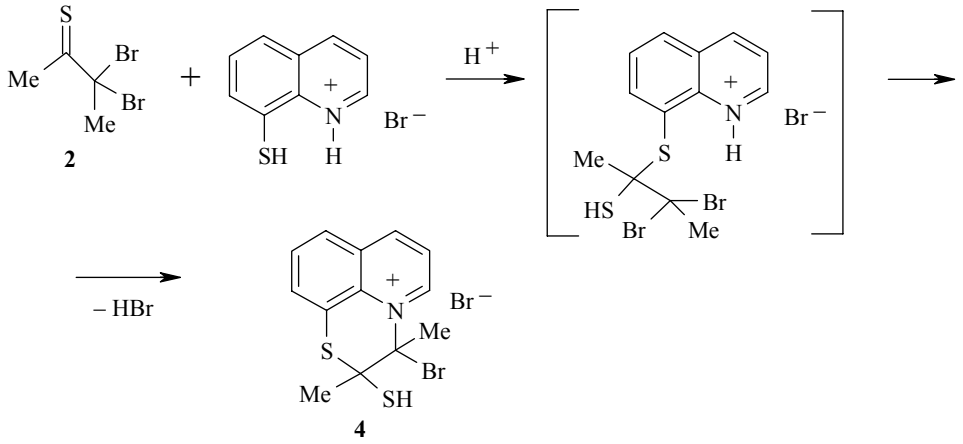


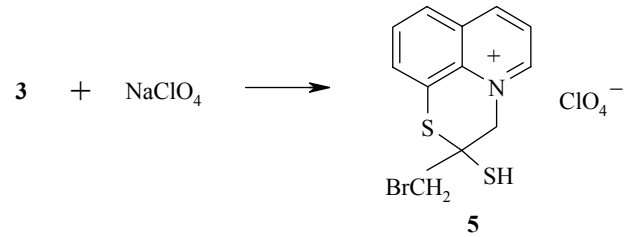
The reaction of 2,2-dibromobutane-3-thione (**2**) with 8-mercaptoquinolinium bromide occurred similarly to give 3-bromo-2,3-dimethyl-2-mercaptotetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium bromide (**4**) in 85% yield.



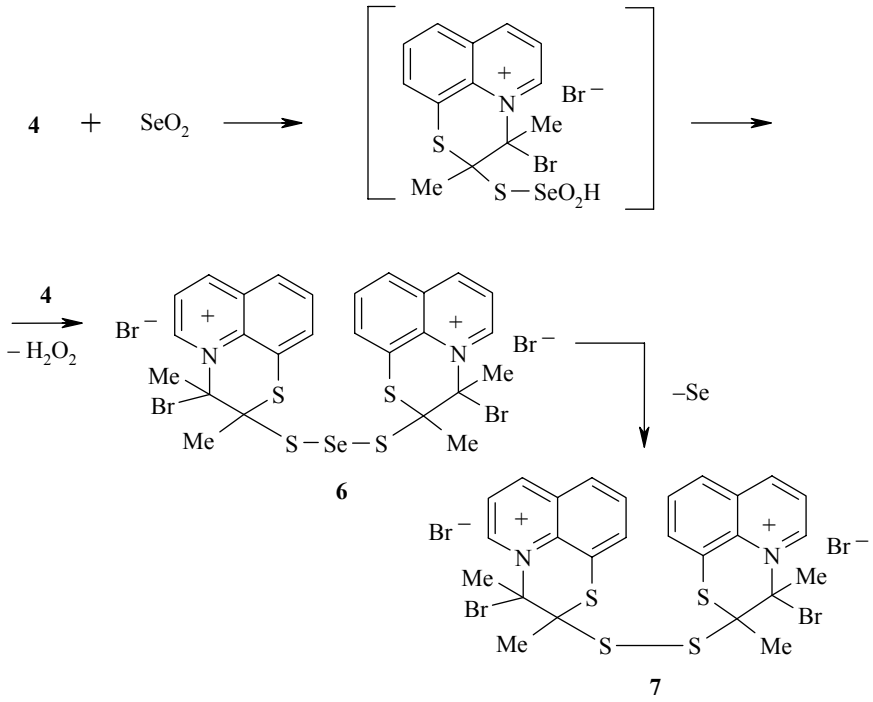
As in the reaction of 8-mercaptoquinolinium halides with monohalo thioacetones [4] the process of forming the salts **3,4** begins with the addition of the thiol group of the 8-mercaptoquinolinium halides to the thiocarbonyl group of thiones **1** and **2** and concludes with an intramolecular cyclization involving the quaternized quinolinium nitrogen atom with elimination of hydrohalide.

The salts **3,4** obtained are soluble in alcohols, DMF, and DMSO but limited in water. Treatment with sodium perchlorate in methanol exchanges the Br^- ion for ClO_4^-.

We have studied the oxidation behaviour of salts **3,4** using selenium dioxide in the example of compound **4**. As is known [5, 8] the oxidation of the SH group in thiophenol, indenethiol, and 2-mercapto-2-methyl-1,4-thiazino[2,3,3,4-*i,j*]quinolinium chloride gives the corresponding disulfides or dithioselenides.



We have found that the oxidation product of salt **4** using selenium dioxide (molar ratio 2 : 1) in methanol medium at 20°C is 2,2-dithiobis(3-bromo-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium) bromide (**7**) in 76% yield.



The reaction probably takes place *via* a stage of forming a thioselenate, interaction of which with a second molecule of salt **4** gives the dithioselenide **6**. The latter eliminates selenium thus converting to disulfide **7**. The dithioselenide **6** is stable only in methanol solution at -20°C. Removal of methanol in vacuo (2 mm Hg) leads to separation of selenium as a red, amorphous powder. The IR spectrum of disulfide **7** shows an absorption band at 507 cm^{-1} corresponding to stretching of the S–S bonds.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained on a DPX-400 spectrometer (400 MHz and 100 MHz respectively) with HMDS external standard at 0.05 ppm. IR spectra were recorded on a Bruker IFS-25 spectrometer using KBr. The course of the reaction was monitored by TLC on Silufol UV-254 plates with $CHCl_3$ eluent.

2-Bromomethyl-2-mercaptotetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium Bromide (3). A solution of 8-mercaptoquinolinium bromide (0.4 g, 2 mmol) in methanol (5 ml) cooled to -40°C was added to a solution of the thioketone **1** (0.5 g, 2 mmol) in methanolic HCl solution (5 ml) at -40°C and left at -20°C for 12 h. The precipitate was filtered off, washed with ether, and dried in vacuo to give compound **3** (0.58 g, 69%) as a yellow-orange powder with decomposition temperature 185-187°C. IR spectrum, ν, cm^{-1}: 2590 (SH, w). ^1H NMR spectrum (CD_3CN), δ, ppm (*J*, Hz): 2.39 (1H, s, SH); 3.32, 3.45, 3.47, 3.49 (2H, AB, q, *J* = 11.3, CH_2N^+); 2.41, 2.43, 3.57, 3.59 (2H, AB, q, *J* = 12.9, CH_2Br); 7.90-9.20 (6H, m, Ar). Found, %: Br 41.10; S 15.98. $C_{12}H_{11}Br_2NS_2$. Calculated, %: Br 40.92; S 16.36.

3-Bromo-2-mercapto-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium Bromide (4). A solution of thioketone **2** (1.6 g, 6 mmol) in anhydrous methanol (10 ml) was mixed with a solution

of 8-mercaptoquinolinium bromide (1.6 g, 6 mmol) in methanol (20 ml) at -40°C and left at -20°C for 12 h. Ether (5 ml) cooled to -40°C was added to this mixture. The precipitate was filtered off, washed with ether, and dried in vacuo. Two reprecipitations from methanol solution gave the salt **4** (2.2 g, 85%) with decomposition temperature 194-195°C. IR spectrum, ν, cm^{-1}: 2590 (SH, w). ^1H NMR spectrum (CD_3OD), δ, ppm: 2.19 (1H, s, SH); 3.31 (3H, s, CH_3); 3.54 (3H, s, CH_3); 7.77-9.23 (6H, m, Ar). ^{13}C NMR spectrum (CD_3OD), δ, ppm: 38.37 (CH_3); 39.29 ($\underline{C}H_3$); 61.28 (>$\underline{C}$(SH)CH_3); 122.52 (>$\underline{C}$(Br)CH_3); 129-147 (9C, Ar). Found, %: Br 39.70; S 15.26. $C_{13}H_{13}BrNS_2$. Calculated, %: Br 39.31; S 15.76.

2-Bromomethyl-2-mercaptotetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium Perchlorate (5). A solution of $NaClO_4$ (0.08 g, 0.7 mmol) in methanol (2 ml) was added to a solution of salt **3** (0.3 g, 0.7 mmol) in methanol (2 ml). The light-orange precipitate was filtered off, washed with ether, and dried in vacuo to give salt **5** (0.28 g, 91%) with decomposition temperature 140-143°C. IR spectrum, ν, cm^{-1}: 2590 (SH, w). ^1H NMR spectrum (CD_3CN), δ, ppm (*J*, Hz): 2.37 (1H, s, SH); 3.41, 3.43, 3.45, 3.91 (2H, AB, q, ^3J = 10.6, CH_2N^+); 2.30, 2.35, 2.39, 2.41 (2H, AB, q, ^2J = 12.5, CH_2Br); 7.91-9.19 (6H, m, Ar). Found, %: C 35.10; H 2.98; N 3.18; S 15.98. $C_{12}H_{11}BrClNO_4S_2$. Calculated, %: C 34.91; H 2.66; N 3.39; S 15.52.

2,2-Dithiobis(3-bromo-2,3-dimethyltetrahydro-1,4-thiazino[2,3,3,4-*i,j*]quinolinium) Bromide (7). A solution of salt **4** (0.3 g, 0.7 mmol) in methanol (7 ml) was mixed with a solution of selenium dioxide (0.03 g, 0.35 mmol) in methanol (50 ml) and left for 12 h. Methanol was removed in vacuo and the red residue was extracted with ethanol. Ethanol was evaporated in vacuo to give the disulfide **7** (0.22 g, 76%) as a colorless powder with decomposition temperature 225-227°C. IR spectrum, ν, cm^{-1}: 507 (S–S). Found, %: Br 39.10; S 16.00. $C_{26}H_{24}Br_4N_2S_4$. Calculated, %: Br 39.40; S 15.76.

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