SYNTHESIS AND ALKYLATION OF 2-MERCAPTO-4-QUINAZOLONE AND THE FUNGICIDAL ACTIVITIES OF THE COMPOUNDS OBTAINED

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A convenient method of obtaining 2-mercapto-4-quinazolone has been developed and the alkylation of its ambidentate anions has been studied. It has been found that they exhibit a dual reactivity in alkylation reactions. It has been shown that alkylated 2-mercapto-4-quinazolones possess a moderate fungicidal activity.

Derivatives of 2-mercapto-4-quinazolone exhibit fungicidal [1] and other types [2-4] of activity, and therefore it appeared of interest to search for biologically active substance in the 2-mercapto-4-quinazolone series. This class of compounds is also attractive from the chemical point of view, since the presence of a $-\overset{\overset{O}{\|}}{C}-NH-\overset{\overset{SH}{|}}{C}=N$ group may be the cause of

the appearance of a dual reactivity, all the more since in the literature there is no information on the quantitative laws in the reactions with electrophilic reagents in general and in the alkylation of quinazoline derivatives, in particular. There is a large amount of information on the formation of S- or N-isomers in alkylation reactions of other heterocyclic compounds [see, for example, [5-10]], but only recently have publications appeared on the quantitative study of the ratio of the S/N isomers of heterocyclic thionamides [11-15].

Continuing investigations on the synthesis and chemical transforms of quinazolines with functional groups in positions 2 [16, 17], we have studied the alkylation reactions of 2-mercapto-4-quinazolone (IV) and its salts.

The initial compound (IV) for our investigations was synthesized from anthranilic acid (I) and ammonium thiocyanate (IIIc) by heating (140-160°C) in the absence of a solvent [18, 19], from ethyl anthranilate (II) and (IIIc) in chlorobenzene [20], and from anthranilic acid hydrochloride and potassium thiocyanate (IIIa) [21], and also from methyl anthranilate via its intermediate hydrothiocyanic acid salt followed by thermal cyclization to (IV) [22, 23]. 7-Chloro-2-mercapto-4-quinazolone was also obtained from 4-chloroanthranilic acid and potassium cyanate in the presence of hydrochloric acid. However, all the methods mentioned either give low yields or require additional reagents or solvents. In order to find a convenient method for obtaining 2-mercapto-4-quinazolone, we condensed anthranilic acid with potassium, sodium, and ammonium thiocyanates (IIIa-c) and ethyl anthranilate with (IIIa) wither in the presence of acids or without them in various solvents (ethanol, chlorobenzene, n-butanol, acetic acid) or in the absence of solvents, varying the reaction conditions and the ratio of the reactants. We also studied the condensation of (I), (II), and anthranilamide (IIa) with thiourea by fusing a mixture of the reactants alone at 180-200°C or in the presence of phosphorus oxychloride at 80-90°C. It must be mentioned that on the reaction of (I) with (IIIa) in the presence of hydrochloric acid, in addition to 2-mercapto-4-quinazolone, tetrahydroquinazoline-2,4-dione was isolated as a by-product. The formation of this compound is apparently due to the hydrolysis of (IV) under the reaction conditions, as has been observed for pyrimidine derivatives [25] and for heterocycles having a thio group [26]. As a result, we found that the most successful method of synthesis is the performance of the condensation of the anthranilic acid with metal thiocyanates in acetic acid.

For the study of the alkylation of 2-mercapto-4-quinazolone we first synthesized salts (sodium, potassium, lithium, triethylammonium) of this compound, which can exist in the form of ambidentate (Va-c) or polydentate (Vd, e) anions.

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TABLE 1. Characteristics of the Compounds Synthesized

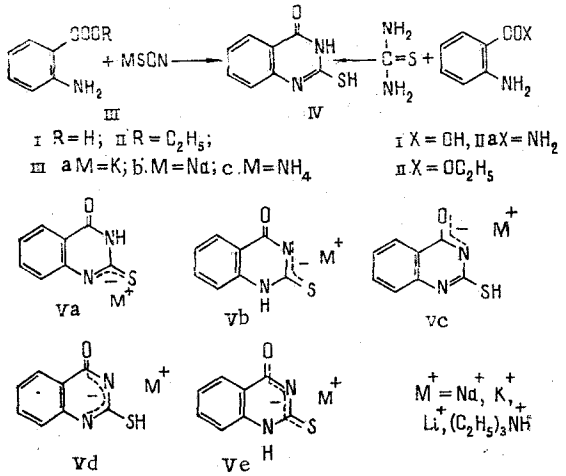
Compound	Yield %	mp, °C (ethanol)	R_f^*	mol. wt. (mass spectrum)	R	λ_{max} λ_1	log ε_1	λ_2	log ε_2	Empirical formula
IV	56	299—300†	0,5	178	—2SH	219	4,20	293	4,34	$C_8H_6ON_2S$
VIa	55	210—211	0,57	192	2—CH_3	227	4,31	275	4,0	$C_9H_8ON_2S$
VIb	78	152—154	0,56	—	2—C_2H_5	232	4,20	275	3,95	$C_{10}H_{10}ON_2S$
VIc	78	130—132	0,64	—	2—C_3H_7	232	4,29	275	4,06	$C_{11}H_{12}ON_2S$
VId	55	122—124	0,88	234	2—C_4H_9	232	4,48	275	4,14	$C_{12}H_{14}ON_2S$
VIe	63	88—90	0,76	—	2—C_5H_{11}	233	5,07	276	4,83	$C_{13}H_{16}ON_2S$
VIf	60	80—81	0,65	—	2—C_6H_{13}	233	5,03	276	4,78	$C_{14}H_{18}ON_2S$
VIg	75	70—72	0,71	—	2—C_7H_{15}	233	4,13	276	4,38	$C_{15}H_{20}ON_2S$
VII	46	230	0,62	192	1—CH_3	220	4,28	291	4,48	$C_9H_8ON_2S$
VIII	85	248—250‡	0,53	192	3—CH_3	219	4,19	293	4,32	$C_9H_8ON_2S$
IX	79	79—80	0,77	206	2,3—$(CH_3)_2$	223	4,48	267	3,85	$C_{10}H_{10}ON_2S$

*R_f values determined on Silufol in the benzene—acetone (4:1) system.
†According to the literature: mp 306°C [20]; 298-300°C [22].
‡According to the literature: mp 260-261°C [35].

The IR spectra of 2-mercapto-4-quinazolone has a strong absorption band of the carbonyl group at 1690 cm^{-1}. For the salts, the band appeared at 1670 cm^{-1}. However, in not one case did we observe the disappearance of this band that is characteristic for a covalent O—M bond [11]. This shows that in the case of these compounds, no coordination of the cation at the oxygen center takes place and therefore the possibility of the formation of the anions (Vc-e) is excluded.

We studied the alkylation of (IV) in the presence of alcoholic solutions of alkalis or that of the sodium salt of 2-mercapto-4-quinazolone by alkyl halides (methyl, ethyl, and heptyl iodides, and propyl, butyl, amyl, and hexyl bromides).

The alkylation of 3-substituted derivatives of 2-mercapto-4-quinazolone with methyl iodide [2] and with amides and piperazides of chloroacetic acid [27-29] is known and there are two publications on the alkylation of 6(7)-chloro-(IV) [18] and also of (IV) and its 6,8-dibromo derivative with dibromoethane or chloroacetic acid [30]. In all cases, only the S-alkyl product was formed.

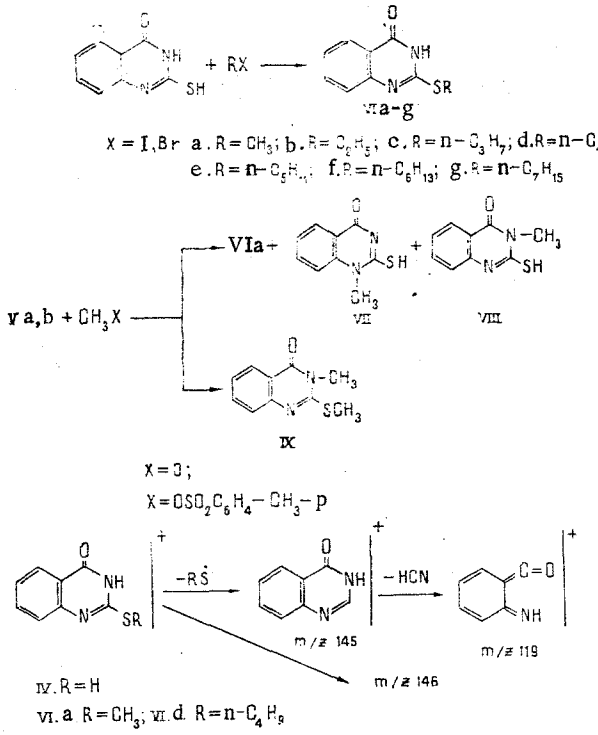


The results of our investigations have shown that the alkylation of (IV) with alkyl halides in ethanolic solution in the presence of equivalent amounts of alkalis likewise leads to alkylthio-4-quinazolones (see Table 1).

In contrast to other alkyl halides on the alkylation of 2-mercapto-4-quinazolone with methyl iodide, in addition to (VIa) 3-methyl-2-methylthio-4-quinazolone (IX) (4%) was formed. Similar results were obtained in the alkylation of the sodium salt of 2-mercapto-4-quinazolone by methyl iodide in dimethylformamide. The alkylation of the same salt with methyl

tosylate under similar conditions gave, in addition to (VIa) (73%), 2-mercapto-3-methyl-4-quinazolone (VIII) (12%), 2-mercapto-1-methyl-4-quinazolone (VII) (3%), and 3-methyl-2-methylthio-4-quinazolone (IX) (12%).

The formation of S-alkyl-substituted derivatives in the alkylation of salts of 2-mercapto-4-quinazolone in ethanolic solutions is due to the selectivity of the solvation of the hard center of the anion — the nitrogen atom — and the reaction takes place at the sulfur atom. This is in harmony with literature information for other heterocyclic systems [12]. In the case of the aprotic polar solvent dimethylformamide, however, the free anion is formed which, as was expected, can react at both reaction centers, as is observed in practice.



Thus, on the basis of the results obtained it may be considered that the anion of 2-mercapto-4-quinazolone exhibits dual reactivity.

The structures of the compounds synthesized were shown by IR, PMR, UV, and mass spectroscopy, and also by their independent synthesis. Thus, 2-mercapto-1-methyl-4-quinazolone was obtained from N-methylanthranilic acid and potassium thiocyanate, while 2-mercapto-3-methyl-4-quinazolone was obtained from anthranilic acid and methyl isothiocyanate.

The methylation of 2-methylthio-4-quinazolone (VIa) formed 3-methyl-2-methylthio-4-quinazolone (IX). Compound (IX) was also obtained by the alklation of (VIII) with methyl iodide.

The IR spectrum of the 2-alkylthio-4-quinazolones exhibits an absorption band at 1670-1685 cm^{-1}. The carbonyl group of 2-mercapto-1-methyl-4-quinazolone absorbs in the region of 1697 cm^{-1} and that of 2-mercapto-3-methyl-4-quinazolone at 1690 cm^{-1}.

The UV spectra of (VIa-e) each have two absorption maxima with λ_{max} 231 and 275 nm, while the initial 2-mercapto-4-quinazolone, its salts, and its 1-methyl, 3-methyl, and 1,3-dimethyl derivatives absorb at 219 and 293 nm. These results show that in ethanolic solution 2-mercapto-4-quinazoline and its 1- and 3-methyl derivatives exist in the thione form.

In the PMR spectrum of 2-methylthio-4-quinazolone, the signals of the protons of the methyl group appear at 2.58 ppm (3 H, singlet); for 2-mercapto-3-methyl-4-quinazolone the protons of the methyl group give signals in the 3.35 ppm region (3 H, singlet), and for 2-mercapto-1-methyl-4-quinazolone signals at 3.70 ppm (3 H, singlet). The values of the chemical shifts of the protons of the methyl group for 3-methyl-2-methylthio-4-quinazolone amount to 2.55 ppm (3 H, singlet, S—CH_3) and 3.35 ppm (3 H, singlet, N—CH_3).

In the mass spectra of compounds (IV) and (VIa), the peaks of the molecular ions have the maximum intensities. In the spectra of (IV) and (VIa and d) there are the peaks of ions with m/z 145 and 119, corresponding to the splitting out of the RS and RSCN fragments from M^+. For compounds (VIa and d), in addition to [M – RS] the presence of a fragment with m/z 146 $[M - RCHS]^+$ is characteristic.

A similar phenomenon has also been detected in the spectra of other classes of heterocyclic compounds: 2-methylthiopyridine [31], benzothiazole [32], and 6-methylthiopurine [33]. The fragmentation of compounds (IV, IVa and d, VII, and VIII) with the formation of the peak of an ion with m/z 119 [m/z 133 for (VII)], is also observed in the case of O-substituted benzyllactams [34]. In the spectrum of (VId), in the region of high mass numbers there are peaks m/z 205, 192, 179, and 178 relating to the fragmentation of the alkyl group.

A study of the fungicidal activities of the compounds synthesized showed that their anti-wilt activity depends on the position of the substituents and the numbers of carbon atoms in the alkyl groups. Thus, while 2-methylthio-4-quinazolone suppresses the growth of the fungi *Verticillium dahliae*, *Fusarium oxysporium*, and *Rizoctoniae solani* by 35, 30, and 33%, respectively, the percentage suppressions of these test fungi for its ethyl analog were 70, 50, and 57%, respectively. A further increase in the length of the alkyl radical led to a decrease in activity. 2-Mercapto-3-methyl-4-quinazolone exhibits a moderate activity, but its isomer — 2-mercapto-1-4-quinazolone — like the initial 2-mercapto-4-quinazolone and its sodium and potassium salts, do not possess this property.

EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer in tablets molded with KBr; UV spectra on a Hitachi EPS-3T spectrometer (solvent ethanol), mass spectra on a MKh-1303 mass spectrometer; and PMR spectra on a JNH-4H-100 instrument (with HMDS as internal standard). The results of elementary analyses of the previously unknown compounds corresponded to the calculated figures.

Synthesis of 2-Mercapto-4-quinazolone (IV). A solution of 1.37 g (10 mmole) of (I) and 0.97 g (10 mmole) of (IIIa) in 9 ml of glacial acetic acid was boiled for 2 h. The crystals that deposited when water was added were separated off and recrystallized from ethanol. This gave 1 g (56%) of (IV) with mp 298-300°C.

Synthesis of the Sodium Salt of 2-Mercapto-4-quinazolone. A mixture of 0.89 g (5 mmole) of (IV) and 0.27 g (5 mmole) of sodium methanolate in 30 ml of absolute methanol was heated in the water bath for 2.5 h. The solvent was distilled off a rotary evaporator, and the residue was dried in a vacuum desiccator over P_2O_5. This gave 1 g (100%) of the sodium salt of 2-mercapto-4-quinazolone.

Potassium Salt of 2-Mercapto-4-quinazolone. A solution of 0.33 g (5 mmole) of caustic potash in methanol was added to a solution of 0.89 g (5 mmole) of (IV) in absolute dioxane, and the mixture was heated in the water bath for 1 h. The product was worked up in a similar manner to that described above. Yield quantitative.

Synthesis of the Triethylammonium Salt of 2-Mercapto-4-quinazolone. A mixture of 8.9 g (50 mmole) of (IV) and 5.05 g (50 mmole) of triethylamine in 100 ml of absolute dioxane was heated on the water bath for 1 h.

By a procedure similar to that described above, 13.8 g (quantitative yield) of the triethylammonium salt (IV) was obtained.

Lithium Salt of 2-Mercapto-4-quinazolone. With stirring, 8.9 g (50 mmole) of (IV) was added to 0.39 g (50 mmole) of lithium hydride in 150 ml of absolute ether, and this mixture was heated for 1 h. Then the ether was distilled off, giving 9.1 g (100%) of the lithium salt of 2-mercapto-4-quinazolone.

2-Mercapto-3-methyl-4-quinazolone (VIII). A solution of 1 g (7.3 mmole) of (I) in 10 ml of absolute ethanol was treated with 0.5 g (6.8 mmole) of methyl isothiocyanate. The reaction mixture was heated in the water bath for 2 h, and then the crystals that had deposited were filtered off and recrystallized from ethanol. This gave 1.11 g (85%) of (VIII) with mp 248-250°C, R_f 0.53 (Al_2O_3; chloroform).

Compound (VIII) was also synthesized by a simplified method [35]. A solution of 1.0 g (7.3 mmole) of (I) and 0.5 g (7 mmole) of methyl isothiocyanate in 3 ml of acetic acid was

boiled for 2 h. The crystals that deposited on cooling were filtered off and recrystallized from ethanol. Yield of (VIII), 9.72 g (55%), mp 250-252°C.

Synthesis of 2-Methylthio-4-quinazolone (VIa). A solution of 1.12 g of caustic potash in 20 ml of ethanol was added to a suspension of 3.56 g (20 mmole) of (IV) in 100 ml of ethanol. The solution so obtained was treated with 1.24 ml (20 mmole) of methyl iodide. The reaction mixture was boiled for 6 h and cooled, and the crystals that had deposited were filtered off and washed with ethanol. This gave 0.89 g of (VIa). The filtrate was diluted with water and extracted with chloroform, and the extract was dried with sodium sulfate and evaporated. The crude mixture obtained (1.56 g) was passed through a column of alumina with elution first by 200 ml of chloroform and then by 200 ml of chloroform–ethanol 0.77 (1:1). This gave 0.15 g (4%) of 3-methyl-2-methylthio-4-quinazolone with mp 78-79°C, R_f (Al_2O_3, chloroform), and 1.21 g of (VIa). The total yield of 2-methylthio-4-quinazolone was 2.1 g (24%), mp 210°C, R_f 0.57 (Al_2O_3, chloroform).

The alkylation of 2-mercapto-4-quinazolone with ethyl and heptyl iodides and with propyl, butyl, amyl, and hexyl bromides was performed similarly (see Table 1).

Synthesis of 2-Mercaptothio-1-methyl-4-quinazolone (VII). To a mixture of N-methylanthranilic acid (3.02 g, 20 mmole) and (IIIa) (2.0 g, 20 mmole) were added 10 ml of n-butanol and 6 ml of hydrochloric acid. The mixture was boiled for 3 h and cooled, and the crystals that had deposited were filtered off, washed with water, and recrystallized from ethanol. The yield of (VII) was 1.42 g (37%), mp 230-232°C.

Methylation of the Sodium Salt of (IV) with Methyl Tosylate. To a solution of 0.1 g (5 mmole) of the sodium salt of 2-mercapto-4-quinazolone in 10 ml of absolute dimethylformamide was added 0.95 g (5 mmole) of methyl tosylate. The reaction mixture was heated on the water bath at 95°C for 5 h and was then poured into 50 ml of cold water. The precipitate that deposited was filtered off, washed with 50 ml of water, and dried in a vacuum desiccator over P_2O_5. This gave 0.5 g of a mixture of 2-mercapto-1- and -3-methyl-4-quinazolones and 2-methylthio-4-quinazolone. The passage of this mixture through a column of alumina (with chloroform–ethanol (1:1) as eluent) yielded 0.04 g (12%) of 3-methyl-2-methylthio-4-quinazolone (mp 78-79°C), 0.04 g (12%) of 2-mercapto-3-methyl-4-quinazolone (mp 248-250°C), 0.01 g (3%) of 2-mercapto-1-methyl-4-quinazolone (mp 230-232°C), and 0.23 g (73%) of 2-methylthio-4-quinazolone (mp 210-211°C).

CONCLUSION

1. The alkylation of anions of 2-mercapto-4-quinazolone with alkyl halides has been studied. It has been found that the direction of the reaction depends on the nature of the alkylating agent and of the solvent. It has been found that the anion of 2-mercapto-4-quinazolone exhibits dual reactivity.

2. It has been shown that in ethanolic solution 2-mercapto-4-quinazolone and 2-mercapto-1- and -3-methyl-4-quinazolones exist in the thione form.

3. A study of the biological activities of the 1- and 2-methyl, 2,3-dimethyl, and 2-alkyl derivatives of 2-mercapto-4-quinazolone has shown that they possess a moderate antiwilt action. It has been found that their fungicidal activity depends on the position of the alkyl group.

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