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Synthesis of 3-Methylquinazolin-4(3*H*)-one Derivatives

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Abstract—Oxidation of 3-methyl-2-sulfanylquinazolin-4(3*H*)-one with chlorine dioxide under different conditions gave 2,2′-disulfanediylbis[3-methylquinazolin-4(3*H*)-one], 3-methyl-4-oxo-3,4-dihydroquinazoline-2-sulfonic acid, 3-methylquinazoline-2,4(1*H*,3*H*)-dione, 6-chloro-3-methylquinazoline-2,4(1*H*,3*H*)-dione, and *N*,*N*-diethyl-3-methyl-4-oxo-3,4-dihydroquinazoline-2-sulfonamide.

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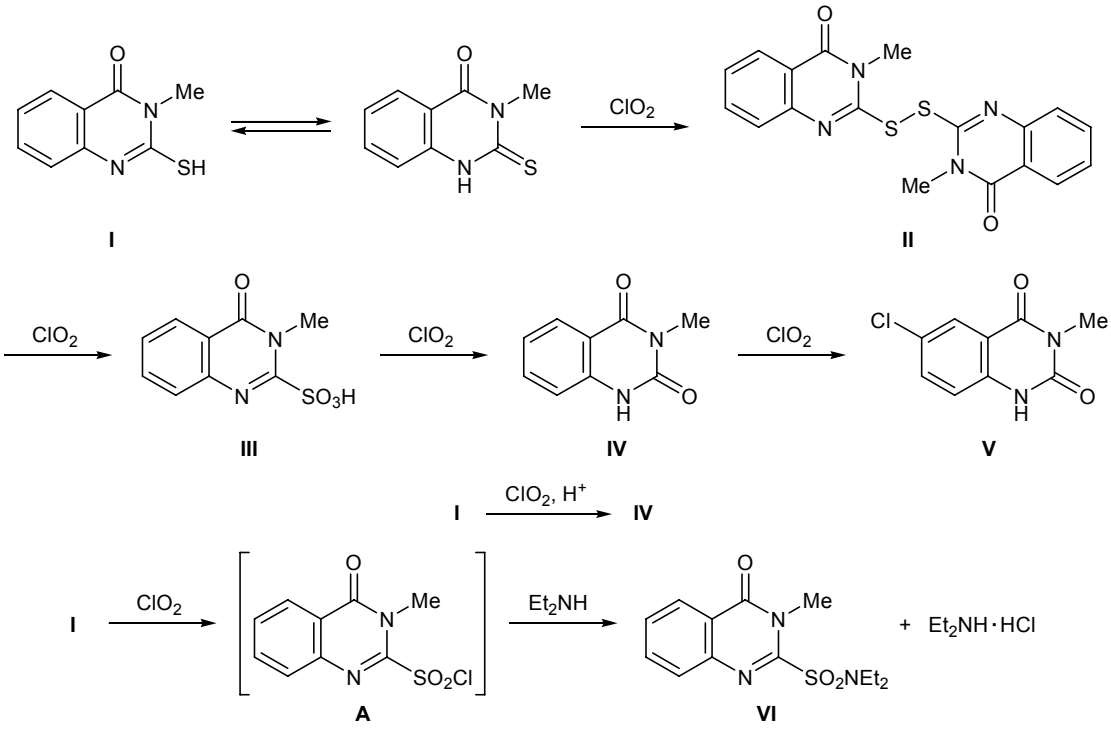
Quinazoline alkaloids exhibit a broad spectrum of pharmacological activity, in particular anti-choline esterase, antimalarial, choleretic, bronchodilator, soporific, diuretic, etc. [1]. Physiological activity of quinazoline derivatives is primarily determined by the nature of substituents in their molecules; therefore, introduction of new functional groups thereinto attracts strong interest from both medical and chemical viewpoints. Oxidative transformations of heterocyclic compounds may be regarded as most interesting ways of their modification.

In the present work we used 3-methyl-2-sulfanylquinazolin-4(3*H*)-one (**I**) containing a structural fragment intrinsic to quinazoline alkaloids to study the possibility for obtaining new derivatives via its oxidation with chlorine dioxide. The latter is produced on a large scale for bleaching of cellulose and decontamination of water and was shown to be a convenient and efficient oxidant ensuring transformation of alkane- and arenethiols into disulfides [2], *S*-alkyl thiosulfonates [3], and sulfonyl chlorides [4]. Oxidation of heterocyclic thiols with ClO_2 was not studied.

Unlike alkane- and arenethiols, heterocyclic thiols are characterized by diverse chemical properties due to their ability to undergo thiol–thione tautomerism. The state of tautomeric equilibrium depends on the solvent nature [5]; therefore, we examined the composition of oxidation products of heterocyclic thiol **I** with chlorine dioxide, obtained under different conditions (solvent, reactant molar ratio, catalyst). As solvents we used benzene, acetic acid, acetonitrile, methanol, pyridine, and diethylamine. Chlorine dioxide in a mixture with atmospheric air was bubbled through the reaction mixture. Taking into account that alkaline medium favors transformation of thione isomer into thiol [5], potassium hydroxide was added. Furthermore, addition of alkali considerably improved the solubility of thiol **I** in methanol. Compound **I** is poorly soluble in most accessible solvents, except for DMSO. Vanadium catalyst $VO(acac)_2$ was used to increase the rate of oxidation and selectivity of the process; this catalyst turned out to be efficient in the oxidation with chlorine dioxide of sulfoxides to sulfones [6] and of diphenyl disulfide to benzenesulfonyl chloride [4]. In order to identify some new compounds, thiol **I** was also oxidized under analogous conditions with iodine which is known to selectively oxidize thiols to disulfides [7]. The product composition and ratio were analyzed by ^{1}H NMR spectroscopy on the basis of signal intensities of the 5-H, 6-H, 7-H, and 8-H protons (see table).

The oxidation of **I** with chlorine dioxide in methanol gave 2,2′-disulfanediylbis[3-methylquinazoline-4(3*H*)-one] (**II**) (Scheme 1). Addition of an equimolar amount of potassium hydroxide allowed us to raise the yield of disulfide **II** from 42 to 65% and reduce the consumption of chlorine dioxide by half (from 1 to 0.5 mol, the conversion of thiol **I** being complete; see table). The oxidation of **I** in methanol with 5 equiv of iodine in neutral and alkaline media also afforded disulfide **II** in the same yields as with chlorine dioxide,

Scheme 1.



but the conversion of compound **I** did not exceed 66%. The ^{1}H NMR spectrum of **II** lacked NH signal (δ 12.95 ppm) typical of the thione tautomer of the initial compound. In the ^{13}C NMR spectrum of **II**, the C^2 signal was displaced upfield (δ_C 152.97 ppm) relative to the corresponding signal of thiol **I** (δ_C 175.41 ppm). Compound **II** displayed no C=S absorption band at 1001 cm^{-1} in the IR spectrum, but a band typical of C–S bond appeared at 690 cm^{-1}.

3,4-Dihydro-3-methyl-4-oxoquinazoline-2-sulfonic acid (**III**) was obtained when compound **I** was oxidized with chlorine dioxide in benzene and pyridine at a substrate-to-oxidant molar ratio of 1:3. The IR spectrum of the product contained absorption bands at 1255, 1226, and 1049 cm^{-1} due to symmetric and antisymmetric stretching vibrations of the SO_2 group. In the ^{13}C NMR spectrum of **III** the C^2 signal was located in a weaker field (δ_C 157.24 ppm) relative to the C^2 signal of **II** (δ_C 152.97 ppm). The relative concentration of sulfonic acid **III** in the reaction mixture ranged from 30 to 45%, depending on he conditions.

Only traces of **III** were present in the reaction mixtures obtained using acetic acid and methanol as solvent. The reason is its easy quantitative transformation into 3-methylquinazoline-2,4(1*H*,3*H*)-dione (**IV**). In the oxidation of **I** with 2 equiv of ClO_2 in acetic acid, quinazolinedione **IV** was formed as the only product (according to the ^{1}H NMR data). Unlike initial thiol **I**, two carbonyl absorption bands were observed in the IR spectrum of **IV** (1689 and 1718 cm^{-1}).

A mixture of dione **IV** and 6-chloro-3-methylquinazoline-2,4(1*H*,3*H*)-dione (**V**) at a ratio of ~2:1 was obtained by oxidation of **I** with 4 equiv of ClO_2 in acetonitrile; in the presence of $VO(acac)_2$ as catalyst, the ratio **IV**:**V** changed to 8:1. Dione **V** was formed as the major product (85% in the product mixture) when catalytic oxidation was carried out with the use of 7 equiv of chlorine dioxide. The position of chlorine in the quinazoline ring (on C^6) was determined by two-dimensional NMR spectroscopy. The C^6 signal in the ^{13}C NMR spectrum of **IV** appeared at δ_C 122 ppm, while in the spectrum of **V**, at δ_C 126 ppm due to electron-withdrawing effect of the 6-Cl atom.

As basic solvents we tried pyridine and diethylamine. The oxidation of **I** with 3 equiv of ClO_2 in diethylamine at –10°C produced 52% of *N,N*-diethyl-3-methyl-4-oxo-3,4-dihydroquinazoline-2-sulfonamide (**VI**). The IR spectrum of **VI** contained absorption bands belonging to stretching vibrations of the SO_2 group (1172, 1377 cm^{-1}), and the C^2 nucleus in **VI** resonated in a weaker field (δ_C 160.62 ppm) as compared to **II**. The reaction is likely to involve intermediate formation of sulfonyl chloride **A**. However, we failed to isolate it as individual substance in any sol-

Oxidation of 3-methyl-2-sulfanylquinazolin-4(3*H*)-one (**I**) with chlorine dioxide and iodine

Solvent	Oxidant [O]	Other reagents	Ratio **I** : [O]	Conversion of **I**, %	Product ratio, % (^{1}H NMR data)			
					II	**III**	**IV**	**V**
Benzene	ClO_2	–	1 : 3	100	–	43	57	–
Pyridine	ClO_2	–	1 : 2	19	–	14	5	–
	ClO_2	–	1 : 3	100	–	32	68	–
Acetic acid	ClO_2	–	1 : 2	100	–	–	100	–
Acetonitrile	ClO_2	–	1 : 2	52	–	19	23	10
	ClO_2	–	1 : 4	100	–	9	57	34
	ClO_2	$VO(acac)_2$	1 : 4	100	–	12	78	10
	ClO_2	$VO(acac)_2$	1 : 7	100	–	12	–	88
Methanol	ClO_2	–	1 : 1	92	42	–	50	–
	ClO_2	KOH	1 : 0.5	100	65	–	35	–
	ClO_2	–	1 : 2	100	–	11	89	–
	I_2	–	1 : 1	0	–	–	–	–
	I_2	–	1 : 5	39	39	–	–	–
	I_2	KOH	1 : 5	66	66	–	–	–

vent, presumably because of its instability. Pyridine lacks labile NH hydrogen atom; therefore, the oxidation of **I** with ClO_2 in pyridine was not accompanied by addition of pyridine molecule to the substrate, but a mixture of compounds **III** and **IV** was formed at a ratio of ~1 : 2.

To conclude, we have synthesized new compounds **II**, **III**, and **VI**, as well as previously described quinazolinediones **IV** and **V**, by oxidation of 3-methyl-2-sulfanylquinazolin-4(3*H*)-one (**I**) with chlorine dioxide. The oxidation of **I** with ClO_2 in neutral and alkaline media gives disulfide **II** and sulfonic acid **III** in moderate yields; the reactions in acid or strongly polar media lead to dione **IV**, while in acetonitrile, to dione **V**, in quantitative yield. The use of $VO(acac)_2$ as catalyst hampers chlorination in the initial steps but favors stepwise formation of compounds **IV** and **V**.

EXPERIMENTAL

The IR spectra were recorded from thin films or KBr pellets on a Shimadzu IR Prestige 21 spectrometer with Fourier transform. The melting points were measured on a Gallenkamp-Sanyo melting point apparatus. The ^{1}H and ^{13}C NMR spectra were run on a Bruker Avance-II-300 instrument at 300.17 and 75.42 MHz, respectively. The elemental compositions were determined using an EA 1110 CHNS-O automatic analyzer.

3-Methyl-2-sulfanylquinazoline-4(3*H*)-one (purity 99%) was synthesized at the *Vekton* closed corporation. Aqueous chlorine dioxide was a commercial product; its concentration was determined by titration according to the procedure described in [8].

2,2′-Disulfanediylbis[3-methylquinazolin-4(3*H*)-one] (II). *a*. Potassium hydroxide, 0.029 g (0.5 mmol), was added to a solution of 0.1 g (0.5 mmol) of thiol **I** in 40 ml of methanol, the mixture was stirred at room temperature until it became homogeneous, and 0.018 g (0.25 mmol) of chlorine dioxide (dried by passing through gas-washing bottles charged with concentrated sulfuric acid and calcium chloride) in a mixture with air was bubbled through the solution over a period of 30 min. A white solid precipitated and was filtered off, washed with methanol, and dried in air. Yield 0.065 g (65%). IR spectrum ν, cm^{-1}: 3433 br.w, 2939–3066 w, 1697 s (C=O), 1609 w, 1580 w, 1551 s, 1472 s, 1412, 1317 s, 1115 w, 1065 s, 771 s, 690. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.93 s (3H, NCH_3), 7.43 d.d.d (1H, 6-H, J = 8.3, 8.0, 1.3 Hz), 7.53 d.d (1H, 8-H, J = 7.0, 1.3 Hz), 7.69 d.d.d (1H, 7-H, J = 8.3, 7.0, 1.4 Hz), 8.25 d.d (1H, 5-H, J = 8.0, 1.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 31.04 (NCH_3), 119.57 (C^{4a}), 126.70 (C^6, C^8), 127.07 (C^5), 134.47 (C^7), 147.07 (C^{8a}), 152.97 (C^2), 161.85 (C^4). Found, %: C 56.40; H 3.63; N 14.50; S 16.74. $C_{18}H_{14}N_4O_2S_2$. Calculated, %: C 56.53; H 3.69; N 14.65; S 16.77.

b. Potassium hydroxide, 0.029 g (0.5 mmol), was added to a solution of 0.1 g (0.5 mmol) of thiol **I** in 10 ml of methanol, the mixture was stirred at room

temperature until it became homogeneous, a solution of 0.66 g (2.5 mmol) of iodine in 30 ml of methanol was added dropwise over a period of 30 min, and the mixture was stirred for 15 min more. The white precipitate was filtered off, washed with methanol, and dried in air. Yield 0.066 g (66%).

3-Methyl-4-oxo-3,4-dihydroquinazoline-2-sulfonic acid (III). *c*. Chlorine dioxide, 0.11 g (1.5 mmol), in a mixture with air was bubbled over a period of 1.5 h through a solution of 0.1 g (0.5 mmol) of thiol **I** in 60 ml of benzene. The mixture was evaporated under reduced pressure, the residue was washed with water, and the precipitate was filtered off and dried. The product was a mixture of compounds **III** and **IV** (fraction of **III** 45% according to the ^{1}H NMR data). The IR and NMR spectral parameters were identified from the spectra of its mixture with **IV**. IR spectrum (KBr), ν, cm^{-1}: 3404 br.w, 2981–3180, 1708 s (C=O), 1639 s (C=N), 1570, 1531, 1485, 1282 (C–N), 1255 s (SO_2), 1226 s (SO_2), 1049 s (SO_2), 972, 817, 763, 648, 634. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.56 s (3H, NCH_3), 7.63–7.68 m (1H, 6-H), 7.74 d (1H, 8-H, J = 8.22 Hz), 7.89–7.95 m (1H, 7-H), 8.21 d (1H, 5-H, J = 7.93 Hz), 8.82 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 34.15 (NCH_3), 120.75 (C^{4a}), 124.60 (C^6), 126.25 (C^8), 127.75 (C^5), 134.92 (C^7), 144.53 (C^{8a}), 157.24 (C^2), 159.95 (C^4).

3-Methylquinazoline-2,4(1*H*,3*H*)-dione (IV) was synthesized according to the procedure described above in *c* using glacial acetic acid (20 ml) as solvent and 0.070 g (1.0 mmol) of chlorine dioxide; reaction time 1 h. The solvent was removed under reduced pressure, and the dry residue was washed with a saturated solution of sodium hydrogen carbonate to neutralize residual acid and dried under reduced pressure. Yield 0.084 g (92%), mp 242–243°C (from DMSO, H_2O); published data [9]: mp 242–243.4°C.

6-Chloro-3-methylquinazoline-2,4(1*H*,3*H*)-dione (V). *d*. Thiol **I**, 0.1 g (0.5 mmol), was dissolved in 30 ml of acetonitrile, 0.007 g (5 mol %) of $VO(acac)_2$ was added, and the mixture was stirred on a magnetic stirrer until it became homogeneous. Chlorine dioxide, 0.25 g (3.5 mmol), in a mixture with air was bubbled through the solution over a period of 4 h. The solvent was removed under reduced pressure, and the residue was recrystallized from DMSO and water. Yield 0.089 g (81%), light yellow solid, mp 268–271°C (from DMSO, H_2O); published data [10]: mp 271–273°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.21 s (3H, NCH_3), 7.15 d (1H, 8-H, J = 7.92 Hz), 7.62 d (1H, 7-H, J = 7.56 Hz), 7.74 s (1H, 5-H), 11.51 s (NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.22 (NCH_3), 115.03 (C^{4a}), 117.40 (C^8), 126.15 (C^5), 126.44 (C^6), 134.72 (C^7), 138.20 (C^{8a}), 150.11 (C^2), 161.22 (C^4).

***N*,*N*-Diethyl-3-methyl-4-oxo-3,4-dihydroquinazoline-2-sulfonamide (VI)** was synthesized according to the procedure described above in *c* using diethylamine (25 ml) as solvent and 0.070 g (1 mmol) of chlorine dioxide (10°C, 45 min). The precipitate of diethylamine hydrochloride was filtered off, most part of the filtrate was evaporated under reduced pressure, and the residue was extracted with methylene chloride. The extract was evaporated, and the residue was recrystallized from DMSO and H_2O. Yield 0.080 g (52%), white flakes. IR spectrum (KBr), ν, cm^{-1}: 1678 (C=O), 1377, 1172 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 t (6H, CH_2CH_3), 3.37 s (3H, NCH_3), 3.50 br.m (4H, CH_2CH_3), 7.43 t (1H, 6-H, J = 7.04 Hz), 7.51 d (1H, 8-H, J = 8.05 Hz), 7.77 t (1H, 7-H, J = 7.08 Hz), 8.07 d.d (1H, 5-H, J = 7.95, 1.39 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.32 (CH_2CH_3), 28.48 (NCH_3), 50.24 (CH_2CH_3), 118.73 (C^{4a}), 125.51 (C^6), 126.17 (C^8), 126.27 (C^5), 134.36 (C^7), 146.87 (C^{8a}), 160.62 (C^2), 160.83 (C^4). Found, %: C 53.08; H 6.07; N 14.70; S 11.10. $C_{13}H_{14}N_4O_3S$. Calculated, %: C 52.87; H 5.80; N 14.23; S 10.86.

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