HETEROCYCLES, Vol. 57, No. 11, 2002, pp. 2035 - 2044, Received, 8th July, 2002

THE PREPARATION OF THE STABLE TAUTOMERS OF 4-MERCAPTO-3-QUINOLINESULFONIC AND 1,4-DIHYDRO-4-THIOXO-3-QUINOLINE-SULFONIC ACIDS *

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Abstract - The reaction of 4-chloro-3-quinolinesulfonic acid (**3)** with sodium hydrosulfide gives the sodium salt of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4**) and 4-mercapto-3-quinolinesulfonic acid (**4b**). The acidification of aqueous solution of the sodium salt of **4** results in 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4a**). It has been found that in the DMSO solution tautomer (**4a**) converts into tautomer (**4b**). The X-Ray analysis of tautomer (**4a**) indicates that it appeared in a form of betaine (**4c**).

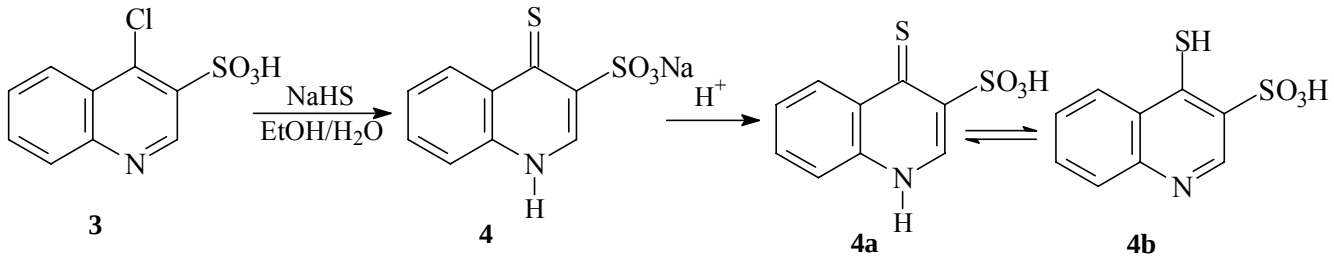
INTRODUCTION

4-Chloro-3-quinolinesulfonylchloride (**2**), which can be obtained in a two step synthesis starting from quinoline *via* thioquinanthrene (**1**),[1] was used to synthesize many 4-mono-, 3,4-di- and 1,3,4-trisubstituted quinolines. [1-5] Biological activity of these compounds stimulated the investigations in this field. [6,7] The large number of the analogues obtained allows the observation of interesting spectroscopic regularities (^{1}H NMR spectrometry).

We hoped that the synthesis of new analogues of this type would contribute to our knowledge of the tautomeric behavior of these compounds. Thus, we aimed for the synthesis of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4a**) starting from 4-chloro-3-quinolinesulfonic acid (**3**) which can be obtained from sulfonyl chloride (**2**).[5]

RESULTS AND DISCUSSION

The reaction of 4-chloro-3-quinolinesulfonic acid (**3**) with sodium hydrosulfide gives the sodium salt of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4a**) or 4-mercapto-3-quinolinesulfonic acid (**4b**). We also obtained sodium salt (**4**) that separated during the reaction.

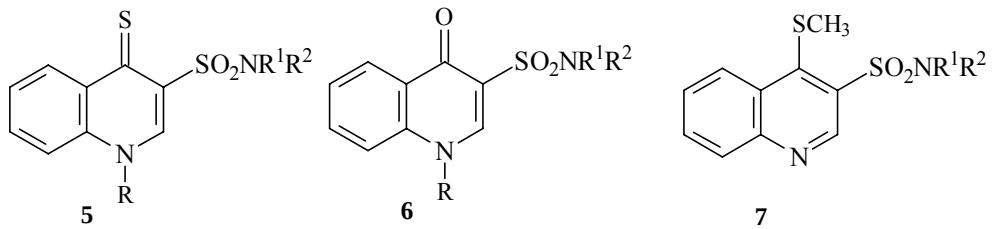


3 **4** **4a** **4b**

Elemental analysis and MS FAB spectrum proved the structure of the product. However, ^{1}H NMR spectral data did not agree with the anticipated product indicating that a separated product most probably takes a tautomeric 4-mercapto form (**4b**) than a thione form (**4a**).

It is well known that 2- or 4-hydroxyquinolines and pyridines take the form of quinolones and pyridones. Sulfur analogues behave similarly, however, it was observed that for oxo and thioxo tautomers ionic structures make an important contribution. [8] The dominating share of tautomers of this type was also proved by the nitrogen NMR spectra. [9,10] The tautomerism of 3- and 4-substituted quinolinethiones can also be studied using ^{1}H NMR spectrum. In this particular case, the most informative is chemical shifts of the H-2 and H-5 protons. The H-5 proton resonates at a different frequency depending on the substituent located in position 4 (*peri* effect), while the substituent on the quinoline nitrogen affects the chemical shift of the H-2 proton (*ortho* effect) and to a minor degree also the substituent in 4-position (*meta* effect). Table 1 compares the chemical shifts of the H-2 and H-5 protons in the compounds synthesized with these of the 1,4-dihydro-4-thioxo-3-quinolinesulfonamides (**5**), their oxygen analogues (**6**) and 4-methylthio-3-quinolinesulfonamides (**7**).

The similarity of the substituents in the position 3 (-SO_2X) of all of the aforementioned analogues is a key factor in enabling such a comparison. Furthermore, it was demonstrated earlier that the type of the X group contributes only to a minor extent to the chemical shifts of the quinoline ring protons.



5 **6** **7**

5a and **5b** for R = H
5b and **6b** for R = alkyl

R^1 = H, Me, Et, Ph $R^1 = R^2$ = morpholide, piperidide
R^2 = H, Me, Et

Table 1. The comparison of the chemical shifts (ppm) of the H-2 and H-5 protons in the ^{1}H NMR spectrum (DMSO-d_6) of the acid (**4b**) and its sodium salt (**4**) with those of the known sulfonamides (**5**, **6**, **7**).

Compounds	n *	$\bar{\delta}$ H-2	$\Delta\delta$ H-2	$\bar{\delta}$ H-5	$\Delta\delta$ H-5
4b	1	9.48	-	8.09	-
7 [11]	5	9.27	0.08	8.61	0.10
4	1	8.84	-	8.59	-
5a [11]	5	8.66	0.06	8.79	0.13
5b [4,5]	7	8.83	0.19	8.92	0.07
6a [2,4]	8	8.59	0.03	8.26	0.09
6b [2,4]	9	8.68	0.12	8.28	0.11

* the number of the compounds analyzed

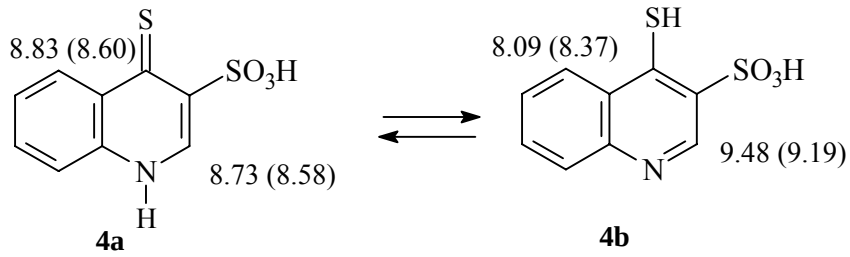
The spectral data given in Table 1 enable us to make following conclusions:

1) Quinolone and quinolinethione form prevails within a group of quinolinethiones (**5**) and quinolones (**6**). This is proved by the similar values of the chemical shifts of the H-2 and H-5 protons in quinolones (**6a** R=H, **6b** R=alkyl), the differences for the individual protons do not exceed 0.1 ppm. Similar differences (max. 0.17 ppm) can be found for these protons in a group of quinolinethiones (**5**), the H-5 protons in compounds (**5**) resonate at lower frequencies than the H-2 protons and the H-5 protons of the compounds (**6**) resonate at higher frequencies than the H-2 protons, which gives the possibility for a clear distinction of the quinolones and quinolinethiones;

2) The comparison of the sulfides (**7**) with quinolinethiones (**5**) indicates that substantial differences can be found within the spectra of the compounds having the substituents at the quinoline nitrogen or sulfur. In comparison to compounds (**5**) that have no substituent at the nitrogen atom, the H-2 protons of the compounds (**7**) resonate at 0.44 and 0.61 ppm downfield (*ortho* effect).

This analysis shows that in DMSO solution the sodium salt of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid takes the form of thione presented by molecular formula (**4**). On the other hand, free acid takes the form of 4-mercapto, namely 4-mercapto-3-quinolinesulfonic acid (**4b**). Nevertheless, this is not enough to prove the existence of the stable tatomeric form of **4b**. It appeared, however, that the thione form given by molecular formula (**4a**) can be separated as the nice orange-brown crystals which can be obtained by acidifing the aqueous solution of sodium salt (**4**). From time to time we observed that a small amount of

tautomer (**4b**) precipitated (yellow crystals). The elemental analysis of the thione form (**4b**) corresponds to the respective formula and the ^{1}H NMR spectrum agrees with the anticipated one (compare Table 1). Figure presented below compares the respective chemical shifts for the H-2 and H-5 protons in the both forms (DMSO-d_6, or D_2O - bracketed numbers).



The analysis of the ^{1}H NMR spectrum (DMSO-d_6) of **4a** tautomer also indicates the chemical shift originating from the **4b** tautomer. It was easy to distinguish H-2 and H-5 protons by comparison and identified the 6% contamination of the 4-mercapto form of **4b**. In order to analyze whether this contamination originated from a simple impurity or from a conversion of tautomeric forms we registered the spectra after 1 h and after 5 d, finding out that 4-mercapto compound (**4b**) amounts to 10% (1 h) and to 88% (5 d) of the mixture. However, this effect was not observed in the aqueous solution (D_2O). Hydrogen bonding between –SH and -SO_3H stabilizes the thiol form **4b** in DMSO. A similar effect was also observed for the esters of 2-alkylthio-4-oxoquinoline-3-carboxylate esters. [12] The hydroxy form dominated for these compounds in inert solvents, while the oxo form prevails in proton solvents.

Surprisingly, the conversion described proved that the 4-mercapto form of **4b** is more stable than the thione form **4a**.

The UV-VIS spectra add further proof for the existence of two stable tautomers.

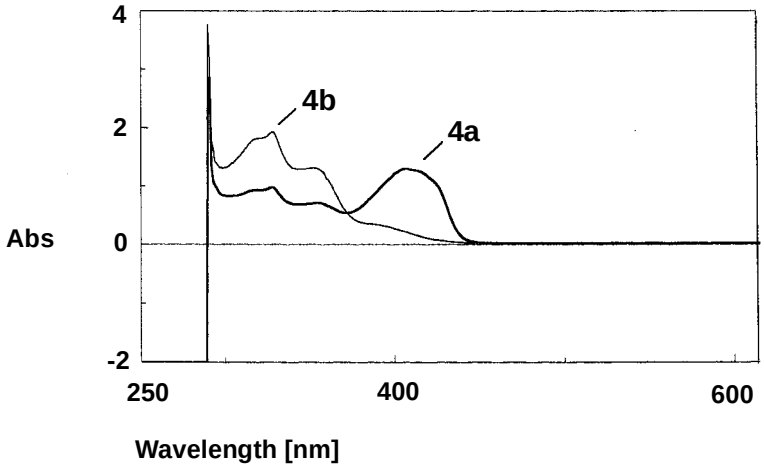
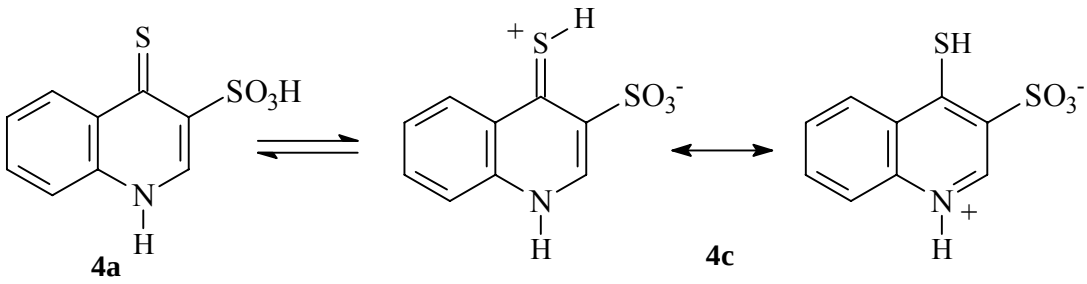


Figure 1. The UV-VIS spectra of **4a** and **4b** tautomers (H_2O).

Both tautomers absorb almost within the same range (UV): λmax 328 nm (abs. 0.916), 355 (abs. 0.716) for tautomer (**4a**) and λmax 328 nm (abs. 1.931), 352 (abs. 1.317) for tautomer (**4b**). However, for the tautomer (**4a**) we observed the absorption band within the visible range at λmax 407 nm (abs. 1.302). The thione group in 2- and 4-quinolinethiones absorbs at *ca*. 400 nm. [13-15] Thus, the above spectra prove the suggested tautomeric structures.

It is worth noticing that tautomer (**4a**) was obtained as nicely formed crystals. Therefore, we performed X-Ray analysis of the crystals. This indicated that in such a form thione (**4a**) creates a structure of betaine that is given by the mesomeric form shown below. Consequently, it can be seen as an intermediate tautomer (**4c**).



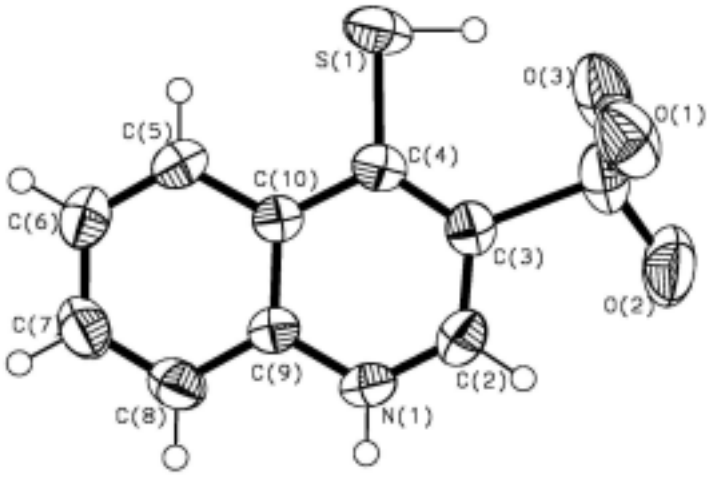


Figure 2. Structure of **4c** in the cryst. bond lenghts (Å):

S(2)-O(3) 1.448(2), S(2)-O(1) 1.440(2), S(2)-O(2) 1.441(3), S(2)-C(3) 1.786(3), S(1)-C(4) 1.739(3), N(1)-C(2) 1.319(3), N(1)-C(9) 1.372(3), C(3)-C(2) 1.383(4), C(3)-C(4) 1.384(4), C(10)-C(9) 1.408(3), C(10)-C(5) 1.413(3), C(10)-C(4) 1.432(3), C(5)-C(6) 1.360(4), C(6)-C(7) 1.391(4), C(8)-C(7) 1.361(4), C(8)-C(9) 1.395(4).

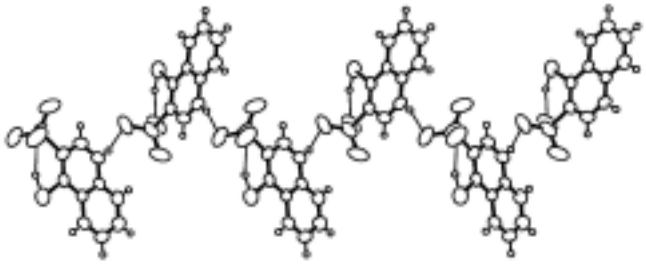


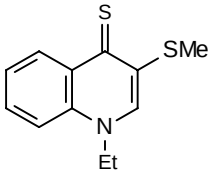
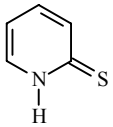
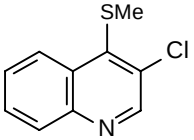
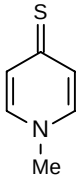
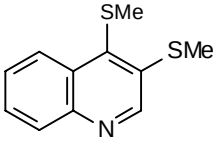
Figure 3. Molecular packing diagram showing intermolecular H-bonds

Table 2. Hydrogen-bonds (Å):

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
S(1)-H(13)···O(3)	1.26(3)	1.92(3)	3.101(3)	153(2)
N(1)-H(1)···O(1)	0.87(3)	1.94(3)	2.777(3)	161(3)

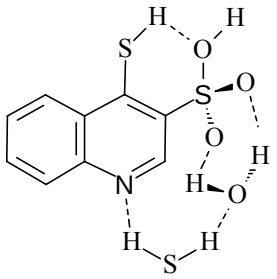
The examination of the tautomerism of the resonance hybrid (**4c**) (=S ↔ -S-H) needs to localize a positive charge, which is very complicated. However, we can achieve this indirectly by the comparison of the bond lengths C(4)-S. In Table below we specified selected X-Ray data for hybrid (**4c**) with the comparable data characterizing the compounds of the most similar structure.

Table 3. The C(4), (2)-S bond lengths (Å) of tautomer (**4c**) was compared with the selected data extracted from the literature.

Compounds	Ref.	C(4), (2)-S (Å)	Compounds	Ref.	C(4)-S (Å)
4c		1.739(2)		18	1.697(4)
	16	1.700(3)		19	1.768(4)
	17	1.697(4)		20	1.777(4)

The data shown in Table 3 indicate that the structure with a positive charge on the sulfur atom makes an important contribution. However, it should be remembered that the bond lengths in tautomer (**4c**) can be modified by the hydrogen bonding, that are formed between the oxygen atom of the sulfonyl group interacting with the S-H proton. This effect can influence the length of the C(4)-SH bond. The importance of the ionic structures in N-substituted pyridinethiones and quinolinethiones has been discussed in the references. [17,18] Probably the X-Ray structure of tautomer (**4b**) should answer these questions, however, as far we were not able to obtain a crystal that can be used to perform such an analysis. In the Cambridge Crystallographic Database we were not able to find any tautomers of pyridine or quinoline containing the 2- or 4-thiol or hydroxy group.

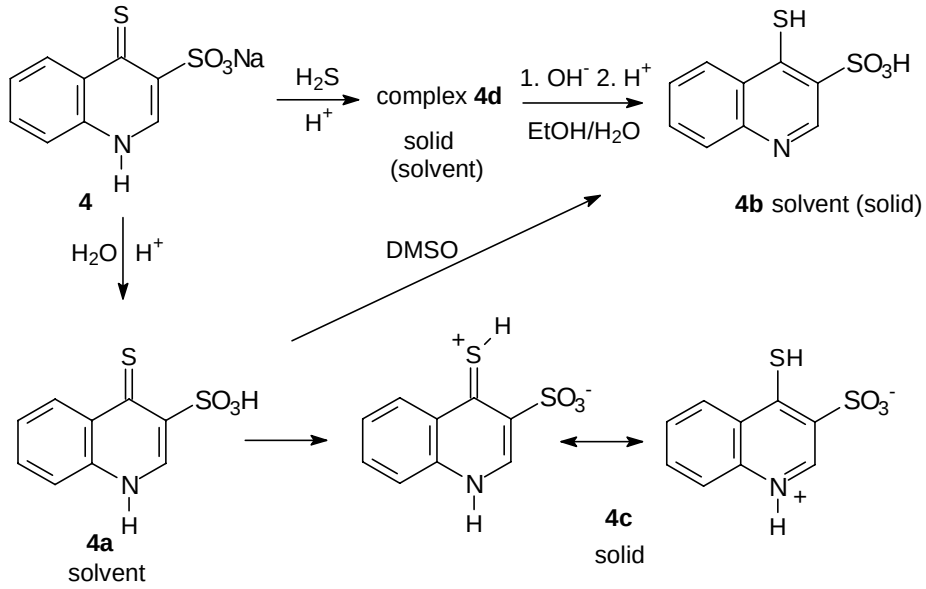
The next question is why tautomer (**4b**) separates from the ethanol-water solution, while tautomer (**4a**) separates from the aqueous solution. We are not able to answer this but we think that the minute difference in the polarity of the ethanol-water and water should not be decisive in this case. In order to prove that salt (**4a**) is dissolved in aqueous-ethanolic solution, we obtained **4a** tautomer after acidification of this solution. Thus, it seems that tautomer (**4b**) is formed by the other type of interactions. We hope that some information can be achieved by the analysis of the compound directly after separation from the reaction mixture of acid (**3**) and sodium hydrosulfide. The mp, ^{1}H NMR and MS spectra of this compound were the same as those of the tautomer (**4b**). However, it has been found that this compound includes a molecule of hydrogen sulfide beside water molecule. Hydrogen sulfide can also be found over the boiling solution of the complex separated. One can speculate the structure of such a complex of **4d**, which can explain a ready formation of tautomer (**4b**).



4d

As a conclusion we can hypothesize that during crystallization a neutral molecule of tautomer (**4a**) converts into the charged form of **4c** that shifts proton to the sulfur atom. The negative charge formed is dispersed on the three electronegative atoms of oxygen in the sulfonic group. Delocalization of positive charge will also be favorable. The charge in hybrid (**4c**) is delocalized from the nitrogen N1 atom *via* the ring to the sulfur atom. Moreover, hybrid (**4c**), if dissolved in aprotic solvent (DMSO), converts into its

normal state by the shifting of hydrogen from sulfur to the sulfonic group converting back to tautomer (**4b**). This is shown in Scheme below.



EXPERIMENTAL

Melting points were determined in open capillary tubes on an electronic mp apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz. FAB MS spectra were recorded on Finnigan MAT spectrometer in FAB mode (Cs+, 13 keV, nba). The spectrophotometric measurements were made using the UV-VIS spectrophotometer JASCO model V-530.

X-Ray data were collected on a Nonius KappaCCD diffractometer. Data collected with 85 frames *via* φ rotation and 23 frames *via* ω rotation (rotation angle 2°) and 2×500 s per frame). 12210 reflections were collected, 1665 unique reflections (R_{int} = 0.019). Diffractometer control program Collect, [21] unit cell parameters and data reduction with Denzo and Scalepak, [22] structure solved by direct methods SHELXS-97 [23] and refined on F^2 by full-matrix least-squares with SHELXL-97, [24] molecular graphics ORTEP-III. [25] All the non-H atoms refined anisotropically and hydrogen atoms were placed in calculated positions and refined using a riding model. Final R factors 0.045 for 1425 observed reflections (I>2\s(I)) and 0.0572 for all 1665 reflections.

Sodium salt of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4**): A solution of sodium hydrosulfide (750 mg, *ca*. 8 mmol) (NaSH x nH_2O) in 50% ethanol (5 mL) was poured into a suspension of 4-chloro-3-quinolinesulfonic acid (**3**) (609 mg, 2.5 mmol) in 50% ethanol (5 mL) and the reaction mixture was stirred for 0.5 h at rt. The separated precipitate was washed with 50% ethanol (2 mL) and recrystallized from ethanol/water (2:1 v/v) to give sodium salt of 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4**) (438 mg, 67%) mp 329-330 ^{o}C (decomp). ^{1}H NMR (DMSO-d_6) δ: 8.82-8.85(m, 1H, **H**5); 8.56(s, 1H, **H**2); 7.67-7.74(m, 2H, **H**8, **H**7); 7.43-7.50(m, 1H, 6**H**); 12.90(s, 1H, N**H**).

4-Mercapto-3-quinolinesulfonic acid (**4b**): A solution of sodium hydrosulfide (750 mg, *ca*. 8 mmol) (NaSH x nH_2O) in 50% ethanol (5 mL) was poured into the suspension of 4-chloro-3-quinolinesulfonic acid (**3**) (609 mg, 2.5 mmol) in 50% ethanol (5 mL) and the reaction mixture was stirred for 0.5 h at rt. The mixture was acidified with 18% hydrochloric acid (4 mL) and the precipitated complex (**4d**) was filtered off mp 233 ^oC (decomp). *Anal*. Calcd for $C_9H_7NO_3S_2$ x H_2O x H_2S: C 36.85, H 3.78, N 4.77, S 32.78. Found: C 36.74, H 3.32, N 4.79, S 33.12. Then acid (**4d**) was dissolved in 5% aqueous sodium hydroxide solution (3 mL) and ethanol was added (3 mL). The solution was acidified with 18% hydrochloric acid (2 mL) and 4-mercapto-3-quinolinesulfonic acid (**4b**) was filtered off (312 mg, 62%), mp 234 ^oC (decomp). MS FAB (-VE), m/z 240(M^+ -1, 86%). ^1H NMR (DMSO-d_6) δ: 9.48(s, 1H, **H**2); 8.08-8.10(m, 1H, **H**5); 7.94-7.97(m, 1H, **H**8); 7.61-7.69(m, 1H, **H**7); 7.26-7.32(m, 1H, **H**6). ^1H NMR (D_2O) δ: 9.19(s, 1H, **H**2); 8.36-8.39(m, 1H, **H**5); 7.98-8.01(m, 1H, **H**8); 7.88-7.93(m, 1H, **H**7); 7.73-7.78(m, 1H, **H**6). *Anal*. Calcd for $C_9H_7NO_3S_2$ x 1/2 H_2O: C 43.19, H 3.22, N 5.60, S 25.62. Found: C 43.37, H 3.20, N 5.51, S 25.42.

1,4-Dihydro-4-thioxo-3-quinolinesulfonic acid (**4a**): Sodium salt of 1,4-dihydro-4-thioxo-3-quinoline-sulfonic acid (**4**) (150 mg, 0.57 mmol) was dissolved in water (2 mL) and acidified with 18% hydrochloric acid (1 mL). After *ca*. 18 h 1,4-dihydro-4-thioxo-3-quinolinesulfonic acid (**4a)** (120 mg, 72%) was filtered off. mp 233 ^oC (decomp). ^1H NMR (DMSO-d_6) δ: 8.77-8.79(m, 1H, **H**5); 8.61(s, 1H, **H**2); 7.61-7.75(m, 2H, **H**8, **H**7); 7.43-7.48(m, 1H, **H**6). ^1H NMR (D_2O) δ: 8.60-8.63(m, 1H, **H**5); 8.58(s, 1H, **H**2); 7.65-7.70(m, 1H, **H**7); 7.44-7.49(m, 2H, **H**8, **H**6). *Anal*. Calcd for $C_9H_7NO_3S_2$ x 1/2 H_2O: C 43.19, H 3.22, N 5.60, S 25.62. Found: C 42.98, H 3.08, N 5.57, S 25.89.

ACKNOWLEDGEMENTS

The autor (L. S.) wish to thank dr K. Pluta from The Medical University of Silesia for his helpful discussion and suggestions.

REFERENCES

* Part LXXII in the series of Azinyl Sulfides.

1. A. Maślankiewicz and L. Skrzypek, *Heterocycles,* 1994, **38**, 1317.
2. L. Skrzypek and A. Maślankiewicz, *Heterocycles,* 1997, **45**, 2015.
3. L. Skrzypek, *Heterocycles,* 1998, **46**, 1249.
4. L. Skrzypek, *Heterocycles,* 1999, **51**, 2111.
5. L. Skrzypek, *Heterocycles*, 1998, **48**, 71.
6. L. Skrzypek, J. Folwarczna, W. Janiec, I. Kaczmarczyk-Sedlak, A. Maślankiewicz, and M. Pytlik,

Polish. J. Chem., 1998, **72**, 1127.
7. R. V. Davies, J. Fraser, and K. J. Nicol, European Pat. 0 206 616 A2, (09.06.1986) (*Chem. Abstr.*, 1987, **107**, P 58881g).
8. C. D. Johnson, 'Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds,' Vol. 2, ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford 1984, p 147.
9. L. Stefaniak, *Tetrahedron*, 1976, **32**, 1065.
10. L. Stefaniak, *Org. Magn. Resonance*, 1979, **12**, 379.
11. L. Skrzypek, unpublishet data.
12. I. T. Hay and P. J. Taylor, *J. Chem. Soc*., 1968, 2656.
13. E. E. Metzler and E. E. Snell, *J. Am. Chem. Soc*., 1955, **77**, 2431.
14. M. Alvarez, M. Salas, L. Rigat, A. Veciana, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1992, 351.
15. A. Albert and G. B. Barlin, *J. Chem. Soc*., 1959, 2384.
16. J. G. Reynolds, S. C. Sendlinger, A. M. Murray, J. C. Huffman, and G. Christou, *Inorg. Chem*., 1995, **34**, 5745.
17. A. Zięba, A. Maślankiewicz, and K. Suwińska, *Acta Cryst.*, 2002, **58**, o32.
18. A. Maślankiewicz, A. Zięba, and K. Suwińska, *J. Chem. Crystallogr.,* 1998, **28**, 701.
19. A. Maślankiewicz, T. Głowiak, H. Chojnacki, L. Skrzypek, and A. Niedbała, *J. Chem. Crystallogr.*, 1995, **25**, 165.
20. A. Maślankiewicz, T. Głowiak, M. Wyszomirski, and L. Skrzypek, *J. Chem. Crystallogr.*, 1995, **25**, 171.
21. B. V. Nonius, "Collect" data collection software, 1998.
22. Z. Otwinowski and W. Minor, 'Methods in Enzymology, Vol. 276: Macromolecular Crystallography, part A', ed. by C.W. Carter, Jr. and R.M. Sweet, Academic Press, 1997, pp. 307-326.
23. G. M. Sheldrick, *Acta Cryst*., 1990, **A46**, 467.
24. G. M. Sheldrick, SHELXL97, Program for the Refinement of Crystal Structures, 1997.
25. M. N. Burnett and C. K. Johnson, 'ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations,' Oak Ridge National Laboratory Report ORNL-6895, 1996.