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SYNTHESIS AND TRANSFORMATIONS OF 2-OXO-2,3-DIHYDRO-(1*H*, 3*H*)-QUINO[4,3-*e*]-1,2,4-THIADIAZINE 4,4-DIOXIDE TO *N*-METHYL-, 2-CHLORO- AND 2-AMINOQUINO[4,3-*e*]-1,2,4-THIADIAZINE 4,4-DIOXIDES[#]

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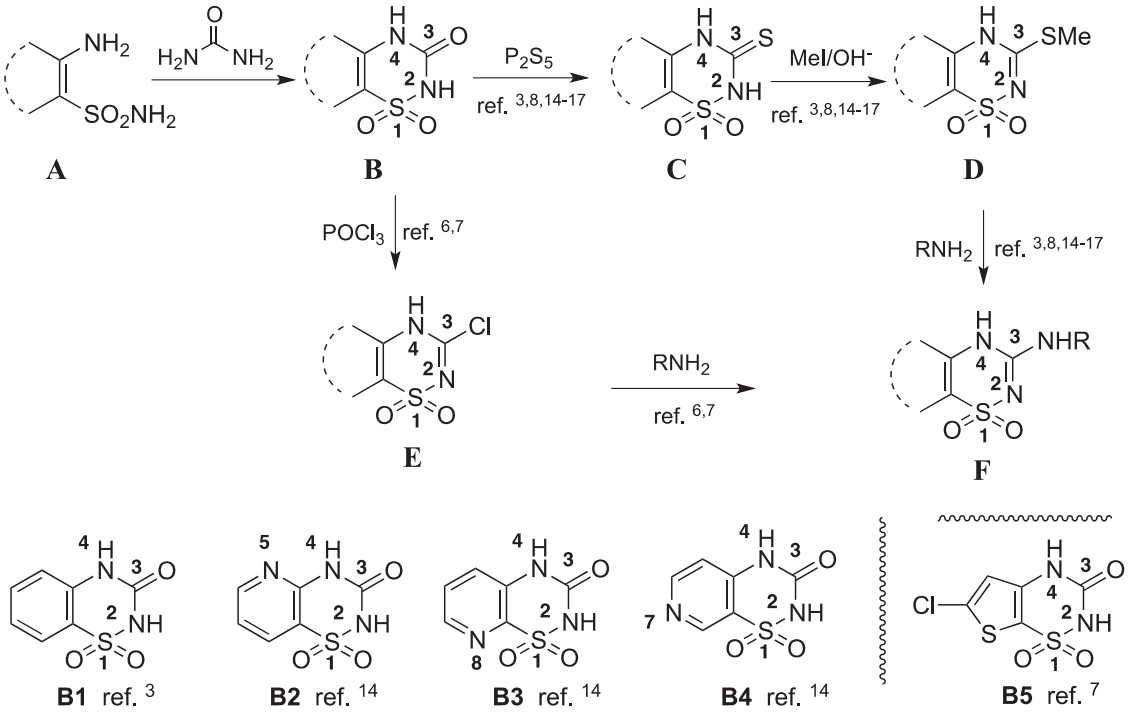
Abstract – Fusion of 4-amino-3-quinolinesulfonamide (**1a**) with urea and *N*-methyl- and *N,N'*-dimethylurea resulted in 2-oxo-2,3-dihydro-(1*H*,3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-oxide (**3a**). Reaction of thiadiazinone **3a** with a MeI/MeOK/DMF system gave a mixture of the 3-methyl derivative **3c** (major product) and 6-methyl derivative **3d** (minor product), and the mixture of **3c** and **3d** could be methylated with the same system as above to afford the 3,6-dimethyl derivative **3e**. Chlorination of **3a** with $P(O)Cl_3$/phosphoric acid system performed in the presence of pyridine hydrochloride resulted in zwitterionic pyridinio-quinothiadiazinate **7** (63%) accompanied by 2-chloroquinothiadiazine **6** (15%), and the same reaction performed with the use of triethylamine hydrochloride gave the expected chloroquinothiadiazine **6** (73%). Chloro derivative **6** was then aminated to 2-aminoquinothiadiazines **8a,b,c**.

INTRODUCTION

The well-established pharmacological activity of areno and heteroareno fused 1,2,4-thiadiazine *S*,*S*-dioxides has induced continuous interest in studies on synthesis and properties of these compounds.[1-9] The biological activities of the abovementioned compounds as potassium channel openers,[3,8,10] AMPA potentiators,[11] cytotoxic agents,[2] and anti-HIV agents attracted researchers' attention as possible

candidates for application in the therapy of hypertension,[3,8,10] diabetes,[10] mental disorders and neurodegenerative diseases,[11] cancers[2] and viral infections.[12]

Several papers have shown[13-20] that fusion of *o*-aminoarene- and aminoheteroarenesulfonamide with urea provides easy access to the respective 1,2,4-thiadiazin-3-one *S,S*-dioxides (Scheme 1, formula **B**). However, the molecules of the most active 3-amino-1,2,4-thiadiazine *S,S*-dioxide derivatives contain an *endocyclic* guanidine fragment incorporated in the 1,2,4-thiadiazine ring. An attempt at direct transformation of 1,2,4-thiadiazin-3-one *S,S*-dioxides **B** to 3-aminothiadiazines **F** using an $RNH_2/(R')_3N/P_2O_5$ system, however, gave low yields of the expected compounds **F**.[7] Therefore, transformation of the 3-oxo-function of the thiadiazinone ring of **B** into amino compounds **F** is usually performed *via* compounds **D** or **E** bearing a leaving group in the $3_{thiadiazinic}$ position. Thiation of thiadiazinone **B** with P_2S_5 leading to thiadiazinethione **C** followed by methylation of **C** to methylthio derivative **D**[3,8,14-17] or chlorination of derivatives **B** to chlorothiadiazine **E**[6,7] were performed for this purpose. The latter route, successfully performed for thieno-1,2,4-thiadiazine derivatives,[6] inspired our study on 2-oxo-2,3-dihydro-(1*H*, 3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**3a**).

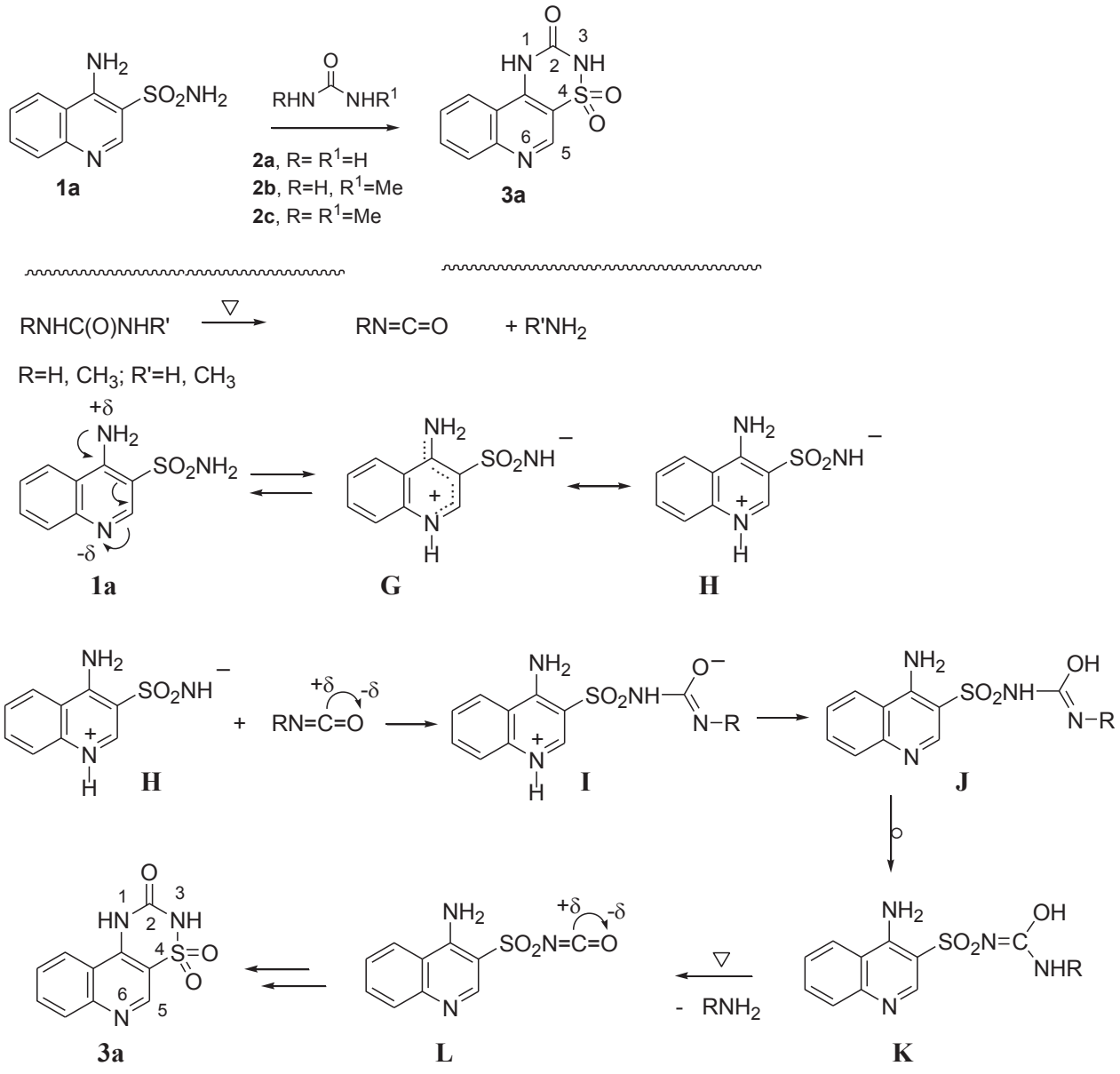


Scheme 1. Types of thiadiazin-3-ones resulted from fusion of aminosulfonamides with urea

RESULTS AND DISCUSSION

Fusion of *o*-aminobenzenesulfonamides or *o*-aminopyridinesulfonamides with urea (1-4 molar equiv) led to the respective 1,2,4-thiadiazin-3-one *S,S*-dioxides of type **B**[13-20] (Scheme 1). This process was usually

carried out at a temperature of about 180 °C (160-200 °C) up to the solidification of the "melt" and proceeded with intensive gaseous substance evolution. The mixture (cold) was triturated with water to give the ammonium salt of the respective 1,2,4-thiadiazin-3-one *S,S*-dioxide. The salt (or the solid reaction product) was decomposed with aqueous alkali followed by acidification to pH ~2 to precipitate thiadiazin-3-one **B**. Similar treatment of 4-amino-3-quinolinesulfonamide (**1a**) with urea gave the title 2-oxo-2,3-dihydro-(1*H*,3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**3a**) (Scheme 2). As 1-methyl and 3-methyl derivatives **3b** or **3c** may be of interest as pharmacologically active compounds, 4-amino-3-quinolinesulfonamide (**1a**) was subjected to fusion with *N*-methyl- and *N,N'*-dimethylurea (**2b**, **2c**). However, the reaction gave in all cases studied the parent quinothiadiazin-2-one **3a**, *i.e.* the product without methyl groups.



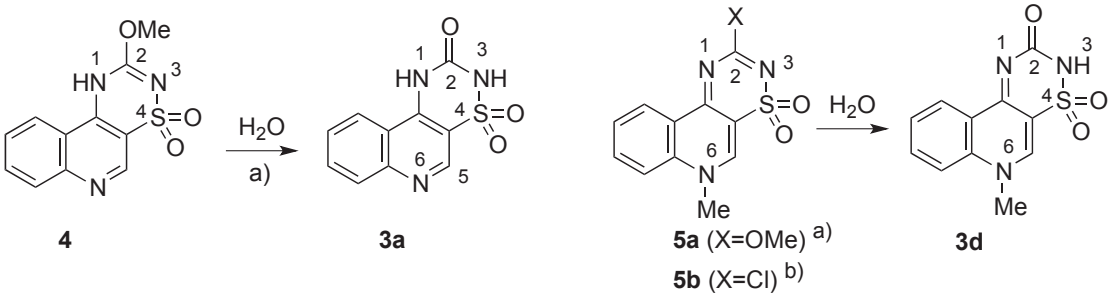
Scheme 2

The formation of the same product **3a** from fusion of 4-amino-3-quinolinesulfonamide (**1a**) with any of urea, *N*-methylurea or *N*,*N'*-dimethylurea (**2a-c**) strongly suggests that the ureas mentioned above supply the same structural fragment in the course of formation of the thiadiazine ring of **3a**. This prompted us to consider reaction pathways leading from **1a** and **2a-c** to **3a**.

It is well-known that urea derivatives with at least one N-H bond undergo thermal decomposition to isocyanic acid or isocyanate and amine or ammonia: $RNH(CO)NR^1R^2 \rightarrow RNCO + HNR^1R^2$.[21] The same conclusions were drawn from a more detailed study on methylureas by Chen and Isa.[22] Thus, decomposition of urea and *N*-methylurea should lead to isocyanic acid, but that of *N*,*N'*-dimethylurea should give methyl isocyanate.

Both amino groups of aminosulfonamide **1a** may react with isocyanic acid derivatives. However, as shown with electronic formulae (Scheme 2), the 4-amino group is deactivated as electron donor – but the highly nucleophilic *endo*cyclic nitrogen atom of 4-aminoquinoline **1a** may extract a *pseudo*acidic proton from sulfonamide group to form sulfonamidate betaine **H**.[23] Thus, as shown in Scheme 2, both isocyanic acid derivatives should carbamoylate aminosulfonamide **1a** at sulfonamide NH_2 group to form sulfonyl *iso*ureas **J**. This assumption falls in agreement with thiocarbamoylation of *o*-aminobenzenesulfonamides by alkyl isothiocyanates at sulfonamide NH_2 group.[24] Following Chen and Isa's pathways of thermal decomposition of ureas,[22] **J** would rearrange to tautomers **K**. Decomposition of **K** would in both cases (R=H and R=Me) lead to 3-quinolinesulfonyl isocyanate **L**, which finally undergoes cyclocondensation to **3a**. The above consideration led us to the conclusion that urea, *N*-methylurea or *N*,*N'*-dimethylurea (**2a-c**) supply the same divalent –C(=O)– structural fragment in the course of formation of the thiadiazine ring of **3a**.

Hydrolysis of 2-methoxyquinothiazine dioxide **4** (boiling azeotropic HCl_{aq}) led to quinothiadiazinone **3a**, but the same treatment of 2-methoxy-6-methylquinothiadiazine **5a** led to a *non*-homogenous mixture containing, as concluded from TLC and the ^{1}H NMR spectra, the expected 6-methyl derivative **3d**. On the other hand, hydrolysis of 2-chloro-6-methylquinothiadiazine **5b** with a DMSO/H_2O/HCl system allowed us to obtain individual 6-methylquinothiadiazinone **3d**.

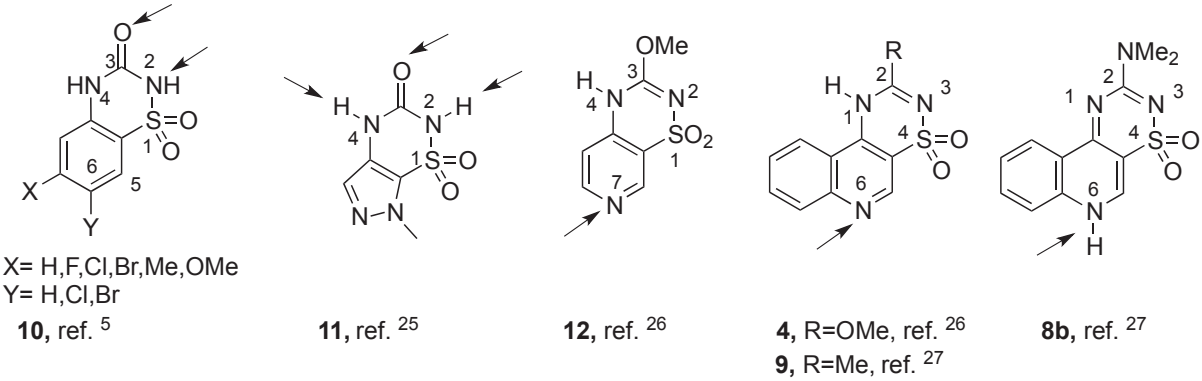


a) HClaq (1:1), boiling temp., b) DMSO, HClaq (one drop), rt

Scheme 3

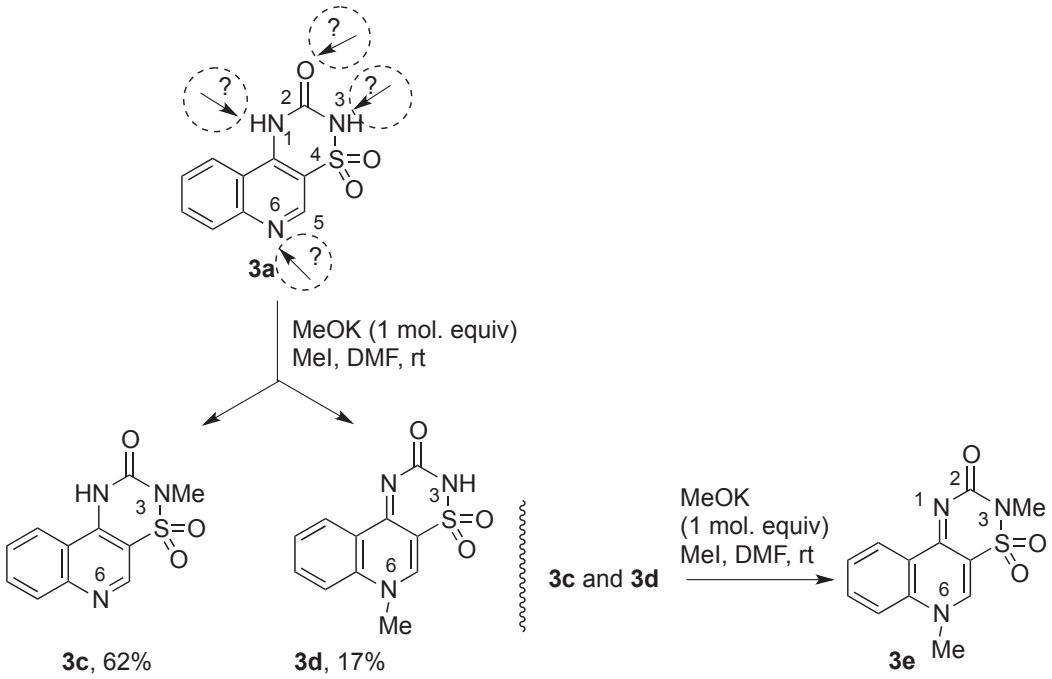
N-Methylation

In the search for biologically active compounds, areno- and heteroareno-fused 1,2,4-thiadiazine *S*,*S*-dioxides were modified by alkylation at N or O heteroatoms.[5,25-27] Several papers deal with the alkylation of areno and heteroareno-fused 1,2,4-thiadiazin-3-one *S*,*S*-dioxides[5,25-27] (see Scheme 4). For the quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxides studied by our group, methylation of sodium (or potassium) salts of 2-methyl- and 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**9**) and (**4**), and 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**8b**) proceeded at the *endocyclic* nitrogen of the pyridine ring and led to the 6-methyl derivatives.[26,27]



Scheme 4. Orientation in the alkylation of some benzo-, pyrazolo-, pyrido- as well as quino-1,2,4-thiadiazinone *S,S*-dioxide derivatives **10**, **11**, **12**, **4**, **9**, and **8b**

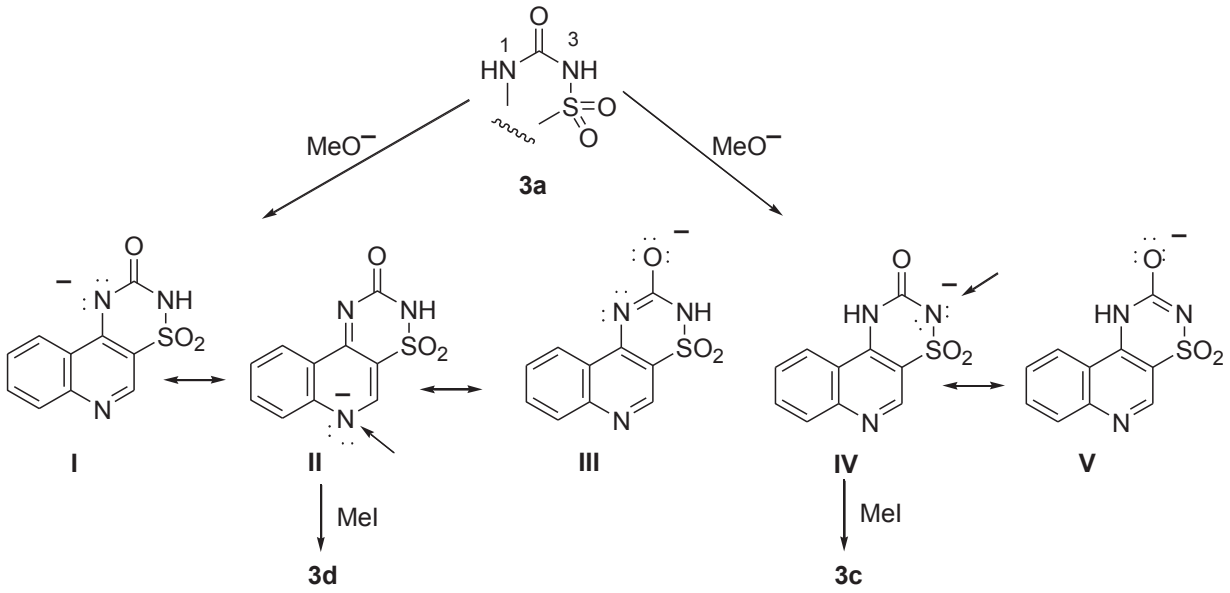
Taking the above into consideration, one would expect that alkylation of quinothiadiazinone **3a** may follow at four heteroatoms, as indicated in Scheme 5.



Scheme 5

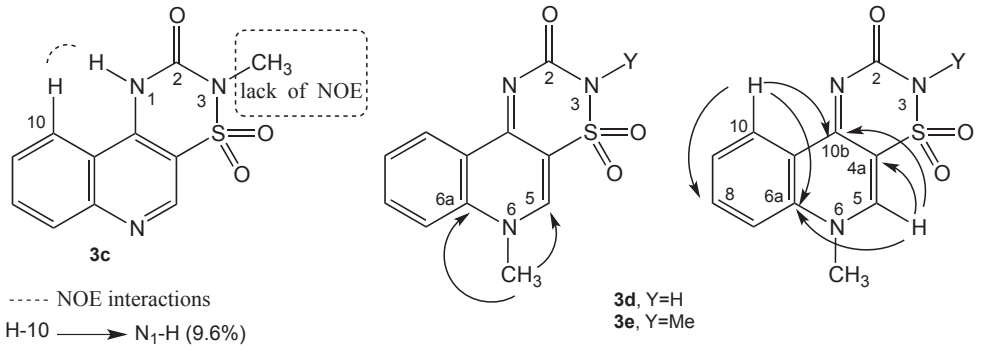
However, treatment of the potassium salt of thiadiazinone **3a** (DMF solution, rt) with 1 molar equiv. of methyl iodide proceeded mainly at nitrogen N3 to give 3-methyl-quinothiadiazinone **3c** (62%), accompanied by 6-methyl isomer **3d** (17%). Methylation of the mixture of **3c** and **3d** with the same system led to the 3,6-dimethyl derivative **3e** (68%).

Alkylation of sodium salts of quinothiadiazinone **3a** may formally proceed through nitrogen anionic forms **I** and **IV** (Scheme 6). In fact, formation of **3c** demonstrates the occurrence of anion **IV**. On the other hand, the formation of **3d** is in agreement with the previous observation that anionic forms derived from 1-NH quinothiadiazines are alkylated at the pyridine ring nitrogen[26,27] (see Scheme 4).



Scheme 6

The structure of **3c-e** and the positions of the newly-introduced N-CH_3 groups were concluded from NOE, HSQC and HMBC experiments as presented in Scheme 7.



Scheme 7

Irradiation of the N-CH_3 proton signal of **3c** (δ = 3.69 ppm) did not affect any C-H or N-H proton signal. This means that the NCH_3 - CH or -NH proton distances are too far to fulfill the steric requirement for the occurrence of NOE (~4 Å)[28] and therefore it suggests that the NCH_3 group should be located at position 3. In fact, as deduced from X-ray diffraction analysis of the **3c** monocrystal (Figure 1), the N-H proton/NCH_3 protons distances are 5.004 Å, 4.362 Å and 4.626 Å. On the other hand, due to the short H-10 proton-N1-H proton distance (2.09 Å), irradiation of the H-10 proton (δ = 8.76 ppm) led to enhancement of the N1-H proton signal (bs, δ = 12.2 ppm) by 9.6%. The structures of the 6-methyl derivative **3d** and the 3,6-dimethyl derivative **3e** were demonstrated by HSQC and HMBC experiments (Scheme 7). Additionally, the structure of **3d** was confirmed by the hydrolysis of 2-metoxyquinothiadiazine **5a** and 2-chloroquinothiadiazine **5b** (see Scheme 3).

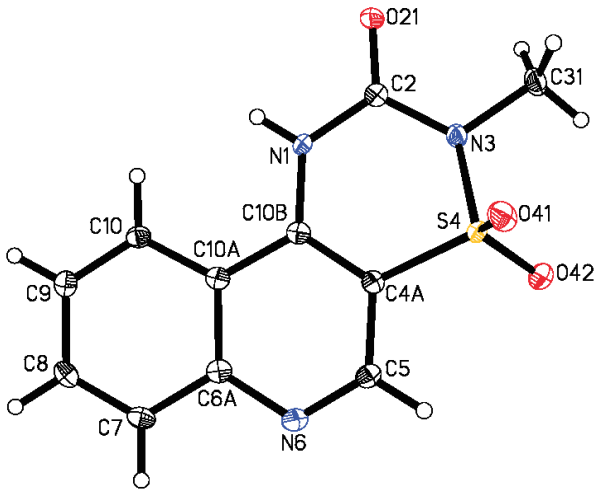


Figure 1. ORTEP drawing of 2-oxo-2,3-dihydro-3-methyl-(1*H*,3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3c**) with the atom labelling scheme. Displacement ellipsoids are drawn at the 70% probability level.

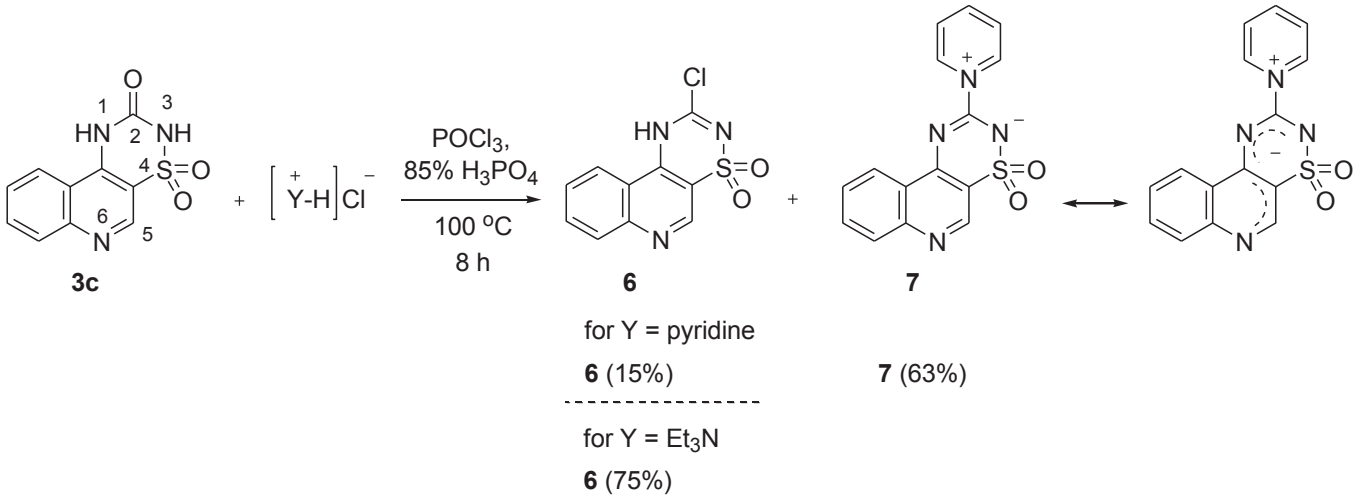
Chlorination

As mentioned above, the transformation of the oxo function at thiadiazine ring of compounds **B** (Scheme 1) into a more active leaving group is necessary for further functionalization of areno and heteroareno-fused 1,2,4-thiadiazine *S*,*S*-dioxides **B**, as a first step toward the preparation of biologically active compounds.

For this purpose, the lactam fragment of oxo derivative **3a** was subjected to *deoxo-chlorination*. Several chlorination reagents or systems were tested. Ineffective reactions occurred with $P(O)Cl_3$, $PhOP(O)Cl_2$ and with the $P(O)Cl_3/Et_3N$ x HCl system (120-150 ºC, 4-8 h). Reaction of **3a** with the $PhOP(O)Cl_2/Et_3N$ x HCl system (150 ºC, 4 h) led to ~90% unreacted substrate **3a** accompanied by a small amount of the desired 2-chlorothiadiazine **6**. Following the Hansen group procedure,[7] thiadiazinone **3a** was then

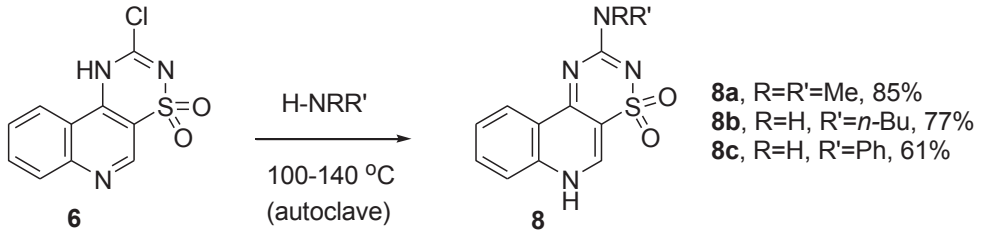
subjected to chlorination with a $P(O)Cl_3$/pyridine hydrochloride/phosphoric acid system and the expected chlorothiadiazine **6** was isolated in 15% yield, although the main product appeared to be zwitterionic pyridinio-quinothiadiazinate **7** (63%). Formation of **7** falls in agreement with literature data concerning the formation of pyridinio salts or pyridinio zwitterionic species (with 1,3-diazine motif) in the reactions of pyrimidinones or 2- and 6-purinones with $PhOP(O)Cl_2$ or $P(O)Cl_3$ in the presence of pyridine.[29] The structure of **7** was assigned a negatively charged N3 nitrogen atom due to stabilization of the negative charge by strong electron withdrawing sulfonyl group.[30]

Since an increase in steric hindrance at the nucleophilic nitrogen of a tertiary amine should lead to a reduction in the formation of aminium species, we tried to replace the pyridine hydrochloride with triethylamine hydrochloride. In fact, the reaction of **3a** with a $P(O)Cl_3$/triethylamine hydrochloride/85% phosphoric acid system afforded 2-chloroquino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**6**) in a good yield of 75%.



Scheme 8

Finally, reactions of chlorothiadiazine **6** with amines led to aminothiadiazines **8a,b,c**.



Scheme 9

CONCLUSIONS

Although areno and heteroareno-fused 1,2,4-thiadiazine *S*,*S*-dioxides may be easily obtained by the fusion

of *o*-aminoarene- and aminoheteroarenesulfonamide with urea, the most important fused 1,2,4-thiadiazine *S*,*S*-dioxides may only be reached in complex multi-step syntheses.

Our study extends previous findings concerning heteroarene-fused 1,2,4-thiadiazine *S*,*S*-dioxides, showing that alkylation of sodium salts of quinothiadiazinone **3a** proceeds mainly at the sulfonamide nitrogen of the thiadiazine ring and to a lesser extent at the pyridine ring nitrogen, *i.e*. outside the thiadiazine ring.

The most valuable results were obtained through functionalization of quinothiadiazinone **3a** to 2-chloroquinothiadiazine **6** in a *deoxo-chlorination* reaction performed with the use of a $P(O)Cl_3$/phosphoric acid system in the presence of triethylamine hydrochloride. Chloro derivative **6** was a convenient substrate for the synthesis of 2-aminoquinothiadiazines **8a,b,c**.

EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. All NMR spectra were recorded on a Bruker AVANCE 400 spectrometer operating at 400.22 MHz and 100.64 MHz for ^1H and ^{13}C nuclei, respectively, in deuterochloroform or in hexadeuterodimethyl sulfoxide solutions with tetramethylsilane (δ 0.0 ppm) as the internal standard. Two-dimensional ^1H-^{13}C HSQC and HMBC experiments were performed using standard Bruker software HSQCGP and HMBCGP, respectively, and the following parameters: the spectral widths in F_2 and F_1 were *ca.* 5 kHz for ^1H and 16.7 kHz for ^{13}C, the relaxation delay was 1.5 s, the refocusing in the HSQC experiment was 1.7 ms and the delay for long-range evolutions was 50 ms in $^1H/^{13}C$ HMBC. 2D spectra were acquired as 2048 x 1024 hypercomplex files, with 1-4 transients. EI MS spectra were determined on a Finnigan MAT 95 spectrometer at 70 eV. IR spectra were recorded with a Magma – IR 500 (Nicolet) spectrometer in potassium bromide pellets. TLC analyses were performed employing Merck's aluminum oxide 60 F_{254} neutral (type E) plates using chloroform as the eluent.

4-Amino-3-quinolinesulfonamide (**1a**),[31] 2-methoxy- and 2-chloro-6-methyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxides (**5a** and **5b**)[26] were prepared as described previously.

N-Methyl- and *N*,*N'*-dimethylureas were commercial products.

Fusion of 4-amino-3-quinolinesulfonamide (1a) with ureas

4-Amino-3-quinolinesulfonamide (**1a**) (0.9 g, 4 mmol) and urea (0.6 g, 10 mmol) were mixed together, powdered and then heated at 200 °C (oil bath temperature). The reaction proceeded with strong evolution of gases and the formation of a clear solution, which solidified after 30 min. After cooling, the mixture was powdered, dissolved in water and filtered to remove small amounts of insoluble material. The filtrate was acidified with concentrated HCl to pH 2. The precipitate of **3a** was collected by filtration, washed with water and dried. For purification, crude **3a** was boiled with EtOH (18 mL) to yield

2-oxo-1,3-dihydro(1*H*, 3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**3a**) (0.88 g, 88%).

Reactions of **1a** (0.89 g, 4 mmol) with *N*-methylurea (4-8 mmol) were performed in the same manner and gave **3a** (0.7-0.8 g, 70-80%).

Reactions of **1a** (0.89 g, 4 mmol) with *N,N'*-dimethylurea (4-8 mmol) were performed in the same manner for 1 h. After cooling, the mixture was powdered, dissolved in water and filtered to recover a small amount (0.075 g; 8%) of insoluble substrate **1a**. The filtrate was acidified with concentrated HCl to pH 2. The precipitate was collected by filtration, washed with water and dried. It consisted mainly of thiadiazinone **3a** and substrate **1a,** as deduced from TLC and ^{1}H NMR data. ^{1}H NMR spectrum showed the ratio **1a**:**3a**=2:5, based on the intensities of singlets of α-quinolinyl proton (δ = 8.92 ppm for **1a**) and H-5 proton (δ = 9.25 ppm for **3a**). The crude product (~0.850 g) was recrystallized from 20 mL of DMF to give 0.530 g (53%) of **3a**. The filtrate was concentrated vacuo at 80 °C to 1/4 volume and cooled to rt, and the solid deposited was separated by filtration to give 0.080 g (9%) of substrate **1a**.

2-Oxo-2,3-dihydro-(1*H*, 3*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3a)

mp 324-326 ºC (decomp.). EIMS (70 eV): *m/z* (%) = 249 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 7.80-7.83 (m, 1H, H_{arom}), 8.01-8.09 (m, 1H, H_{arom}), 8.09-8.10 (m, 1H, H_{arom}), 8.86-8.88 (m, 1H, H_{arom}), 9.25 (s, 1H, H-5), 11.52 (bs, 1H, NH), 13.8 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6), δ: 114.1, 116.9, 124.3, 124.4, 128.6, 134.1, 141.9, 142.0, 146.4, 151.5. *Anal.* Calcd for $C_{10}H_7N_3O_3S$: C 48.19, H 2.83, N 16.86. Found: C 48.03, H 3.15, N 16.65.

Hydrolysis of 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (4)

A mixture of 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**) (0.2 g, 0.76 mmol) and 4 mL of hydrochloric acid (1:1) was heated at 100 °C (oil bath temperature) for 30 min with occasional shaking. The mixture was clarified after 5 min. It was then diluted with 4 mL of water and cooled to rt. The precipitate of **3a** was collected by filtration, washed with a few drops of cold water, and dried to give 0.12 g (64%) of **3a** with an mp 317-320 °C and an ^{1}H NMR spectrum identical to that of the authentic material prepared as above.

The filtrate was concentrated in vacuo at 60 °C. The residue was neutralized with 5% aqueous $NaHCO_3$. The solid was filtered off, washed with water and dried to give 0.06 g (30%) of unreacted **4** as based on mp, TLC and ^{1}H NMR data.

Hydrolysis of 2-methoxy-6-methyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (5a)

Hydrolysis of 2-methoxy derivative **5a** was performed with hydrochloric acid as described above for compound **4**. Both solids were non-homogenous, as concluded from the ^{1}H NMR (DMSO-d_6) spectra and TLC data, but the presence of the 6-methyl derivative **3d** was observed in a total amount of ~20% (as judged from the ^{1}H NMR spectra).

Hydrolysis of 2-chloro-6-methyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (5b)

2-Chloro derivative (100 mg, 0.36 mmol), 3 mL of DMSO and one drop of a solution of HCl in DMSO (0.1 mL of 5% HCl_{aq} and 0.9 mL of DMSO) were stirred at rt for 32 h. The solution was diluted with 20 mL of cold water. The solid was filtered off and dried in air to give a mixture (80 mg) of substrate **5b** and 6-methyl derivative **3d** in a ratio of *ca.* 5:1. The mixture was triturated with 1 mL of 5% aqueous KOH. The insoluble substrate **5b** (64 mg) was filtered off and washed with water. The filtrate was acidified with 5% HCl to pH 2 to give 14 mg (~15%) of **3d** with the same properties [^{1}H NMR (DMSO-d_6) spectra and TLC data] as the sample prepared from the methylation of **3a**, as described below.

***N*-Methylation of 2-oxo-2,3-dihydro-(1*H*,3*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3a)**

Potassium methoxide (0.290 g, *ca.* 4.1 mmol) was added with stirring to a suspension of 2-oxo-2,3-dihydro-(1*H*,3*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**3a**) (1 g, 4 mmol) in dry DMF (8 mL). The mixture was stirred for 5-10 min until the mixture became clear. Then, a solution of methyl iodide (1.6 mL, *ca.* 4 mmol) in DMF (2.6 mL) was added dropwise for 15 min and the mixture was stirred at rt for 20 h. The solid was filtered off, washed with cold water and dried on air to give a mixture (0.87 g) of *N*-methylquinothiadiazinones **3c** and **3d**. It was boiled for 5 min with DMF (50 mL), cooled to rt and filtered off to give **3d** (0.18 g, 17%). The filtrate was concentrated in vacuo at 80 °C to 1/3 volume, cooled to rt and filtered off to give **3c** (0.65 g, 62%).

A mixture of **3c** and **3d** (ratio 1 : 0.27, 0.53 g, 2.0 mmol) was methylated as above with potassium methoxide (0.145 g, *ca.* 2.05 mmol) and a solution of methyl iodide (0.8 mL, *ca.* 2 mmol) in DMF (1.3 mL) to give 3,6-dimethyl-2-oxo-2,3-dihydro-(3*H*,6*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**3e**) (0.38 g, 68%).

3-Methyl-2-oxo-2,3-dihydro-(1*H*,3*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3c)

mp 293-296 ºC ($CHCl_3$/EtOH). EIMS (70 eV): *m/z* (%) = 263 (100, M^+). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.30 [(s, 3H, CH_3N3); 26.5 (CH_3N3) / 150.0 (C2)], 7.78 [(m, 1H, H9); 128.6 (C9) / 116.5 (C10a); 130.2 (C7)], 7.98 [(m, 1H, H8); 133.4 (C8) / 123.8 (C10); 149.6 (C6a)], 8.10 [(d, 1H, H7); 130.2 (C7) / 116.5 (C10a); 128.6 (C9)], 8.74 [(d, 1H, H10); 123.8 (C10) / 133.4 (C8); 140.0 (C10b); 149.6 (C6a)], 9.12 [(s, 1H, H5); 142.5 (C5) / 113.2 (C4a); 140.0 (C10b); 149.6 (C6a)], 12.2 (br s, 1H, NH). *Anal.* Calcd for $C_{11}H_9N_3O_3S$: C 50.18, H 3.45, N 15.96. Found: C 49.97, H 3.48, N 15.89.

NOE experiments: irradiation of the H-10 proton (δ = 8.76 ppm) led to enhancement of the NH proton signal (bs, δ = 12.2 ppm) by 9.6%; irradiation of the N-CH_3 protons signal (δ = 3.69 ppm) did not affect any C-H or N-H proton signal, irradiation of the H7 proton signal (δ = 8.12 ppm) and H10 proton signal (δ = 8,76 ppm) (δ = 3.69 ppm) did not affect CH_3 protons signal.

6-Methyl-2-oxo-2,3-dihydro-(3*H*,6*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3d)

mp 297-300 ºC (DMF). EIMS (70 eV): *m/z* (%) = 263 (100, M^+). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons

from single bond and / long range proton-carbon correlations]: 4.38 [(s, 3H, CH_3N); 43.8 (CH_3N) / 145.4 (C5); 139.3 (C6a)], 7.94 [(m, 1H, H9); 129.2 (C9) / 117.6 (C10a); 119.9 (C7)], 8.19 [(m, 1H, H8); 135.6 (C8) / 125.3 (C10); 139.3 (C6a)], 8.29 [(m, 1H, H7); 119.9 (C7) / 117.6 (C10a); 129.2 (C9)], 9.01 [(m, 1H, H10); 125.3 (C10) / 135.6 (C8); 139.3 (C6a); 148.2 (C10b)], 9.55 [(s, 1H, H5); 145.4 (C5) / 114.0 (C4a); 139.3 (C6a); 148.2 (C10b)], 11.69 [(br s, 1H, N3-H) / 114.0 (C4a)], no correlation was observed with C2 carbon signal δ_C = 150.9 ppm. *Anal.* Calcd for $C_{11}H_9N_3O_3S$: C 50.18, H 3.45, N 15.96. Found: C 49.99, H 3.48, N 15.85.

3,6-Dimethyl-2-oxo-2,3-dihydro-(3*H*,6*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3e)

mp 279-281 ºC (EtOH). EIMS (70 eV): *m/z* (%) = 277 (54, M^+), 183 (100). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.18 [(s, 3H, CH_3N3); 25.7 (CH_3N3) / 155.4 (C2)], 4.17 [(s, 3H, CH_3N6); 42.4 (CH_3N6) / 138.9 (C6a); 142.8 (C5)], 7.76 [(m, 1H, H9); 127.7 (C9) / 118.4 (C7); 123.9 (C10a); 134.4 (C8); 138.9 (C6a)], 8.02 [(m, 1H, H8); 134.4 (C8) / 127.7 (C9); 138.9 (C6a); 123.9 (C10a)], 8.04 [(m, 1H, H7); 118.4 (C7) / 127.7 (C9); 138.9 (C6a)], 8.67 [(m, 1H, H10); 125.9 (C10) / 134.4 (C8); 138.9 (C6a); 154.8 (C10b)], 9.27 [(s, 1H, H5); 142.8 (C5) / 112 (C4a); 123.9 (C10a); 138.9 (C6a); 154.8 (C10b). *Anal.* Calcd for $C_{12}H_{11}N_3O_3S$: C 51.98, H 4.00, N 15.15. Found: C 51.64, H 3.84, N 15.14.

Chlorination of 2-oxo-2,3-dihydro-(1*H*,3*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (3a) with P(O)Cl$_3$/ pyridine or triethylamine hydrochlorides /phosphoric acid systems

A mixture of **3a** (0.5 g, ca. 2 mmol), phosphorus oxychloride (2.4 mL), pyridine hydrochloride (0.8 g, 7 mmol) and 85% *ortho*-phosphoric acid (0.14 mL) was stirred at 100 °C for 8 h. The mixture was concentrated in vacuo at 50 °C, and the residual oil was carefully treated with ice water (10 mL) with stirring at 0 °C. The crude product was isolated by filtration, washed with water, and triturated with saturated aqueous $NaHCO_3$ (10 mL). The solid was filtered off, washed with water and dried in air to give pyridinio-quinothiadiazinate **7** (0.44 g, 63%). The filtrate was acidified with 5% HCl with stirring at 0 °C and the white precipitate that formed was filtered, washed with water, and dried to give 0.08 g (15%) of 2-chloro-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**6**).

The same reaction performed with the use of triethylamine hydrochloride (0.96 g, 7 mmol), instead of pyridine hydrochloride, gave 0.40 g (74%) of chloroquinothiadiazine **6**.

2-Chloro-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (6)

mp >350 ºC (dec.). EIMS (70 eV): *m/z* (%) = 269 [36.8, (M+2)], 267 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 7.82-7.86 (m, 1H, H_{arom}), 8.05-8.06 (m, 2H, H_{arom}), 8.63-8.65 (m, 1H, H_{arom}), 9.56 (s, 1H, H-5), no N1- H proton signal was seen (hidden in a broad H_2O peak). ^{13}C NMR (DMSO-d_6), δ: 114.1, 116.8, 123.0, 124.6, 129.0, 134.9, 140.4, 141.2, 147.3, 151.3. *Anal.* Calcd for $C_{10}H_6ClN_3O_2S$: C 44.87, H 2.26, N 15.70. Found: C 44.57, H 2.11, N 15.45.

2-(1-Pyridinio)-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazinate 4,4-dioxide (7)

mp >306 ºC (EtOH). EIMS (70 eV): *m/z* (%) = 310 (100). ^{1}H NMR (DMSO-d_6), δ: 7.71-7.79 (m, 1H, H_{arom}), 7.86-7.95 (m, 1H, H_{arom}), 8.01-8.09 (m, 1H, H_{arom}), 8.22-8.32 (m, 2H, H_{arom}), 8.81-8.87 (m, 1H, H_{arom}), 8.87-8.95 (m, 1H, H_{arom}), 9.10 (s, 1H, H5), 10.12-10.22 (m, 2H, H_{arom}).). ^{13}C NMR (DMSO-d_6), δ: 114.5, 124.0, 125.1, 127.5, 127.9, 128.0, 129.4, 131.7, 141.3, 145.2, 148.8, 149.0, 150.1, 150.7, 155.5. *Anal.* Calcd for $C_{15}H_{10}N_4O_2S$: C 58.06, H 3.22, N 18.06. Found: C 57.79, H 3.19, N 17.70.

Amination of 2-chloro-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (6)

a) dimethylamine

Chloroquinothiadiazine **6** (270 mg, ~1 mmol) and 4 mL of a 40% aqueous Me_2NH solution were placed in a steel autoclave. It was heated in an oil bath at 100 ºC for 2 h. The mixture was cooled down to rt, transferred to a distillation flask and the excess Me_2NH was then distilled off under vacuum. The solid was filtered off, washed with cold water and boiled with EtOH. Hot solution was decanted off to leave dimethylamino derivative **8a** (181 mg, 85%) with mp 313-316 ºC (EtOH); according to ref. [27] the mp 313-316 ºC and ^{1}H NMR spectrum are identical with the sample prepared previously.[27]

b) with *n*-butylamine

Chloroquinothiadiazine **6** (270 mg, ~1 mmol) and *n*-butylamine (4 mL) were refluxed for 1 h. The excess of *n*-butylamine was then evaporated to dryness under reduced pressure in a water bath. The residue was cooled down to rt and triturated with water (4 mL). The solid was filtered off, washed with cold water and dried in air. The crude product was purified by column chromatography (SiO_2, $CHCl_3$/EtOH, 3:1, v/v) and recrystallized from EtOH to give **8b** (234 mg, 77%).

c) with aniline

Chloroquinothiadiazine **6** (270 mg, ~1 mmol) and aniline (1.2 mL, 12 mmol) were stirred at 100 ºC for 1 h. The mixture was cooled down to rt and triturated with a mixture of $CHCl_3$/EtOH (3:1, v/v) (4 mL). The solid was filtered off and dried in air, and finally recrystallized from EtOH to give **8c** (200 mg, 61%).

2-Butylamino-(6*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (8b)

mp 248-250 ºC (EtOH). EIMS (70 eV): *m/z* (%) = 304 (37.4, M^+). ^{1}H NMR (DMSO-d_6), δ: 0.91-0.95 (m, 3H, CH_3), 1.35-1.41 (m, 2H, CH_2), 1.52-1.59 (m, 2H, CH_2), no NH-C**H**$_2$ protons signal was seen, hidden in a broad H_2O peak, at δ = 3.33 ppm, 7.70-7.78 (m, 2H, H_{arom}), 7.86-7.97 (m, 1H, H_{arom}), 8.47-8.49 (m, 1H, H_{arom}), 8.95 (s, 1H, H5), 8.06 (s, 1H, NH), 11.47 (s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ: 14.0, 19.7, 31.1, 40.7, 113.0, 117.8, 123.0, 123.2, 127.8, 129.3, 132.6, 143.1, 143.9, 152.7. *Anal.* Calcd for $C_{14}H_{16}N_4O_2S$: C 55.25, H 5.30, N 18.41. Found: C 54.97, H 5.15, N 18.12.

2-Phenylamino-(6*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (8c)

mp 302-306 ºC (EtOH). EIMS (70 eV): *m/z* (%) = 324 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 2.95-3.90 (bs, 1H, NH), 7.03-7.16 (m, 1H, H_{arom}), 7.28-7.45 (m, 2H, H_{arom}), 7.60-7.84 (m, 3H, H_{arom}), 7.86-8.10 (m, 2H,

H_{arom}), 8.46-8.75 (m, 1H, H_{arom}), 9.06 (s, 1H, H5), 9.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6), δ: 112.8, 117.9, 121.1, 123.8, 124.1, 124.7, 127.7, 129.1, 129.7, 133.6, 139.3, 140.3, 142.8, 157.0. *Anal.* Calcd for $C_{16}H_{12}N_4O_2S$: C 59.25, H 3.73, N 17.27. Found: C 58.97, H 3.59, N 16.99.

X-Ray structure analysis

The diffraction data were collected with a four – circle Xcalibur diffractometer with Sapphire3 CCD detector using graphite monochromated Mo Kα radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software.[32] The crystal structures were solved by direct methods with the program SHELXS-97[33] and refined by full-matrix least-squares method on F2 with SHELXL-97.[33]

Crystals of 2-oxo-2,3-dihydro-3-methyl-(1*H,*3*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3c**) were obtained by slow evaporation of DMF solution at room temperature. Crystal data for **3c**: monoclinic, space group $P2_1/c$, a = 5.6446(1) Å, b = 20.1260(2) Å, c = 10.1508(1) Å, α = 90º, β = 113.781(1)º, γ = 90º, V = 1055.25 Å^3, Z = 4, d_x = 1.657 Mg m^{-3}, T = 100(1) K, Data were collected for a crystal of dimensions 0.07 x 0.44 x 0.53 mm^3. Final R indices for 1841 reflections with $I > 2\sigma(I)$ and 184 refined parameters are R_1 = 0.0266, wR_2 = 0.0693 (R_1 = 0.0268, wR_2 = 0.0693 for all 1867 data).

Crystallographic data for compound **3c** has been deposited with Cambridge Crystallographic Data Centre (CCDC deposition number 1054243) Copies of the data can be obtained upon request from CCDC, 12 Union road, Cambridge CB2 1EZ, UK).

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REFERENCES (AND NOTES)

Part CXLV in the series of Azinyl Sulfides.

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1. Z. Brzozowski, J. Sławiński, M. Gdaniec, A. Innocenti, and C. T. Supuran, *Eur. J. Med. Chem*., 2011, **46**, 4403.
2. A. Kamal, Y. V. V. Srikanth, M. N. A. Khan, Md. Ashraf, M. K. Reddy, F. Sultana, T. Kaur, G. Chashoo, N. Suri, I. Sehar, Z. A. Wani, A. Saxena, P. R. Sharma, S. Bhushan, D. M. Mondhe, and A. K. Saxena, *Bioorg. Med. Chem.*, 2011, **19**, 7136.
3. B. Pirotte, P. de Tullio, Q.-A. Nguyen, F. Somers, P. Fraikin, X. Florence, P. Wahl, J. B. Hansen, and P. Lebrun, *J. Med. Chem*., 2010, **53**, 147.

4. P. Lebrun, B. Becker, N. Morel, P. Ghisdal, M.-H. Antoine, P. de Tullio, and B. Pirotte, *Biochem. Pharmacol.*, 2008, **75**, 468.
5. B. Pirotte, P. de Tullio, S. Boverie, C. Michaux, and P. Lebrun, *J. Med. Chem*., 2011, **54**, 3188.
6. F. E. Nielsen, S. Ebdrup, A. Frost Jensen, L. Ynddal, T. B. Bodvarsdottir, C. E. Stidsen, A. Worsaae, H. C. M. Boonen, P. O. G. Arkhammar, T. Fremming, P. Wahl, H. T. Kornø, and J. B. Hansen, *J. Med. Chem.*, 2006, **49**, 4127.
7. F. E. Nielsen, T. B. Bodvarsdottir, A. Worsaae, P. Mackay, C. E. Stidsen, H. C. M. Boonen, L. Pridal, P. O. G. Arkhammar, P. Wahl, L. Ynddal, F. Junager, N. Dragsted, T. M. Tagmose, J. P. Mogesen, A. Koch, S. P. Treppendahl, and J. B. Hansen, *J. Med. Chem.*, 2002, **45**, 4171.
8. S. Boverie, M. H. Antoine, F. Somers, B. Becker, S. Sebille, R. Ouedraogo, S. Counerotte, B. Pirotte, P. Lebrun, and P. de Tullio, *J .Med .Chem*., 2005, **48**, 3492.
9. A. Cherepakha, V. O. Kovtunenko, A. Tolmachev, and O. Lukin, *J. Heterocycl. Chem*., 2013, **50**, 1071.
10. B. Ng, Y. Kang, C. L. Elias, Y. He, H. Xie, J. B. Hansen, P. Wahl, and H. Y. Gaisano, *Diabetes*, 2007, **56**, 2124.
11. P. Francotte, P. de Tullio, T. Podona, O. Diouf, P. Fraikin, P. Lestage, L. Danober, J. Y. Thomas, D. H. Caignard, and B. Pirotte, *Bioorg. Med. Chem*., 2008, **16**, 9948.
12. a) X. Liu, R. Yan, N. G. Chen, and W. F. Xu, *Chin. Chem. Lett.*, 2007, **18**, 137; b) X. Liu, R. Yan, Y. Wang, P. Zhan, E. DeClerq, C. Pannecouque, M. Witvrouw, M. T. Molina, and S. Vega, *Arch. Pharm. Life Sci.*, 2008, **341**, 216.
13. L. Raffa, A. Monzani, and A. Albasini, *Il Farmaco – Ed. Sc.*, 1964, **XIX**, 35.
14. B. Pirotte, P. de Tullio, B. Masereel, J. Delarge, J. Lepagnol, and P. Renard, US Patent, 5 459 138 (Oct. 17, 1995).
15. B. Pirotte, P. de Tullio, P. Lebrun, M. H. Antoine, J. Fontaine, B. Masereel, M. Schynts, L. Dupont, A. Herchuelz, and J. Delarge, *J. Med. Chem.*, 1993, **36**, 3211.
16. P. de Tullio, B. Pirotte, P. Lebrun, J. Fontaine, L. Dupont, M. H. Antoine, R. Ouedraogo, S. Khelili, C. Maggetto, B. Masereel, O. Diouf , T. Podona, and J. Delarge, *J. Med. Chem*., 1996, **39**, 937.
17. C. G. Neill, P. N. Preston, and R. H. Wightman, *Tetrahedron*, 1998, **54**, 13645.
18. F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M Sprague, *J. Org. Chem.*, 1960, **25**, 970.
19. E. Magnien, W. Tom, and W. Oroshnik, *J. Med. Chem*., 1964, **7**, 821.
20. S. Kotovskaya, G. Mokrushina, I. Postovskii, E. Pidémskii, A. Goleneva, and T. Vysokova, *Khim. Farm. Zh.*, 1979, **13**, 389.
21. F. Hegarty, vol. 2, subchapter 9.10.4.2, ed. by D. Barton and W. D. Ollis, 'Comprehensive Organic

Chemistry', Pergamon Press, Oxford-New York-Toronto-Sydney-Paris-Frankfurt, 1979.

22. J. P. Chen and K. Isa, *J. Mass Spectrom. Soc. Jpn.*, 1998, **46**, 299.
23. A species similar to **H** was observed as torasemide tautomer by A. Danilovski, D. Filić, M. Orešić, and M. Dumić, *Croat. Chem. Acta*, 2001, **74**, 103.
24. P. de Tullio, S. Boverie, B. Becker, M.-H. Antoine, Q.-A. Nguyen, P. Francotte, S. Counerotte, S. Sebille, B. Pirotte, and P. Lebrun, *J. Med. Chem*., 2005, **48**, 4990 – to activate of sulfonamide group, the reaction was performed in the presence of K_2CO_3/acetone system.
25. X. Liu, R. Yan, N. Chen, W. Xu, M. T. Molina, and S. Vega, *Molecules*, 2006, **11**, 827.
26. E. Chrobak, M. Wlekliński, A. Maślankiewicz, J. Kusz, M. Zubko, and E. Michalik, *Heterocycles*, 2011, **83**, 1819.
27. E. Chrobak, M. Wlekliński, A. Maślankiewicz, J. Kusz, M. Zubko, and A. Zięba, *Heterocycles*, 2010, **81**, 1799.
28. D. Neuhaus and M. Williamson, 'The Nuclear Overhauser Effect In Structural and Conformational Analysis', VCH Publisher, New York, 1989, pp. 451-502.
29. a) R. W. Adamiak, E. Biała, Z. Gdaniec, S. Mielewczyk, and B. Skalski, *Chem. Scr*., 1986, **26**, 3; b) B. Skalski, G. Wenska, Z. Gdaniec, and R. W. Adamiak, *Tetrahedron*, 1993, **49**, 5859.
30. J. Shorter, "*Electronic Effects of the Sulfinyl and Sulfonyl Groups*", chapter 10, ed. by S. Patai, Z. Rappoport, and C. Stirling, 'The Chemistry of Sulphones and Sulphoxides', John Willey & Sons, Chichester-New York-Brisbane-Toronto-Singapore, 1988, a) p 531, b) pp. 523-524.
31. A. Maślankiewicz and L. Skrzypek, *Heterocycles*, 1994, **38**, 1317.
32. Oxford Diffraction (2006) CrysAlis CCD and CrysAlis RED. Versions 1.171.32.29. Oxford Diffraction Ltd, Wrocław, Poland.
33. G. M. Sheldrick, *Acta Cryst*., 2008, **A 64**, 112.