PYRIDO- AND QUINO-1,2,4-THIADIAZINE S,S-DIOXIDES FROM REACTIONS OF 4-CHLORO-3-PYRIDINESULFONYL- AND 4-CHLORO-3-QUINOLINESULFONYL CHLORIDES WITH O-METHYLISOUREA #

Elwira Chrobak,a) ↓ Michal Wlekliński,a) Andrzej Maślankiewicz,a) ↓,* Joachim Kusz,b) Maciej Zubko,b) and Ewa Michalik a)↓

a) Department of Organic Chemistry, Medical University of Silesia, Jagiellońska 4, 41-200 Sosnowiec, Poland. b) Institute of Physics, University of Silesia, Uniwersytecka 4, 40-007 Katowice, Poland. E-mail: maslankiewicz@sum.edu.pl

Abstract – Reaction of 4-chloro-3-pyridinesulfonyl (or quinoline)sulfonyl chlorides (1) or (6) with O-methylisourea led to 4-chloro-3-pyridinesulfonyl-O-methylisourea (2a) or its quinoline analog 2b, respectively. Compounds 2a and 2b underwent dehydrochlorination to the title methoxy-pyrido or quino[4,3-e]-1,2,4-thiadiazine S,S-dioxides (3 and 7). X-Ray studies proved that both methoxy derivatives (3 and 7) exist as γazine-NH-tautomers. Reaction of N-H derivatives 3 and 7 with CH₃I/CH₃OK/DMF system proceeded at the pyridine-ring nitrogen and led to 7-methylpyrido derivative 4a or the 6-methylquino derivative 8a, respectively. After treatment with PhOP(O)Cl₂ at 120-150 ºC compounds 4a or 8a were converted to chloro derivatives 4b or 8b, respectively, which were then transformed to aminothiadiazines 5a,b,c or 9a,b,c.

INTRODUCTION

Benzo- and heteroarenofused 1,2,4-thiadiazine S,S-dioxides are promising candidates for drugs.¹⁻⁹ The above mentioned compounds are usually obtained in the processes of 1,2,4-thiadiazine S,S-dioxides moiety formation.¹,⁴,⁵,⁸⁻¹⁰ As concluded from a literature review⁵,¹¹ and our previous study,¹² a convenient short way leading to 1,2,4-thiadiazine S,S-dioxide derivatives consists in the reactions of ortho-chloroaren or heteroarensulfonyl chlorides with appropriate R-C(=NH)-NH₂ compounds such as amidines and guanidines. Since amino-de-chlorination at the chlorosulfonyl group is the first step in the transformations mentioned above, we turned to review the sulfonylation of other R-C(=NH)-NH₂ compounds. As sulfonylation of S-alkylisothioureas appeared to be ineffective, the same treatment of O-alkylisoureas was reported as a good preparative source of sulfonylureas.¹³ This induced the present study
on the reactions of 4-chloro-3-pyridinesulfonyl and 4-chloro-3-quinolinesulfonyl chlorides 1 or 6 with O-methylisourea as a source of the title pyrido- and quino-1,2,4-thiadiazine S,S-dioxide derivatives 3, 4, and 5 or 7, 8, and 9, respectively.

RESULTS AND DISCUSSION

Amination of \( \gamma \)-chloro-\( \beta \)-chlorosulfonylazine (pyridine or quinoline) (1) or (6)\(^{10,11,14} \) proceeded stepwise starting from the \textit{amino-de-chlorination} at the chlorosulfonyl group followed by \textit{amino-de-chlorination} at the \( \gamma \)-chloroazinyl position to give \( \gamma \)-amino-\( \beta \)-pyridinesulfonamides or \( \gamma \)-amino-\( \beta \)-quinolinesulfonamides, which were then subjected to cyclization to 1,2,4-thiadiazine S,S-dioxide derivatives.\(^{1,10,12} \) The same \textit{amino-de-chlorinations} sequence was observed for the reaction of \( \gamma \)-chloro-\( \beta \)-chlorosulfonylpyridine (1) and its quinoline analog 6 with guanidines,\(^{12} \) this procedure was thus applied for reactions of 4-chloro-3-pyridine- and 4-chloro-3-quinoline sulfonyl chlorides (1) or (6) with O-methylisourea. The reaction proceeded as sulfonylation and led to 4-chloro-3-pyridinesulfonyl-O-methylisourea (2a) or its quinoline analog 2b, respectively, in good yield. Compounds 2a and 2b were identified as sulfonamide-imino tautomers on the basis of \( ^1 \text{H} \) NMR spectra showing two non-identical NH signals. To perform the final \textit{amino-de-chlorination} at the \( \gamma \)-chloroazinyl positions, azinesulfonyl-O-methylisoureas 2a or 2b were subjected to reaction with the Cs\(_2\)CO\(_3\)/methanol system, which gave the expected pyrido and quino-1,2,4-thiadiazine S,S-dioxides 3 or 7. The structure of 3 or 7 as \( \gamma \)-aminoazine tautomers was deduced from X-ray diffraction studies, presented in Figures 1 and 2.

\[
\begin{align*}
\text{Cl} & \quad \text{SO}_2\text{Cl} & \quad \text{NH}_2 & \quad \text{OMe} \quad \text{Cl}^- \quad \xrightarrow{20\% \text{NaOH aq., acetone, } -5\,^\circ\text{C}} \quad \text{Cl} & \quad \text{SO}_2\text{NH} & \quad \text{OMe} \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{Cl} & \quad \text{NH}_2 & \quad \text{OMe} \\
\text{N} & \quad \text{Me} & \quad \text{S} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
\text{N} & \quad \text{Me} & \quad \text{S} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
\text{Cl} & \quad \text{SO}_2 & \quad \text{Cl} & \quad \text{NH}_2 & \quad \text{OMe} & \quad \text{Cl}^- \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{N} & \quad \text{N} & \quad \text{OMe} \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{N} & \quad \text{N} & \quad \text{OMe} \\
\end{align*}
\]

\[ \begin{align*}
\text{Cl} & \quad \text{SO}_2 \quad \text{Cl} & \quad \text{H}_2 \text{N} & \quad \text{OMe} \quad \text{Cl}^- & \xrightarrow{\text{a}) \text{ Cs}_2\text{CO}_3, \text{MeOH, autoclave, } 90\,^\circ\text{C}} \quad \text{Cl} & \quad \text{SO}_2 \quad \text{NH} & \quad \text{OMe} \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{N} & \quad \text{N} & \quad \text{OMe} \\
\text{N} & \quad \text{Me} & \quad \text{S} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
\text{N} & \quad \text{Me} & \quad \text{S} & \quad \text{O} & \quad \text{N} & \quad \text{Me} \\
\text{Cl} & \quad \text{SO}_2 & \quad \text{Cl} & \quad \text{NH}_2 & \quad \text{OMe} & \quad \text{Cl}^- \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{N} & \quad \text{N} & \quad \text{OMe} \\
\text{N} & \quad \text{Cl} & \quad \text{SO}_2 & \quad \text{N} & \quad \text{N} & \quad \text{OMe} \\
\end{align*} \]

a) \text{Cs}_2\text{CO}_3, \text{MeOH, autoclave, } 90\,^\circ\text{C}. b) \text{Et}_3\text{NH}^+\text{Cl}^- . c) \text{aqueous NH}_3 \text{ or Me}_2\text{NH solutions, autoclave, } 100-105\,^\circ\text{C}, 2h. d) \text{n-BuNH}_2 \text{ at boiling temp., } 1\,\text{h.}

Scheme 1
Scheme 2

Figure 1. ORTEP drawing of 3-methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3) semi-DMSO solvate with the atom labelling scheme. Displacement ellipsoids are drawn at the 70% probability level.
**Figure 2.** ORTEP drawing of 2-methoxy-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7) hydrate with the atom labelling scheme. Displacement ellipsoids are drawn at the 70% probability level.

**N-Methylation**

Methylation of sodium (or potassium) salts of 2-methyl-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (11) and 2-dimethylamino-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (12) proceeded at the *endocyclic* nitrogen of the pyridine-ring and led to 6-methyl derivatives.\textsuperscript{12} Methylation of sodium (or potassium) salts of 3-dimethylaminopyrido-1,2,4-thiadiazine dioxide (10), proceeded also at the *endocyclic* nitrogen of the pyridine-ring to form 7-methyl derivative.\textsuperscript{12}

**Scheme 3.** Orientation in the alkylation of some pyrido- and quino-1,2,4-thiadiazine S,S-dioxide derivatives 10, 11, 12,\textsuperscript{12} and 6,7-disubstituted benzothiadiazine 1,1-dioxide derivatives 13.\textsuperscript{4}
The same regioorientation during methylation was observed in this work for potassium salts of 2-methoxy-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7) and 3-methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3), which underwent transformation to 6-methyl derivative 8a or 7-methyl derivative 4a. (Schemes 1 and 2). Although alkylation of sodium (or potassium) salts of pyrido and quinothiadiazine S,S-dioxides 3 or 7 may formally follow through the nitrogen anionic forms I, II, III, the least hindered pyridine-ring nitrogen anion III appears to be the most reactive nucleophilic agent.

The structure of 4a and 8a and the position of the newly-introduced N-CH₃ group was concluded from HSQC and HMBC experiments as presented in Scheme 5.

The synthesis of the pyrido- and quino-1,2,4-thiadiazine S,S-dioxides 4a or 8a, presented above (Schemes 1 and 2) provides easy access to the 1,2,4-thiadiazine derivatives fused with a 1,4-dihydropyridine or a 1,4-dihydroquinoline unit. Transformation of methoxy substituent at thiadiazine ring of compounds 4a or 8a into more active leaving group is however necessary for further functionalization of pyrido- and quino-1,2,4-thiadiazine S,S-dioxides 4a or 8a, as a first step to the preparation of biologically active compounds. For this purpose, methoxy derivatives 4a or 8a, were subjected to demethoxy-chlorination. Although no reaction was observed in a boiling POCl₃/Et₃N x HCl system, in the reaction with PhOP(O)Cl₂/Et₃N x HCl system the compounds 4a (120 ºC) or 8a (150 ºC) were converted to chlorothiadiazines 4b or 8b, respectively. Finally, reactions of chlorothiadiazines 4b or 8b with amines led to aminothiadiazines 5a,b,c or 9a,b,c, respectively.
\(^1\)H NMR spectra of \(n\)-butylamino derivatives 5b and 9b show resonances of the alkyl and aromatic protons of two species having very similar coupling patterns in the ratio of 1:0.3 (as deduced from the intensities of \(\alpha\)-methylene protons as well as from \(\alpha\)-azinyl protons). This observation could be interpreted in terms of restricted rotation about the \textit{exo}cyclic amine bond taking into account that in the case of numerous unsymmetrical \(N\)-alkyl(aryl)guanidines hindered rotation can give rise to cis- and trans-rotational isomers\(^ {18}\) and that the electronic structure of the guanidine part of compounds 5b and 9b should be described with mesomeric formulae A, B, C and D (see Scheme 6).

\[ \text{Scheme 6} \]

**CONCLUSIONS**

The title pyrido- and quinol[4,3-e]-1,2,4-thiadiazine \(S,S\)-dioxides 3, 7 are easily available in a two-step process starting from reaction of \(O\)-methylisourea with 4-chloro-3-pyridine-(and quinoline)sulfonyl chlorides (1) and (6) followed by cyclization of the \(O\)-methylsulfonylisoureas 2a,b to compounds 3, 7. Although both 1,2,4-thiadiazine \(S,S\)-dioxides exist in the form of \(4_{\text{thiadiazinic}}\) NH-tautomers, the potassium salts of 3, 7 were methylated outside the thiadiazine ring at the pyridine ring nitrogen, which led to 7-methyl derivative 4a or 6-methyl derivative 8a, respectively. Transformation of methoxythiadiazines 4a, 8a to chlorothiadiazines 4b, 8b followed by amination of the latter to aminothiadiazines 5a,b,c or 9a,b,c opens a new route to 1,2,4-thiadiazine \(S,S\)-dioxide derivatives fused with 1,4-dihydropyridine or 1,4-dihydroquinoline unit.

**EXPERIMENTAL**

Melting points were taken 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 \(^1\)H and \(^{13}\)C nuclei, respectively, in DMSO-\(d_6\) solutions with tetramethylsilane (\(\delta\) 0.0 ppm) as internal standard. Two-dimensional \(^1\)H-\(^{13}\)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 \(^1\)H 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 \(^1\)H/\(^{13}\)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. TLC analyses were performed employing Merck’s SiO\(_2\) oxide 60 F\(_{254}\) neutral (type E) plates and using CHCl\(_3\)/EtOH mixture (3 : 1, v/v) as an eluent.
O-Methylisourea hydrochloride was commercial product. 4-Chloro-3-pyridinesulfonfyl chloride (1)\textsuperscript{10,15} and 4-chloro-3-quinolinesulfonfyl chloride (6) were prepared as described previously.\textsuperscript{14}

Sulfonylation of O-methylisourea hydrochloride to \(N^1\)-(4-chloro-3-pyridinesulfonfyl)-O-methylisourea (2a) and to \(N^1\)-(4-chloro-3-quinolinesulfonfyl)-O-methylisourea (2b):

A suspension of 4-chloro-3-quinolinesulfonfyl chloride (1) (0.52 g, 2 mMol) in 4 mL of acetone and a solution of O-methylisourea hydrochloride 0.22 g (2 mMol) in water (1.3 mL) were stirred at -5 °C and aqueous NaOH (160 mg + 0.75 mL of water) was added in three portions. Each portion was added once the mixture became neutral (pH~7). The mixture was kept in refrigerator at 0 °C for 16 h. The solid was filtered off and washed with cold acetone. Sulfonyl-O-methylisourea 2a (53%) and 2b (50%) were recrystallized from methanol or ethanol.

\(N^1\)-(4-Chloro-3-pyridinesulfonfyl)-O-methylisourea (2a):

\(N^1\)-(4-Chloro-3-quinolinesulfonfyl)-O-methylisourea (2b):

\[\text{mp 153-156 °C (MeOH), decomp. EIMS (70 eV): m/z (\%) = 249 (23.5, M^+), 250 [(7.8, (M + 1)^+], 251 [(8.9, (M + 2)^+).}\]

\[\text{\(1^H\) NMR (DMSO-d_6), \(\delta\): 3.68 (s, 3H, OCH_3), 7.48 (bs, 1H, NH), 7.63 (d, \(3J = 5.3\) Hz, 1H, H5), 8.48 (bs, 1H, NH), 8.73 (d, \(3J = 5.6\)Hz, 1H, H6), 9.11 (s, 1H, H2).}\]


\(N^1\)-(4-Chloro-3-quinolinesulfonfyl)-O-methylisourea (2b):

\[\text{mp 181-183 °C (EtOH), decomp. EIMS (70 eV): m/z (\%) = 299 (89.6, M^+), 301 [34.6, (M+2)^+].}\]

\[\text{\(1^H\) NMR (DMSO-d_6), \(\delta\): 3.64 (s, 3H, OCH_3), 7.52 (bs, 1H, NH), 7.82-7.86 (m, 1H, H_\text{arom}), 7.95-7.99 (m, 1H, H_\text{arom}), 8.12-8.14 (m, 1H, H_\text{arom}), 8.36-8.39 (m, 1H, H_\text{arom}), 8.45 (bs, 1H, NH), 9.34 (s, 1H, H-2).}\]

\[\text{Anal. Calcd for C_{11}H_{10}ClN_3O_3S: C 44.08, H 3.36, N 14.02. Found: C 44.53, H 3.17, N 14.04.}\]

Cyclization of \(N^1\)-(4-chloro-3-pyridinesulfonfyl)-O-methylisourea (2a) and \(N^1\)-(4-chloro-3-quinolinesulfonfyl)-O-methylisourea (2b) to 3-methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3) and 2-methoxy-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7):

Pyridinesulfonfyl-O-methylisourea 2a or quinolinesulfonfyl-O-methylisourea 2b (3 mMol), cesium carbonate (1.45 g, 4.5 mMol) and 20 mL of dry methanol were placed in a steel autoclave. It was kept in an oil-bath at 110 °C for 3 h. The mixture was cooled down to rt, transferred to distillation flask and then concentrated to dryness under vaccum. The residue was dissolved in water (ca. 9 mL for 2a, 30 mL for 2b) and acidified at 0 °C with formic acid up to pH ~ 3. The solid was filtered off, washed with cold water and dried on air. Crude thiadiazines 3 or 7 were recrystallized from methanol (or acetone) to give pyridothiadiazine 3 (0.38 g, 60%) or quinothiadiazine 7 (0.55 g, 70%).

3-Methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3)
mp 158-160 °C decomp. (MeOH). EIMS (70 eV): m/z (%) = 213 (94.1, M⁺), 156 (100). ¹H NMR (DMSO-
-d6), δ: 3.93 (s, 3H, OCH₃), 7.19 (d, 3J = 5.6 Hz, 1H, H5), 8.64 (d, 3J = 5.6Hz, 1H, H6), 8.92 (s, 1H, H8),
12.57 (bs, 1H, NH). Anal. Calcd for C₇H₇N₃O₃S x H₂O: C 36.36, H 3.92, N 18.17. Found: C 36.50, H 4.0,
N 17.81.

2-Methoxy-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7)
mp 139-140 °C decomp. (acetone). EIMS (70 eV): m/z (%) = 263 (100, M⁺). ¹H NMR (DMSO-
d6), δ: 3.95 (s, 3H, OCH₃), 7.75-7.79 (m, 1H, H arom), 7.95-7.99 (m, 1H, H arom), 8.02-8.04 (m, 1H, H arom), 8.67-8.69 (m, 1H, H arom), 9.19 (s, 1H, H-5). Anal. Calcd for C₁₁H₁₀N₃O₃S x H₂O: C 46.97, H 3.94, N 14.94. Found: C 46.53, H 3.87, N 14.80.

N-Methylation of 3-methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3) and 2-methoxy-(1H)-
quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7):
Potassium methoxide (0.150 g, ca. 2.1 mM) was added on stirring to the suspension of 2 mmol of
pyridothiadiazine 1,1-dioxide 3 or quinothiadiazine 4,4-dioxide 7 in dry DMF (5 mL). The mixture was
stirred for 5-10 min until the mixture became clear. Then, a solution of methyl iodide (0.8 mL, ca. 2
mM) in DMF (2.5 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. It was boiled with EtOH to give 3-
methoxy-7-methylpyridothiadiazine 1,1-dioxide 4a (240 mg, 52%) or 2-methoxy-6-methylquino
thiadiazine 4,4-dioxide 8a (380 mg, 69%).

3-Methoxy-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (4a)
mp 253-254 ºC (EtOH), decomp. EIMS (70 eV): m/z (%) = 227 (43.5, M⁺). ¹H NMR (DMSO-
d6), δ [δC
for carbons from single bond and / long range proton-carbon correlations]: 3.77 [(s, 3H, CH₃O); 54.3
(CH₃O)/ 163.4 (C3)], 4.05 [(s, 3H, CH₃N); 45.5 (CH₃N)/ 142.1 (C8), 143.4 (C6)], 7.2 [(d, 3J=7.2 Hz, 1H,
H5); 120.1 (C5)/ 119.5 (C8a), 143.4 (C6)], 8.27 [(dd, 3J=7.2 Hz, 4J=1.6 Hz, 1H, H6); 143.4 (C6)/ 45.5
(CH₃N), 120.1 (C5), 142.1 (C8), 157.9 (C4a)], 9.08 [(d, 4J=1.6 Hz, 1H, H8); 142.1 (C8)/ 45.5 (CH₃N),
119.5 (C8a), 143.4 (C6), 157.9 (C4a)]. Anal. Calcd for C₈H₉N₃O₃S: C 42.28, H 3.99, N 18.49. Found: C
42.48, H 3.88, N 18.28.

2-Methoxy-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (8a)
mp 263-266 ºC (DMF). EIMS (70 eV): m/z (%) = 277 (54.4, M⁺), 183 (100). ¹H NMR (DMSO-
d6), δ [δC
for carbons from single bond and / long range proton-carbon correlations]: 3.88 [(s, 3H, CH₃O); 54.5
(CH₃O)/ 163.0 (C2)], 4.28 [(s, 3H, CH₃N); 42.7 (CH₃N)/ 138.6 (C6a), 145.1 (C5)], 7.81 [(m, 1H, H9);
127.9 (C9)/ 118.5 (C7), 123.9 (C10a)], 8.06 [(m, 1H, H8); 134.1 (C8)/ 138.6 (C6a), 125.4 (C10)], 8.11
[(m, 1H, H7); 118.5 (C7)/123.9 (C10a), 127.9 (C9), 157.1 (C10b)], 9.41 [(s, 1H, H5); 145.1 (C5)/ 42.7
(CH₃N), 111.8(C4a), 138.6 (C6a), 157.1 (C10b)]. Anal. Calcd for C₁₂H₁₁N₃O₃S: C 51.98, H 4.00, N 15.15.
Reaction of methoxy-azino-thiadiazines 4a or 8a with phenyl dichlorophosphate leading to chloro-azino-thiadiazines 4b or 8b

Suspension of 1 mMol of methoxy derivative 4a or 8a and triethylamine hydrochloride (15 mg) in phenyl dichlorophosphate (1 mL, ca. 6.8 mMol) was stirred at 120 ºC for 4a or 150 ºC for 8a (both oil-bath temperature) for 4 h. The mixture was cooled down to rt and poured into 10 g of the mixture of water and ice and then neutralized with 25 % ammonia to pH~6.7. The solid was filtered off, washed with water and dried on air. Crude product was boiled with EtOH. Hot solution was decanted off to leave 3-chloro-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (4b) (145 mg, 62%) or 2-chloro-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (8b) (230 mg, 82%).

3-Chloro-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (4b)

mp 330 ºC decomp. (EtOH). EIMS (70 eV): m/z (%) = 231 (34, M+), [11.2, (M + 2)+]. 1H NMR (DMSO-d_6), δ: 4.15 (s, 3H, CH_3N), 7.49 (d, J=7.1 Hz, 1H, H5), 8.54 (dd, J=7.1 Hz, 4J=1.5 Hz, 1H, H6), 9.38 (d, 4J=1.5 Hz, 1H, H8). Anal. Calcd for C_7H_6ClN_3O_2S: C 36.29, H 2.61, N 18.14. Found: C 36.62, H 2.97, N 17.42.

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

mp 281-284 ºC (EtOH), decomp. EIMS (70 eV): m/z (%) = 281 (100, M+), 282 [12.9, (M + 1)], 283 [35.5, M + 2]). 1H NMR (DMSO-d_6), δ: 4.40 (s, 3H, CH_3N), 7.90-7.94 (m, 1H, H_ arom), 8.14-8.19 (m, 1H, H_ arom), 8.24-8.26 (m, 1H, H_ arom), 8.73-8.76 (m, 1H, H_ arom), 9.71 (s, 1H, H5). Anal. Calcd for C_{11}H_8ClN_3O_2S: C 46.90, H 2.86, N 14.92. Found: C 46.54, H 3.10, N 14.57.

Amination of 3-chloro-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (4b) and 2-chloro-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (8b):

a) with aqueous ammonia or with aqueous dimethylamine

Chloropyridothiadiazine 4b or chloroquinothiadiazine 8b (1 mmol), and 5 mL of conc. aqueous ammonia or 4 mL of 40 % aqueous Me_2NH solution was 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 distillation flask and an excex of NH_3 or Me_2NH was then distilled off under vaccum. The solid was filered off, washed with cold water and boiled with EtOH. Hot solution was decanted off to leave amino derivatives 5a (181 mg, 85%) or 9a (228 mg, 87%), or dimethylamino derivatives 5c (180 mg, 79%) and 9c (256 mg, 88%).

b) with n-butylamine

Chloropyridothiadiazine 4b or chloroquinothiadiazine 8b (1 mmol) and n-butylamine (4 mL) was refluxed for 1 h. Excess of n-butylamine was then evaporated to dryness under reduced pressure from
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 on air to give crude 5c (220 mg) or crude 9c (280 mg). Products were purified by column chromatography ((SiO₂, CHCl₃/EtOH, 3:1, v/v) and recrystallized from ethanol to give 5b (205 mg, 77%) or 9b (237 mg, 75%).

**3-Amino-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (5a)**

mp 316-319 °C (EtOH). EIMS (70 eV): m/z(%) = 212 (45, M⁺), 148 (100). ¹H NMR (DMSO-d₆), δ: 3.93 (s, 3H, NCH₃), 6.86 (d, ³J=7.2 Hz, 1H, H5), 6.9 (bs, 2H, NH₂), 8.01 (dd, ³J=7.2 Hz, ⁴J=1.6 Hz, 1H, H6), 8.73 (d, ⁴J=1.7 Hz, 1H, H8). Anal. Calcd for C₇H₈N₄O₂S: C 39.62, H 3.80, N 26.40. Found: C 39.23, H 3.76, N 25.81.

**3-Butylamino-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (5b)**

mp 219-222 °C (EtOH). EIMS (70 eV): m/z(%) = 268 (6.9, M⁺), 133 (100). ¹H NMR spectrum contains the spectral lines of the same functional groups of two species A and B in the ratio 1:0.3, despite the fact that the product seems to be chromatographically homogeneous. ¹H NMR (DMSO-d₆), species A δ: 0.86-0.90 (m, 3H, CH₃), 1.25-1.34 (m, 2H, CH₂), 1.42-1.49 (m, 2H, CH₂), 3.11-3.16 (m, 2H, CH₂), 3.90 (s, 3H, NCH₃), 6.78 (d, ³J=7.3 Hz, 1H, H5), 7.51-7.53 (m-t, 1H, NH), 7.96 (dd, ³J=7.3 Hz, ⁴J=1.7 Hz, 1H, H6), 8.67 (d, ⁴J=1.7 Hz, 1H, H8), species B δ: 0.86-0.90 (m, 3H, CH₃), 1.25-1.34 (m, 2H, CH₂), 1.42-1.49 (m, 2H, CH₂), 3.29-3.30 (m, 2H, CH₂), 3.94 (s, 3H, NCH₃), 6.96 (d, ³J=7.2 Hz, 1H, H5), 7.25-7.30 (m-t, 1H, NH), 8.44 (dd, ³J=7.2 Hz, ⁴J=1.7 Hz, 1H, H6), 8.75 (d, ⁴J=1.7 Hz, 1H, H8). Anal. Calcd for C₁₁H₁₆N₄O₂S: C 49.24, H 6.01, N 20.88. Found: C 49.02, H 5.96, N 20.51.

**3-Dimethylamino-7-methyl-(7H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (5c)**

mp 261-263 ºC (EtOH). Mp and ¹H NMR spectrum in DMSO-d₆ were identical with the reported data.³

**2-Amino-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (9a):**

mp 324-325 °C (EtOH). EIMS (70 eV): m/z(%) = 262 (100, M⁺). ¹H NMR (DMSO-d₆), δ: 4.15 (s, 3H, NCH₃), 7.15 (bs, 2H, NH₂), 7.70-7.74 (m, 1H, Hₐrom), 7.95-7.97 (m, 2H, Hₐrom, NH), 8.66-8.68 (m, 1H, Hₐrom), 9.06 (s, 1H, H₅). Anal. Calcd for C₁₁H₁₀N₄O₂S: C 50.37, H 3.84, N 21.36. Found: C 50.05, H 3.93, N 20.99.

**2-Butylamino-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (9b):**

mp 209-212 °C (EtOH). EIMS (70 eV): m/z(%) = 318 (7.1, M⁺), 183 (100). ¹H NMR spectrum contains the spectral lines of the same functional groups of two species A and B in the ratio 1:0.3, despite the fact that the product seems to be chromatographically homogeneous. ¹H NMR (DMSO-d₆), species A δ: 0.86-0.93 (m, 3H, CH₃), 1.30-1.39 (m, 2H, CH₂), 1.49-1.56 (m, 2H, CH₂), 3.20-3.23 (m, 2H, CH₂), 4.12 (s, 3H, NCH₃), 7.68-7.72 (m, 1H, Hₐrom), 7.77-7.80 (m, 1H, Hₐrom), 7.92-7.95 (m, 2H, Hₐrom, NH), 8.63-8.65 (m, 1H, Hₐrom), 8.99 (s, 1H, H₅); species B δ: 0.86-93 (m, 3H, CH₃), 1.30-1.39 (m, 2H, CH₂), 1.49-
2.56 (m, 2H, CH₂), 3.47-3.52 (m, 2H, CH₂), 4.17 (s, 3H, NCH₃), 7.55-7.58 (m, 1H, Hₐrom), 7.74-7.76 (m, 1H, Hₐrom), 7.98-7.99 (m, 2H, Hₐrom, NH), 8.71-8.73 (m, 1H, Hₐrom), 9.09 (s, 1H, H₅). Anal. Calcd for C₁₅H₁₈N₄O₂S: C 56.58, H 5.70, N 17.60. Found: C 56.71, H 5.51, N 17.59.

2-Dimethylamino-6-methyl-(6H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (9c):

mp 283-286 °C (EtOH). Mp and ¹H NMR spectrum in DMSO-d₆ were identical with the reported data.³

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. The crystal structures were solved by direct methods with the program SHELXS-97²¹ and refined by full-matrix least-squares method on F² with SHELXL-97.¹⁷

Crystals of 3-methoxy-(4H)-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (3) semi-DMSO solvate were obtained by slow evaporation of DMSO solution at room temperature. Crystal data for 3: monoclinic, space group P2₁/c, a = 8.2579(1) Å, b = 16.0022(2) Å, c = 15.7348(2) Å, α = 90°, β = 92.093(1)°, γ = 90°, V = 2077.88(4) Å³, Z = 4, dₓ = 1.613 Mg m⁻³, T = 100(1) K, Data were collected for a crystal of dimensions 0.48 x 0.16 x 0.16 mm³. Final R indices for 3385 reflections with I > 2σ(I) and 313 refined parameters are R₁ = 0.0255, wR₂ = 0.0681 (R₁ = 0.0279, wR₂ = 0.0690 for all 3674 data).

Crystals of 2-methoxy-(1H)-quino[4,3-e]-1,2,4-thiadiazine 4,4-dioxide (7) hydrate were grown by slow evaporation from acetone – water (5 : 1, v/v) solution at room temperature. Crystal data for 7: monoclinic, space group P2₁/c, a = 20.0087(3) Å, b = 8.8774(1) Å, c = 20.1801(4) Å, α = 90°, β = 139.600(1)°, γ = 90°, V = 2323.18(8) Å³, Z = 8, dₓ = 1.608 Mg m⁻³, T = 100(1) K, Data were collected for a crystal of dimensions 0.32 x 0.24 x 0.17 mm³. Final R indices for 6823 reflections with I > 2σ(I) and 376 refined parameters are R₁ = 0.0322, wR₂ = 0.0954, (R₁ = 0.0463 and wR₂ = 0.0980 for all 9195 data).

Crystallographic data for compounds 3 and 7 have been deposited with Cambridge Crystallographic Data Centre (CCDC deposition numbers 802223 and 802222 respectively) Copies of the data can be obtained upon request from CCDC, 12 Union road, Cambridge CB2 1EZ, UK).

REFERENCES AND NOTES

# Part CXXVI in the series of Azinyl Sulfides.

┴ These authors contributed equally to the work.


