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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 [#]

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Abstract – Reaction of 4-chloro-3- pyridine- (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 γ_{azine}-NH-tautomers. Reaction of N-H derivatives **3** and **7** with CH_3I/CH_3OK/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 $PhOP(O)Cl_2$ 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**.

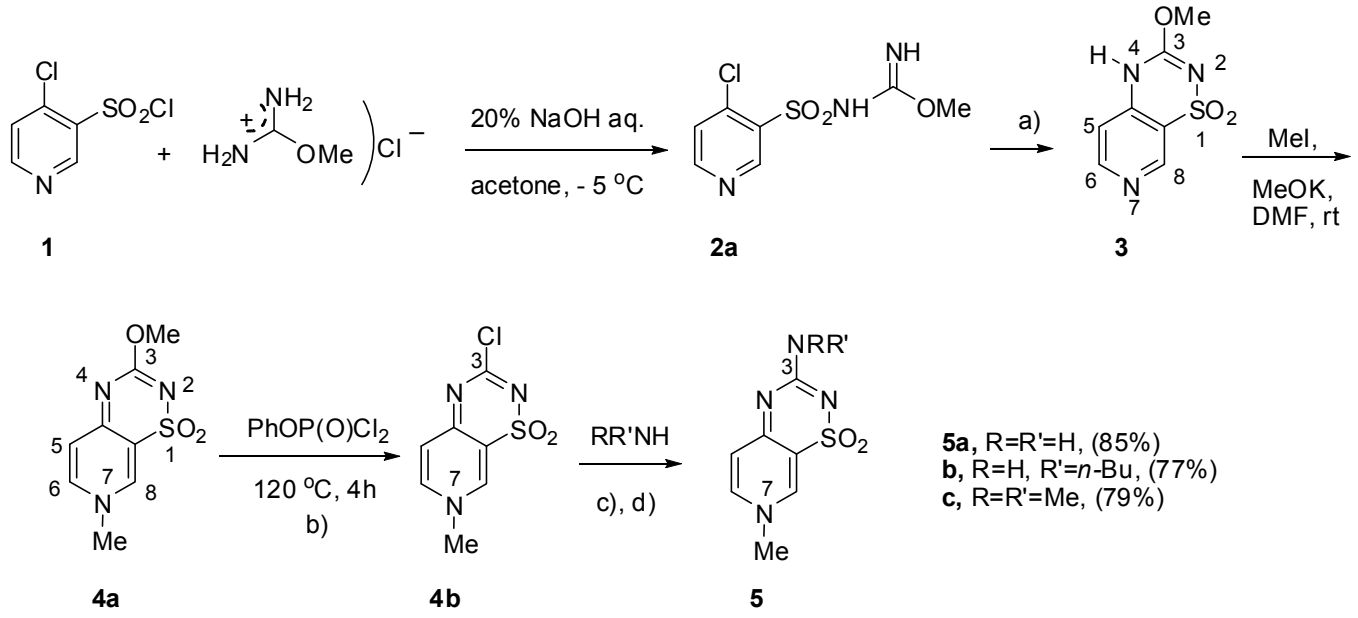
INTRODUCTION

Benzo- and heteroareno-fused 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 review[5,11] 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*-chloroareno or heteroarenosulfonyl chlorides with appropriate R-C(=NH)-NH_2 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)-NH_2 compounds. As sulfonylation of *S*-alkylisothioureas appeared to be uneffective, 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

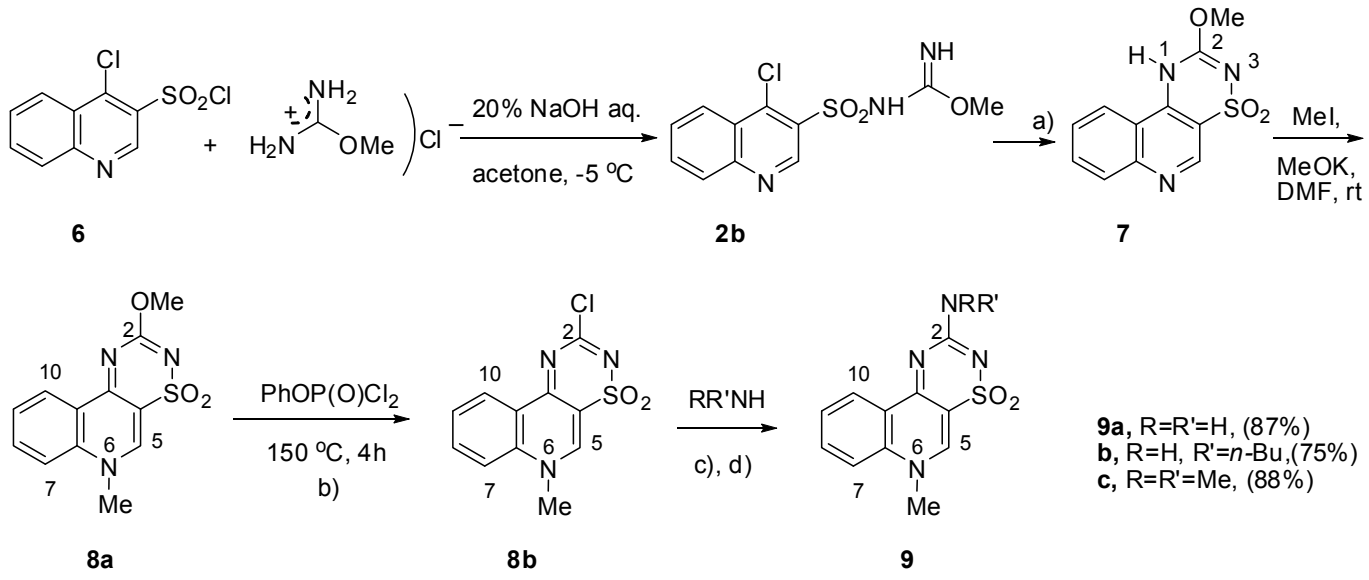
Amination of γ-chloro-β-chlorosulfonylazine (pyridine or quinoline) (**1)** or (**6**)[10,11,14] proceeded stepwise starting from the *amino-de-chlorination* at the chlorosulfonyl group followed by *amino-de-chlorination* at the γ-chloroazinyl position to give γ-amino-β-pyridinesulfonamides or γ-amino-β-quinolinesulfonamides, which were then subjected to cyclization to 1,2,4-thiadiazine *S,S*-dioxide derivatives.[1,10,12] The same *amino-de-chlorinations* sequence was observed for the reaction of γ-chloro-β-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}H NMR spectra showing two non-identical NH signals. To perform the final *amino-de-chlorination* at the γ-chloroazinyl positions, azinesulfonyl-*O*-methylisoureas **2a** or **2b** were subjected to reaction with the Cs_2CO_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 γ-aminoazine tautomers was deduced from X-ray diffraction studies, presented in Figures 1 and 2.



1 **2a** **3** **4a** **4b** **5**

a) Cs_2CO_3, MeOH, autoclave, 90 °C. b) $Et_3NH^+Cl^-$. c) aqueous NH_3 or Me_2NH solutions, autoclave, 100-105 °C, 2h. d) *n*-$BuNH_2$ at boiling temp., 1 h.

Scheme 1



a) Cs_2CO_3, MeOH, autoclave, 90 °C. b) $Et_3NH^+Cl^-$. c) aqueous NH_3 or Me_2NH solutions, autoclave, 100-105 °C, 2h. d) *n*-$BuNH_2$ at boiling temp., 1 h.

Scheme 2

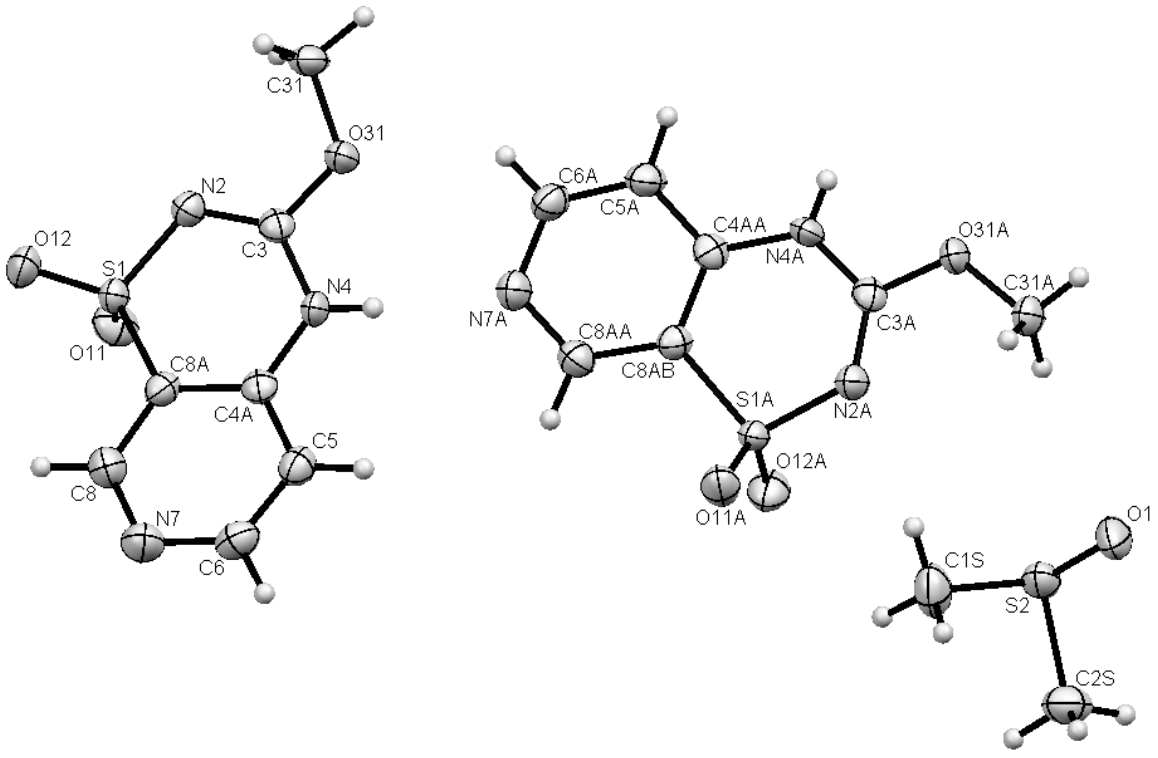


Figure 1. ORTEP drawing of 3-methoxy-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3**) semi-DMSO solvate with the atom labelling scheme. Displacement ellipsoids are drawn at the 70% probability level.

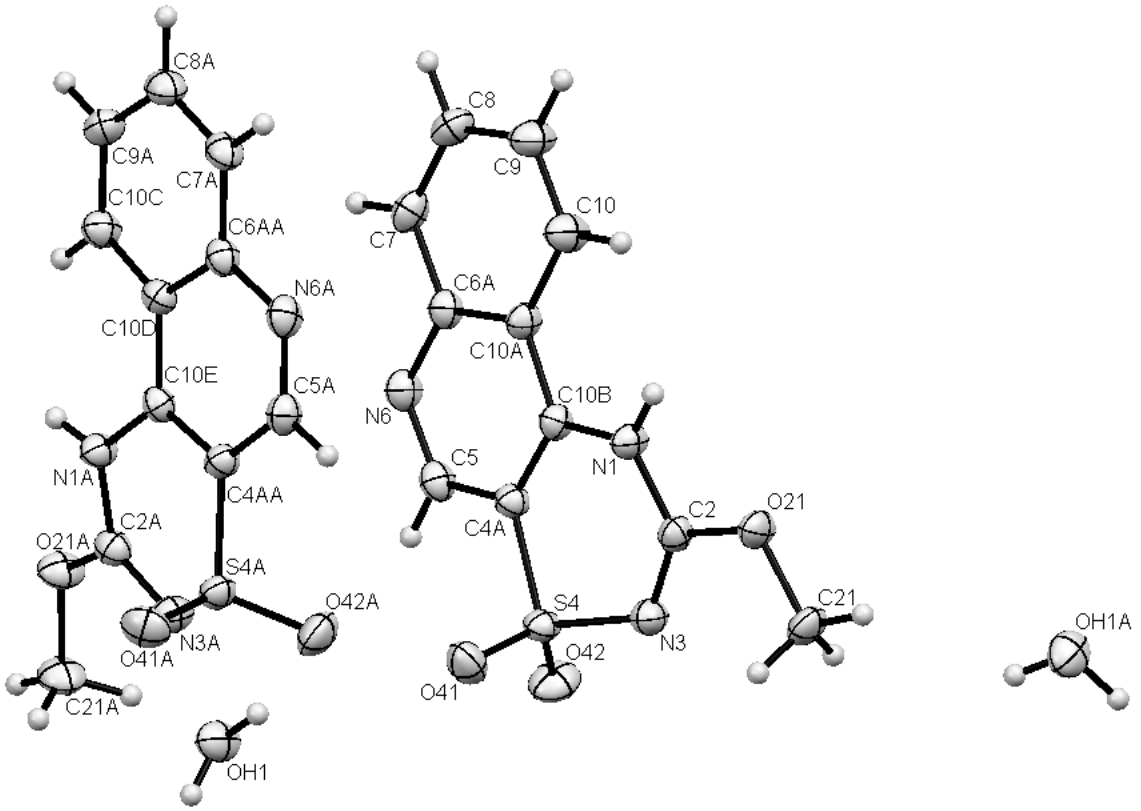
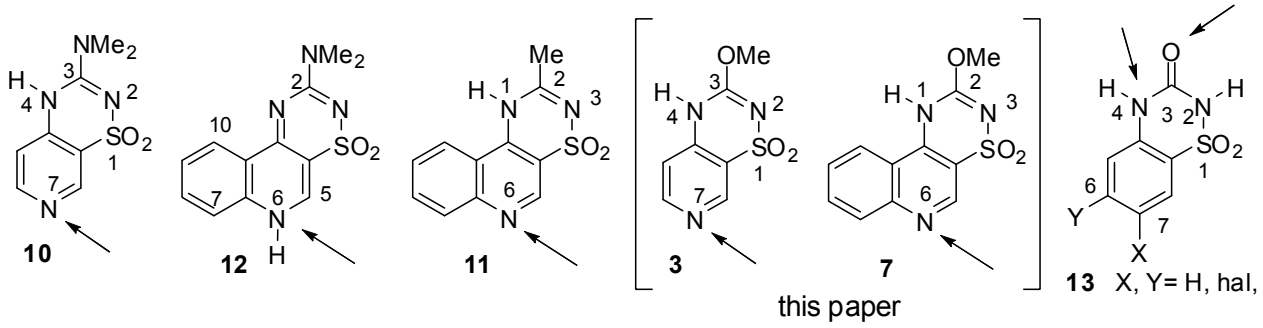


Figure 2. ORTEP drawing of 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7**) hydrate with the atom labelling scheme. Displacement ellipsoids are drawn at the 70% probability level.

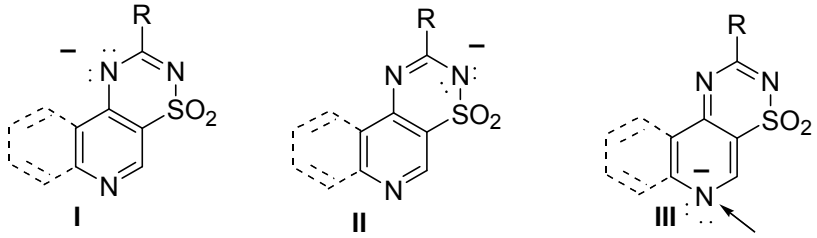
N-Methylation

Methylation of sodium (or potassium) salts of 2-methyl-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**11**) and 2-dimethylamino-(6*H*)-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.[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.[12]



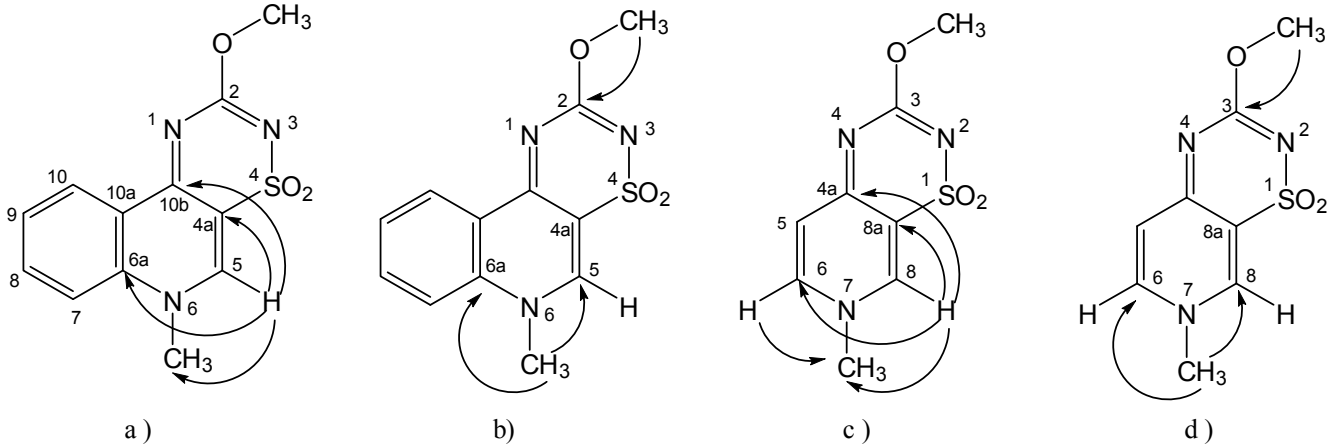
Scheme 3. Orientation in the alkylation of some pyrido- and quino-1,2,4-thiadiazine *S,S*-dioxide derivatives **10, 11, 12**,[12] and 6,7-disubstituted benzothiadiazine 1,1-dioxide derivatives **13**.[4]

The same regioorientation during methylation was observed in this work for potassium salts of 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7**) and 3-methoxy-(4*H*)-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.



Scheme 4

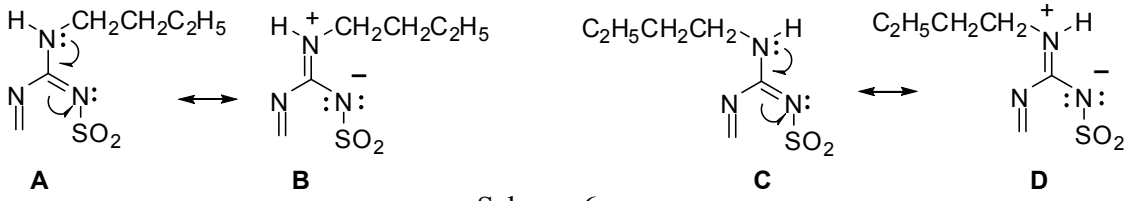
The structure of **4a** and **8a** and the position of the newly-introduced N-CH_3 group was concluded from HSQC and HMBC experiments as presented in Scheme 5.



Scheme 5. Selected long-range proton-carbon correlations used in the NMR assignment of 7-methylpyridothiadiazine dioxide **4a** and 6-methylquinothiadiazine dioxide **8a**

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 $POCl_3/Et_3N$ x HCl system, in the reaction with $PhOP(O)Cl_2/Et_3N$ 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 α-methylene protons as well as from α-azinyl protons). This observation could be interpreted in terms of restricted rotation about the *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).



Scheme 6

CONCLUSIONS

The title pyrido- and quino[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 $4_{thiadiazinic}$ 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 (δ 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-pyridinesulfonyl chloride (**1**)[10,15] and 4-chloro-3-quinolinesulfonyl chloride (**6**) were prepared as described previously.[14]

Sulfonylation of *O*-methylisourea hydrochloride to N^1-(4-chloro-3-pyridinesulfonyl)-*O*-methylisourea (**2a**) and to N^1-(4-chloro-3-quinolinesulfonyl)-*O*-methylisourea (**2b**):

A suspension of 4-chloro-3-quinolinesulfonyl 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 ºC 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 ºC 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-pyridinesulfonyl)-*O*-methylisourea (**2a**):

mp 153-156 ºC (MeOH), decomp. EIMS (70 eV): m/z (%) = 249 (23.5, M^+), 250 [(7.8, $(M + 1)^+$], 251 [(8.9, $(M + 2)^+$]. ^{1}H NMR (DMSO-d_6), δ: 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 = 5.6Hz, 1H, H6), 9.11 (s, 1H, H2). *Anal.* Calcd for $C_7H_8ClN_3O_3S$: C 33.67, H 3.23, N 16.83. Found: C 33.94, H 3.07, N 16.80.

N^1-(4-Chloro-3-quinolinesulfonyl)-*O*-methylisourea (**2b**):

mp 181-183 ºC (EtOH), decomp. EIMS (70 eV): m/z (%) = 299 (89.6, M^+), 301 [34.6, $(M+2)^+$]. ^{1}H NMR (DMSO-d_6), δ: 3.64 (s, 3H, OCH_3), 7.52 (bs, 1H, NH), 7.82-7.86 (m, 1H, $\mathbf{H}_{arom}$), 7.95-7.99 (m, 1H, $\mathbf{H}_{arom}$), 8.12-8.14 (m, 1H, $\mathbf{H}_{arom}$), 8.36-8.39 (m, 1H, $\mathbf{H}_{arom}$), 8.45 (bs, 1H, NH), 9.34 (s, 1H, **H**-2). *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-pyridinesulfonyl)-*O*-methylisourea (**2a**) and N^1-(4-chloro-3-quinolinesulfonyl)-*O*-methylisourea (**2b**) to 3-methoxy-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3**) and 2-methoxy-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7**):

Pyridinesulfonyl-*O*-methylisourea **2a** or quinolinesulfonyl-*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 ºC 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 ºC 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-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3**)

mp 158-160 ºC $_{decomp.}$ (MeOH). EIMS (70 eV): m/z (%) = 213 (94.1, M^+), 156 (100). ^{1}H NMR (DMSO-d_6), δ: 3.93 (s, 3H, OCH_3), 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 $C_7H_7N_3O_3S$ x H_2O: C 36.36, H 3.92, N 18.17. Found: C 36.50, H 4.0, N 17.81.

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

mp 139-140 ºC$_{decomp.}$ (acetone). EIMS (70 eV): m/z (%) = 263 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 3.95 (s, 3H, OCH_3), 7.75-7.79 (m, 1H, $\mathbf{H}_{arom}$), 7.95-7.99 (m, 1H, $\mathbf{H}_{arom}$), 8.02-8.04 (m, 1H, $\mathbf{H}_{arom}$), 8.67-8.69 (m, 1H, $\mathbf{H}_{arom}$), 9.19 (s, 1H, **H**-5). *Anal.* Calcd for $C_{11}H_9N_3O_3S$ x H_2O: C 46.97, H 3.94, N 14.94. Found: C 46.53, H 3.87, N 14.80.

N-Methylation of 3-methoxy-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3**) and 2-methoxy-(1*H*)-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 mMol) 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-(7*H*)-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^+). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.77 [(s, 3H, CH_3O); 54.3 (CH_3O)/ 163.4 (C3)], 4.05 [(s, 3H, CH_3N); 45.5 (CH_3N)/ 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 (CH_3N), 120.1 (C5), 142.1 (C8), 157.9 (C4a)], 9.08 [(d, ^4J=1.6 Hz, 1H, H8); 142.1 (C8)/ 45.5 (CH_3N), 119.5 (C8a), 143.4 (C6), 157.9 (C4a)]. *Anal.* Calcd for $C_8H_9N_3O_3S$: C 42.28, H 3.99, N 18.49. Found: C 42.48, H 3.88, N 18.28.

2-Methoxy-6-methyl-(6*H*)-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). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.88 [(s, 3H, CH_3O); 54.5 (CH_3O)/ 163.0 (C2)], 4.28 [(s, 3H, CH_3N); 42.7 (CH_3N)/ 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 (CH_3N), 111.8(C4a), 138.6 (C6a), 157.1 (C10b)]. *Anal.* Calcd for $C_{12}H_{11}N_3O_3S$: C 51.98, H 4.00, N 15.15.

Found: C 52.07, H 3.95, N 15.16.

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-(7*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**4b**) (145 mg, 62%) or 2-chloro-6-methyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**8b**) (230 mg, 82%).

3-Chloro-7-methyl-(7*H*)-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, $(M + 2)^+$]. ^{1}H NMR (DMSO-d_6), δ: 4.15 (s, 3H, CH_3N), 7.49 (d, ^3J=7.1 Hz, 1H, H5), 8.54 (dd, ^3J=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-(6*H*)-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)]. ^{1}H 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-(7*H*)-pyrido[4,3-*e*]-1.2.4-thiadiazine 1,1-dioxide (**4b**) and 2-chloro-6-methyl-(6*H*)-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 exces 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 ((SiO_2, $CHCl_3$/EtOH, 3:1, v/v) and recrystallized from ethanol to give **5b** (205 mg, 77%) or **9b** (237 mg, 75%).

3-Amino-7-methyl-(7*H*)-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). ^{1}H NMR (DMSO-d_6), δ: 3.93 (s, 3H, NCH_3), 6.86 (d, ^3J=7.2 Hz, 1H, H5), 6.9 (bs, 2H, NH_2), 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 $C_7H_8N_4O_2S$: C 39.62, H 3.80, N 26.40. Found: C 39.23, H 3.76, N 25.81.

3-Butylamino-7-methyl-(7*H*)-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). ^{1}H 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. ^{1}H NMR (DMSO-d_6), species **A** δ: 0.86-0.90 (m, 3H, CH_3), 1.25-1.34 (m, 2H, CH_2), 1.42-1.49 (m, 2H, CH_2), 3.11-3.16 (m, 2H, CH_2), 3.90 (s, 3H, NCH_3), 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, CH_3), 1.25-1.34 (m, 2H, CH_2), 1.42-1.49 (m, 2H, CH_2), 3.29-3.30 (m, 2H, CH_2), 3.94 (s, 3H, NCH_3), 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 $C_{11}H_{16}N_4O_2S$: C 49.24, H 6.01, N 20.88. Found: C 49.02, H 5.96, N 20.51.

3-Dimethylamino-7-methyl-(7*H*)-pyrido[4,3-*e*]-1.2.4-thiadiazine 1,1-dioxide (**5c**)

mp 261-263 ºC (EtOH). Mp and ^{1}H NMR spectrum in DMSO-d_6 were identical with the reported data.[3]

2-Amino-6-methyl-(6*H*)-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^+). ^{1}H NMR (DMSO-d_6), δ: 4.15 (s, 3H, NCH_3), 7.15 (bs, 2H, NH_2), 7.70-7.74 (m, 1H, H_{arom}), 7.95-7.97 (m, 2H, H_{arom} , NH), 8.66-8.68 (m, 1H, H_{arom}), 9.06 (s, 1H, H5). *Anal*. Calcd for $C_{11}H_{10}N_4O_2S$: C 50.37, H 3.84, N 21.36. Found: C 50.05, H 3.93, N 20.99.

2-Butylamino-6-methyl-(6*H*)-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). ^{1}H NMR spectrum contains the spectral lines of the same functional groups of two species **A** and **B** in the ratio of 1:0.3, despite the fact that the product seems to be chromatographically homogeneous. ^{1}H NMR (DMSO-d_6), species **A** δ: 0.86-0.93 (m, 3H, CH_3), 1.30-1.39 (m, 2H, CH_2), 1.49-1.56 (m, 2H, CH_2), 3.20-3.23 (m, 2H, CH_2), 4.12 (s, 3H, NCH_3), 7.68-7.72 (m, 1H, H_{arom}), 7.77-7.80 (m, 1H, H_{arom}), 7.92-7.95 (m, , 2H, H_{arom} , NH), 8.63-8.65 (m, 1H, H_{arom}), 8.99 (s, 1H, H5); species **B** δ: 0.86-93 (m, 3H, CH_3), 1.30-1.39 (m, 2H, CH_2), 1.49-

1.56 (m, 2H, CH_2), 3.47-3.52 (m, 2H, CH_2), 4.17 (s, 3H, NCH_3), 7.55-7.58 (m, 1H, H_{arom}), 7.74-7.76 (m, 1H, H_{arom}), 7.98-7.99 (m, 2H, H_{arom} , NH), 8.71-8.73 (m, , 1H, H_{arom}), 9.09 (s, 1H, H5) . *Anal*. Calcd for $C_{15}H_{18}N_4O_2S$: C 56.58, H 5.70, N 17.60. Found: C 56.71, H 5.51, N 17.59.

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

mp 283-286 ºC (EtOH). Mp and ^{1}H NMR spectrum in DMSO-d_6 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[16] The crystal structures were solved by direct methods with the program SHELXS-97[17] and refined by full-matrix least-squares method on F^2 with SHELXL-97.[17]

Crystals of 3-methoxy-(4*H*)-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 $P2_1/c$, a = 8.2579(1) Å, b = 16.0022(2) Å, c = 15.7348(2) Å, α = 90º, β = 92.093(1)°, γ = 90º, V = 2077.88(4) Å^3, Z = 4, d_x = 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 mm^3. Final R indices for 3385 reflections with $I > 2\sigma(I)$ and 313 refined parameters are R_1= 0.0255, wR_2= 0.0681 (R_1= 0.0279, wR_2= 0.0690 for all 3674 data).

Crystals of 2-methoxy-(1*H*)-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 $P2_1/c$, 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) Å^3, Z = 8, d_x = 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 mm^3. Final R indices for 6823 reflections with $I > 2\sigma(I)$ and 376 refined parameters are R_1= 0.0322, wR_2= 0.0954, (R_1= 0.0463 and wR_2= 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.

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