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NEW DERIVATIVES OF 3,4-POLYMETHYLENE-1,2,4-BENZOTHIADIAZINE S,S-DIOXIDES

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A new method is proposed for obtaining 3,4-polymethylene-1,2,4-benzothiadiazine 1,1-dioxides by reacting o-halobenzenesulfonamides with lactim ethers. Attempts were undertaken to synthesize quaternary salts of the heterocycles obtained.

Keywords: *o*-halobenzenesulfonamides, 6a,7,8,9,10,11-hexahydro-6H-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxides, 2,3-dihydro-1H-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxides, 8,9,10,11-tetrahydro-7H-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxides, lactim ethers, N-sulfonylamidines.

Many of the recently obtained derivatives of 3,4-polymethylene-1,2,4-benzothiadiazine 5,5-dioxides show high pharmacological activity. For example, 1-imino(oxo)-2,3-dihydro-1H-pyrrolo[2,1-*c*][1,2,4]-benzothiadiazine 5,5-dioxides and their 2,3,3a,4-tetrahydro derivatives are used as diuretics [1, 2], and 2,3,3a,4-tetrahydro-1H-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine 5,5-dioxide is an agonist (positive modulator) of AMPK receptors [3,4].

It was shown previously by us that 1,2-polymethylene-4-quinazolones may be obtained by the interaction of *o*-halo substituted benzamides with an excess of O-methylcaprolactim [5]. In the present work we have therefore studied the reaction of *o*-halobenzenesulfonamides with lactim ethers with the aim of synthesizing 3,4-polymethylene-1,2,4-benzothiadiazine S,S-dioxides, close in structure to 1,2-polymethylene-4-quinazolone.

Two main approaches to the synthesis of such compounds are known: construction of the saturated ring through derivatives of aliphatic acids [2, 3, 6-10] and cyclization of 2-(1-azacycloalkyl)benzenesulfonamides and related compounds [11-15]. Both these approaches are based on the use of *o*-aminobenzenesulfonamides often available with difficulty. However the relatively easily available *o*-halobenzenesulfonamides have not been used up to the present in the synthesis of derivatives of 3,4-polymethylene-1,2,4-benzothiadiazine S,S-oxides.

We found that, like other benzenesulfonamides [16, 17], *o*-fluoro- and chlorobenzenesulfonamides **3a-c** react readily with lactim ethers **1**, **2** on boiling in alcohol with the formation of N-sulfonylamidines **4**, **5a-c**. However all attempts at further conversion of **4**, **5** into 5,5-oxides **6**, **7** both on heating and under the action of base proved to be unsuccessful.

Nevertheless, when carrying out this reaction under more forcing conditions (heating sulfonamides **3** in an excess of lactim ethers **1, 2** at 150-160°C) we succeeded in obtaining 3,4-tri- and 3,4-pentamethylene-1,2,4-

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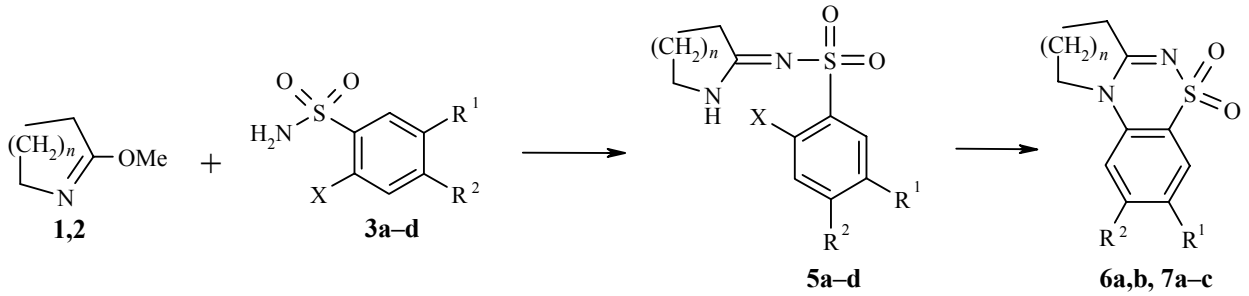
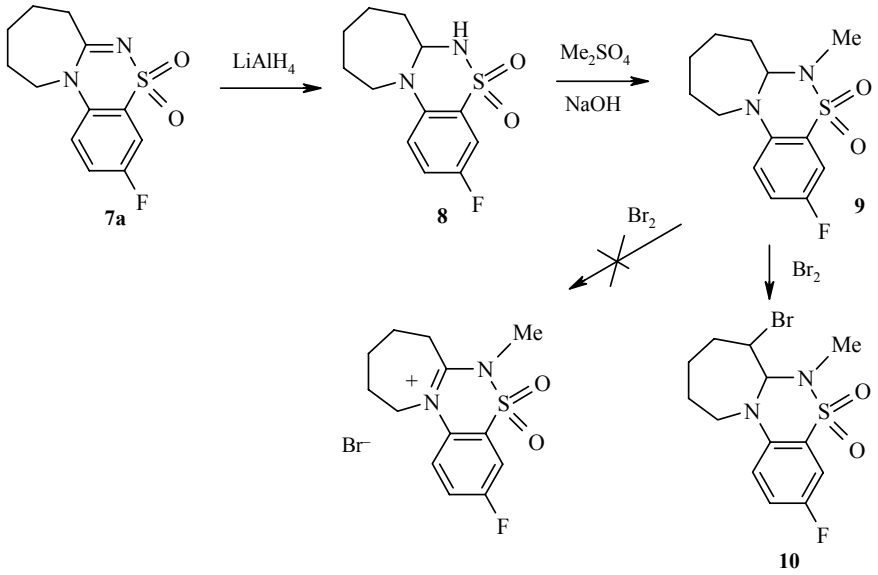
benzothiazine S,S-oxides **6a,b** and **7a,b**. In the case of the *o*-chloro-substituted benzenesulfonamides additional activation by electron-withdrawing groups (NO_2, COOMe) was required but compounds **4d** and **5d** were not subject to cyclization.



1,2 **3a–d** **5a–d** **6a,b, 7a–c**

1, **4, 6** n = 1; **2, 5, 7** n = 3; **a** X = R^1 = F, R^2 = H; **b** X = Cl, R^1 = NO_2, R^2 = H; **c** X = R^2 = Cl, R^1 = COOMe, **d** X = R^2 = Cl, R^1 = H

The alkylation of 1,2-polymethylene-4-quinazolones, close in structure to compounds **6** and **7**, with various alkylating agents was described in the literature and the quaternary salts obtained were investigated in detail [18, 19]. In the present work we attempted to obtain quaternary salts of 3,4-polymethylene-1,2,4-benzothiadiazine 1,1-dioxides with the aim of synthesizing cyanine dyes from them. For this we used a broad spectrum of alkylating agents (CH_3I, $CH_3I/AgBF_4$, dimethyl sulfate, ethyl tosylate, triethyloxonium tetrafluoroborate), however in no case was a quaternary salt isolated. We then attempted to use another route for synthesizing salts interesting to us. We hoped that the sequential reduction of thiadiazine dioxide **7a**, alkylation of the hexahydro derivative in basic medium [3, 7], and oxidation of the product obtained would lead to the required quaternary salt. In reality, compound **7a** is readily reduced with lithium aluminum hydride to the hexahydro derivative **8**, which gives the N-methyl derivative **9** on alkylation with dimethyl sulfate in alkaline medium. However subsequent treatment of the latter with bromine led not to the expected oxidation but to bromination at the 7-CH_2 group (compound **10**).



7a **8** **9** **10**

The structures of the products obtained were confirmed by ^1H and ^{13}C NMR spectra. In the ^1H NMR spectra of compounds **8-10** the spin picture was complicated in comparison with that of the initial **7a** due to the appearance of an asymmetric center. A characteristic feature of the ^1H NMR spectra of compounds **8-10** is the

presence of a signal belonging to H-6. In the spectra of compounds **8** and **9** it appeared as a multiplet at about 4.7 and 5.1 ppm respectively, but in the spectrum of compound **10** as a doublet at 4.6 ppm (J = 9.9 Hz).

A direct confirmation of the structure of compounds **9** and **10** is the presence in their ^{13}C NMR spectra of a signal belonging to C-6a. In the spectrum of **9** it appeared at 76.4 and in the spectrum of **10** at about 87.9 ppm. In addition the ^{13}C NMR spectrum of compound **10** contains only four signals belonging to the carbon atoms of the methylene groups.

EXPERIMENTAL

A check on the progress of reactions and the purity of products was effected by TLC on Silufol UV 254 plates in ethanol or in the system ethyl acetate–hexane, 1:1. Visualization was with iodine vapor or in UV light.

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 (300 and 75 MHz respectively) in DMSO-D_6 and in $CDCl_3$ (^{1}H NMR) and in $CDCl_3$ (^{13}C NMR), internal standard was TMS.

2-Chloro-5-nitro-N-(2-pyrrolidinylidene)benzenesulfonamide (4b). A mixture of lactim ether **1** (0.4 ml, 4.0 mmol) and sulfonamide **3b** (0.7 g, 3.0 mmol) was boiled in 2-propanol for 3 h. The mixture was cooled, the solid filtered off, and washed with 2-propanol. Yield 59%; mp 207-208°C (2-propanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.01-2.21 (2H, q, CH_2-4); 2.75-2.80 (2H, t, CH_2-3); 3.69-3.74 (2H, t, CH_2-5); 7.68 (1H, d, J = 9.0, H-3); 8.10 (1H, br. s, NH); 8.31 (1H, dd, J = 9.0, J = 2.4, H-4); 9.03 (1H, d, J = 2.4, H-6). Found, %: N 13.68; S 10.41. $C_{10}H_{10}ClN_3O_4S$. Calculated, %: N 13.84; S 10.56.

2,4-Dichloro-N-(2-pyrrolidinylidene)benzenesulfonamide (4d) was obtained analogously from compound **1** and sulfonamide **3d**. Yield 88%; mp 166-167°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.11 (2H, q, CH_2-4); 2.75 (2H, t, CH_2-3); 3.66 (2H, t, CH_2-5); 7.41 (2H, s, H-3,4); 8.17 (1H, s, H-6); 8.30 (1H, br. s, NH). Found, %: N 9.46; S 10.98. $C_{10}H_{10}Cl_2N_2O_2S$. Calculated, %: N 9.56; S 10.94.

2,5-Difluoro-N-(hexahydro-2-azepinylidene)benzenesulfonamide (5a) was obtained analogously from compound **2** and sulfonamide **3a**. Yield 67%; mp 121-122°C (2-propanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.71-1.81 (6H, m, CH_2-4,5,6); 2.52-2.55 (2H, m, CH_2-3); 3.41-3.46 (2H, m, CH_2-7); 7.11-7.25 (2H, m, H-3,4); 7.68-7.73 (1H, m, H-6); 8.92 (1H, br s, NH). Found, %: N 9.49; S 11.18. $C_{12}H_{14}F_2N_2O_2S$. Calculated, %: N 9.72; S 11.12.

2,4-Dichloro-N-(hexahydro-2-azepinylidene)benzenesulfonamide (5d) was obtained analogously from compound **2** and sulfonamide **3d**. Yield 80%; mp 150-151°C (EtOAc–hexane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.78 (6H, m, CH_2-4,5,6); 2.51 (2H, m, CH_2-3); 3.44 (2H, m, CH_2-7); 7.42 (2H, s, H-3,4); 8.18 (1H, s, H-6), 8.85 (1H, br s, NH). Found, %: N 9.04; S 9.78. $C_{12}H_{14}Cl_2N_2O_2S$. Calculated, %: N 8.72; S 9.98.

7-Fluoro-2,3-dihydro-1H-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine 5,5-Dioxide (6a). A mixture of compound **1** (1.3 ml, 13.1 mmol) and sulfonamide **3a** (0.5 g, 2.5 mmol) was heated at 150°C for 1 h until precipitation of a solid. The mixture was cooled, the solid filtered off, washed with water, and dried. Yield 65%; mp 233-234°C (EtOH–$CHCl_3$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.22 (2H, q, CH_2-2); 2.98 (2H, t, CH_2-3); 4.16 (2H, t, CH_2-1); 7.46 (1H, dd, J = 9.0, J = 4.2, H-9); 7.60 (1H, dt, J = 9.0, J = 2.7, H-8); 7.66 (1H, dd, J = 7.5, J = 2.7, H-6). Found, %: N 11.82; S 13.21. $C_{10}H_9FN_2O_2S$. Calculated, %: N 11.66; S 13.35.

7-Nitro-2,3-dihydro-1H-pyrrolo[2,1-*c*][1,2,4]benzothiadiazine 5,5-Dioxide (6b) was obtained analogously from compounds **1** and **3b**. Yield 67%; mp 217-218°C (AcOH) (220°C [11, 14]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 2.18-2.28 (2H, q, J = 7.8, CH_2-S); 3.00-3.06 (2H, t, J = 8.1, CH_2-3); 4.20-4.25 (2H, t, J = 7.5, CH_2-1); 7.61-7.65 (1H, m, H-9); 8.54 (2H, m, H-6,8). Found, %: N 15.58; S 12.11. $C_{10}H_9N_3O_4S$. Calculated, %: N 15.72; S 12.00.

3-Fluoro-8,9,10,11-tetrahydro-7H-azepino[2,1-*c*][1,2,4]-benzothiadiazine 5,5-Dioxide (7a). A mixture of lactim ether **2** (1.9 ml, 13.3 mmol) and sulfonamide **3a** (0.5 g, 2.5 mmol) was heated at 150°C for 3 h. The mixture was cooled, precipitated with water, the precipitated solid was filtered off, washed with water,

and dried. Yield 66%; mp 195-196°C (EtOH–DMF). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J,* Hz): 1.80 (6H, m, CH_2-8,9,10); 2.96 (2H, m, CH_2-7); 4.26 (2H, m, CH_2-11); 7.57-7.65 (2H, m, H-2,4); 7.72 (1H, dd, *J* = 9.0, *J* = 4.2, H-1). Found, %: N 10.48; S 11.80. $C_{12}H_{13}FN_2O_2S$. Calculated, %: N 10.44; S 11.95.

3-Nitro-8,9,10,11-tetrahydro-7H-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-Dioxide (7b) was obtained analogously from compounds **2** and **3b**. Yield 62%; mp 194-195°C (AcOH) (191°C [11], 194°C [14]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.91-1.97 (6H, m, CH_2-8,9,10); 3.02 (2H, m, CH_2-7); 4.18-4.21 (2H, m, CH_2-11); 7.46 (1H, d, *J* = 9.3, H-1); 8.49 (1H, d d, *J* = 9.3, *J* = 2.7, H-2); 8.87 (1H, d, *J* = 3.0, H-4). Found, %: N 13.98; S 10.71. $C_{12}H_{13}N_3O_4S$. Calculated, %: N 14.23; S 10.86.

Methyl Ester of 2-Chloro-8,9,10,11-tetrahydro-7H-azepino[2,1-*c*][1,2,4]benzothiadiazine-3-carboxylic Acid 5,5-Dioxide (7c). A mixture of lactim ether **2** (0.7 ml, 4.9 mmol) and sulfonamide **3c** (0.66 g, 2.1 mmol) was refluxed in xylene (7 ml) for 5 h. The solution was decanted from the oil, cooled, the precipitated crystals were filtered off, and washed with xylene. Yield 46%; mp 185-186°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.74-1.81 (6H, m, CH_2-8,9,10); 2.99 (2H, m, CH_2-7); 3.90 (3H, s, CH_3); 4.29 (2H, m, CH_2-11); 7.85 (1H, s, H-1); 8.28 (1H, s, H-4). Found, %: N 8.22; S 9.26. $C_{14}H_{15}ClN_2O_4S$. Calculated, %: N 8.17; S 9.35.

3-Fluoro-6a,7,8,9,10,11-hexahydro-6H-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-Dioxide (8). Dioxide **7a** (1.43 g, 5.3 mmol) was added in portions with stirring to a suspension of $LiAlH_4$ (0.53 g, 14.0 mmol) in dry ether, and the mixture was stirred for 1 h further. Water was then added carefully, the solid was filtered off, washed with water, with 0.1 N HCl, and with water. Yield 73%; mp 168-169°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.34-2.10 (8H, m, CH_2-7,8,9,10); 3.27-3.29 (1H, m, CH_2-11); 3.56-3.64 (1H, m, CH_2-11); 4.68-4.77 (1H, m, H-6a); 7.00 (1H, dd, *J* = 9.0, *J* = 4.5, H-1); 7.29 (1H, dt, *J* = 9.0, *J* = 3.0, H-2); 7.38 (1H, dd, *J* = 8.1, *J* = 3.0, H-4); 7.86 (1H, d, *J* = 11.1, NH). Found, %: N 10.67; S 11 74. $C_{12}H_{15}FN_2O_2S$. Calculated, %: N 10.36; S 11.86.

3-Fluoro-6-methyl-6a,7,8,9,10,11-hexahydro-6H-azepino[2,1-*c*][1,2,4]benzo-thiadiazine 5,5-Dioxide (9). Dioxide **8** (0.5 g, 1.9 mmol) was added to a solution of NaOH (0.11 g, 2.7 mmol) in dry DMSO. Dimethyl sulfate (0.2 ml, 2.1 mmol) was added with stirring to the obtained mixture and the mixture was heated at 60°C for 1 h. The reaction mixture was cooled, and poured into water. The precipitated solid was filtered off, and washed with water. Yield 85%; mp 142-143°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.35-2.25 (8H, m, CH_2-7,8,9,10); 2.66 (3H, s, CH_3); 3.50-3.70 (2H, m, CH_2-11); 5.17 (1H, d d, *J* = 11.4, *J* = 3.6, H-6a); 6.85 (1H, dd, *J* = 9.3, *J* = 4.2, H-1); 7.09-7.16 (1H, m, H-2); 7.43 (1H, dd, *J* = 7.5, *J* = 3.0, H-4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz); 26.54 (s, $C_{(9)}$); 29.84 (s, $C_{(8)}$); 30.57 (s, $C_{(10)}$); 30.99 (s, CH_3); 32.43 (s, $C_{(11)}$); 49.94 (s, $C_{(7)}$); 76.43 (s, $C_{(6a)}$); 113.27-113.60 (d, $J_{C–F}$ = 24.7, $C_{(2)}$); 117.45-117.53 (d, $J_{C–F}$ = 6.0, $C_{(1)}$); 121.74-122.05 (d, $J_{C–F}$ = 23.1, $C_{(4)}$); 123.18-123.26 (d, *J* = 6.3, $C_{(4a)}$); 142.17 (d, $C_{(12a)}$); 154.10-157.31 (d, $J_{C–F}$ = 242.0, $C_{(3)}$). Found, %: N 9.68; S 11.19. $C_{13}H_{17}FN_2O_2S$. Calculated, %: N 9.85; S 11.28.

7-Bromo-3-fluoro-6-methyl-6a,7,8,9,10,11-hexahydro-6H-azepino[2,1-*c*][1,2,4]benzothiadiazine 5,5-Dioxide (10). A solution of bromine (0.036 ml, 0.7 mmol) in dry chloroform was added to a solution of dioxide **9** (0.2 g, 0.7 mmol) in dry chloroform. The reaction mixture was stirred for 0.5 h until it had completely decolorized. The solution obtained was evaporated, and the solid residue rubbed with ether, the solid was filtered off, and washed with ether. Yield 61%; mp 152-153°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.44-2.36 (6H, m, CH_2-8,9,10); 2.95 (3H, s, CH_3); 3.21-3.32 (1H, m, CH_2-11); 3.91-3.99 (1H, m, CH_2-11); 4.63 (1H, d, *J* = 9.9, H-6a); 5.07-5.14 (1H, m, H-7); 6.71 (1H, dd, *J* = 9.3, *J* = 3.0, H-1); 7.12-7.19 (1H, m, H-2); 7.43 (1H, dd, *J* = 7.5, *J* = 3.0, H-4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 23.97 (s, $C_{(9)}$); 26.79 (s, $C_{(8)}$); 36.53 (s, $C_{(10)}$); 39.85 (s, CH_3); 51.01 (s, $C_{(11)}$); 53.77 (s, $C_{(7)}$); 87.88 (s, $C_{(6a)}$); 113.26-113.60 (d, $C_{(2)}$, $J_{C–F}$ = 25.6); 114.83-114.91 (d, $C_{(1)}$, $J_{C–F}$ = 6.3); 121.03 (d, $C_{(4a)}$); 122.44-122.73 (d, $C_{(4)}$, $J_{C–F}$ = 22.3); 138.31 (s, $C_{(12a)}$); 153.80-157.01 (d, $C_{(3)}$, $J_{C–F}$ = 242.4). Found, %: Br 21.95; N 7.67; S 8.83. $C_{13}H_{16}BrFN_2O_2S$. Calculated, %: Br 22.00; N 7.71; S 8.83.

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