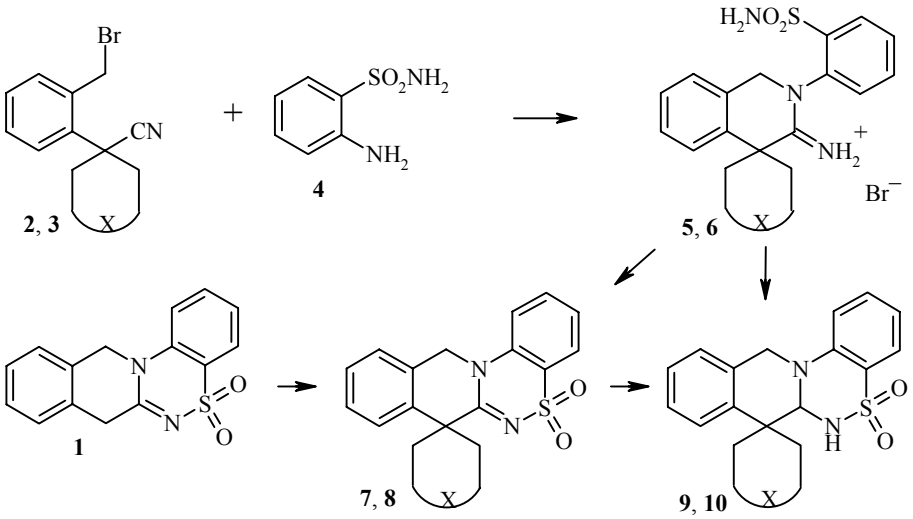
CONDENSED ISOQUINOLINES. 14.* SPIROCYCLIC SYSTEMS CONTAINING A BENZO[5,6][1,2,4]-THIADIAZINO[4,3-*b*]ISOQUINOLINE RING

V. M. Kisel, E. O. Kostyrko, and V. A. Kovtunenko

We propose a convenient preparative method for synthesis of derivatives of novel heterospirane systems with a benzo[5,6][1,2,4]thiadiazino[4,3-b]isoquinoline ring, based on the reaction of 1-(2-bromomethylphenyl)-1-cyclopentanecarbonitrile and 4-(2-bromomethylphenyl)-3,4,5,6-tetrahydro-2H-pyran-4-carbonitrile with o-aminobenzenesulfamide.

Keywords: benzothiadiazines, isoquinolines, spirocyclic compounds.

The basic structural group for diuretics is the 1,2,4-benzothiadiazine ring [2], which is why a promising approach is to search for new biologically active substances in a series of new derivatives of this heterocyclic compound and condensed systems based on it. Earlier we described synthesis of 7,12-dihydrobenzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-5,5-dioxide (**1**), a derivative of a novel heterocyclic system [3]. This paper develops this approach, applying it to heterospirane compounds containing the indicated system that have not been described previously.



2, **5**, **7**, **9** X = bond; **3**, **6**, **8**, **10** X = O

* For Communication 13, see [1].

Taras Shevchenko Kiev National University, Kiev 01033, Ukraine; e-mail: kvm@sbet.com, v_kysil@mai.univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1289-1292, September, 2002. Original article submitted July 27, 2000.

 0009-3122/02/3809-1130$27.00

We have studied the reaction of previously synthesized [1, 4] 1-(2-bromomethylphenyl)-1-cyclopentanecarbonitrile (**2**) and 4-(2-bromomethylphenyl)-3,4,5,6-tetrahydro-2H-pyran-4-carbonitrile (**3**) with *o*-aminobenzenesulfamide (**4**). We found that heating a mixture of bromo nitrile **2** with an equimolar amount of aminosulfamide **4** in 2-propanol leads to the hydrobromide of 2-(2-sulfamoylphenyl)-1,2,3,4-tetrahydrospiro[isoquinoline-4,1'-cyclopentane]-3-imine (**5**). Under the same conditions, 2-(2-sulfamoylphenyl)-1,2,3,3',4,4',5',6'-octahydrospiro[isoquinoline-4,4'-2H-pyran]-3-imine hydrobromide (**6**) is formed from compounds **3** and **4**.

The absence of a band from nitrile absorption and the presence of $C=N^+$ and N–H bands in the IR spectra of the compounds obtained eliminate the structure of both the intermediates of conventional alkylation and possible products of further cyclization. The ^{1}H NMR spectra of these compounds are characterized by the presence of two one-proton singlets of the salt imino group, disappearing in the presence of D_2O, and two one-proton doublets from the protons on $C_{(1)}$ of the isoquinoline ring. We should note that the magnetic nonequivalence of the protons of the indicated methylene group, due to hindered rotation of the 2-aryl substituent, is observed for all salts of 2-(*o*-R-aryl)-1,2,3,4-tetrahydroisoquinoline-3-imines [5].

Isoquinoline imines **5, 6** are high-melting compounds that are difficultly soluble in low-boiling solvents. When attempting to recrystallize them from DMF, we observed their further cyclization to the target 7,12-dihydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]-isoquinoline-7,1'-cyclopentane]-5,5-dioxide (**7**) and 3',4',5',6',7,12-hexahydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,4'-2H-pyran]-5,5-dioxide (**8**) respectively. For preparative purposes, this reaction is preferably conducted in the presence of a hydrogen bromide acceptor (piperidine, morpholine, triethylamine). The structure of the cyclization products is confirmed by their IR spectra, in which there are no bands from an NH group, and the ^{1}H NMR spectra, which are characterized by the absence of signals from protons capable of deuterium exchange.

We also studied the feasibility of an alternate route for synthesis of compound **7** via cycloalkylation of benzothiadiazine isoquinoline **1** by 1,4-dibromobutane in anhydrous DMF medium, using sodium hydride as the base. In this case, we also obtained product **7** in high yield. However, this synthesis route is less convenient because *o*-bromomethylphenylacetone nitrile, needed to obtain compound **1**, is less available.

According to data in [6], of the 34 benzo[5,6][1,2,4]thiadiazines used in medical practice, the structures of 24 drugs contain a 3,4-dihydro-2H-thiadiazine ring; so we studied borohydride reduction of the synthesized spiro compounds **7** and **8**. We found that the double bond $N_{(6)}=C_{(6a)}$ is easily reduced upon treatment with sodium borohydride in methanol solution in the presence of DMF, addition of which is needed to increase the solubility of the starting compounds. In this case, we obtain 6,6a,7,12-tetrahydrospiro-[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,1'-cyclopentane]-5,5-dioxide (**9**) and 3',4',5',6,6',6a,7,12-octa-hydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,4'-2H-pyran]-5,5-dioxide (**10**) in high yields. As we should expect [7], the sulfodioxide group is not involved under these conditions, evidence for which comes from the preservation of the S=O group bands in the IR spectra of the reduction products. The presence of a $C_{(6a)}H–N_{(6)}H$ moiety in their structures is confirmed by ^{1}H NMR spectra, in which we observe AX spin systems of signals from the corresponding protons with a rather high value of the vicinal coupling constant (12 Hz). Furthermore, the presence of an asymmetric $C_{(6a)}$ atom is apparent in the magnetic nonequivalence of the protons at $C_{(12)}$ in the case of compound **10**, giving an AB spin system of signals in the spectrum.

It is interesting that compounds **8** and **9** can be obtained under the same conditions directly from isoquinoline imines **4** and **5**. Obviously in the first step, the sodium borohydride used in large excess plays the role of the base, promoting their cyclization to compounds **6** and **7**, which undergo subsequent reduction.

EXPERIMENTAL

The IR spectra were recorded on an SP3-300 Pye-Unicam (KBr disks). The 1H NMR spectra were obtained on a Bruker WP-100 SY (100 MHz) for compound **8** in CF_3CO_2D, the rest were obtained in DMSO-d_6, internal standard TMS.

2-(2-Sulfamoylphenyl)-1,2,3,4-tetrahydrospiro[isoquinoline-4,1'-cyclopentane]-3-imine Hydrobromide (5). A solution of bromonitrile **2** (0.79 g, 3 mmol) and 2-aminobenzenesulfamide (0.52 g, 3 mmol) in 2-propanol (10 ml) was boiled for 6 h. The precipitate of product **5** falling out of the cooled reaction mixture was filtered out, washed on the filter with propanol, water, propanol, and then recrystallized. Yield 0.75 g (57%); mp 201°C (EtOH). IR spectrum (KBr), ν, cm^{-1}: 1165, 1345 (SO_2); 1650 (C=N); 3040, 3180, 3320 (N–H). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.80-2.60 (8H, m, $4CH_2$); 4.85 (1H, d, J_{gem} = 16, $C_{(1)}H_B$); 5.15 (1H, d, J_{gem} = 16, $C_{(1)}H_A$); 7.30-8.30 (8H, m, H arom); 7.90* (2H, s, SO_2NH_2); 8.40* (1H, s, N^+H); 8.95* (1H, s, N^+H). Found, %: C 52.45; H 5.18; Br 18.22; N 9.77; S 7.44. $C_{19}H_{21}N_3O_2S{\cdot}HBr$. Calculated, %: C 52.30; H 5.08; Br 18.31; N 9.63; S 7.35.

2-(2-Sulfamoylphenyl)-1,2,3,3',4,4',5',6'-octahydrospiro[isoquinoline-4,4'-2H-pyran]-3-imine Hydrobromide (6) was obtained in 53% yield similarly to compound **5**, starting from bromonitrile **3**; mp 282°C (EtOH). IR spectrum (KBr), ν, cm^{-1}: 1160, 1345 (SO_2N); 1650 (C=N); 3040, 3160, 3300 (N–H). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 3.50-4.10 (4H, m, $O(CH_2)_2$); 1.90-2.40 (4H, m, $C(4')(CH_2)_2$); 4.80 (1H, d, J_{gem} = 17, $C_{(1)}H_B$); 5.32 (1H, d, J_{gem} = 17, $C_{(1)}H_A$); 7.20-8.20 (8H, m, H arom); 7.90* (2H, s, SO_2NH_2); 8.80* (1H, s, N^+H); 9.10* (1H, s, N^+H). Found, %: C 50.55; H 4.98; Br 17.84; N 9.40; S 7.12. $C_{19}H_{21}N_3O_3S{\cdot}HBr$. Calculated, %: C 50.45; H 4.90; Br 17.66; N 9.29; S 7.09.

7,12-Dihydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,1'-cyclopentane]-5,5-dioxide (7). A. A mixture of hydrobromide **5** (0.44 g, 1 mmol), triethylamine (2 ml), and DMF (5 ml) was heated for 15 min, cooled, diluted two-fold with water; the precipitate was filtered out, and then washed with water and alcohol. Yield 0.31 g (91%); mp 227°C (AcOH). IR spectrum (KBr), ν, cm^{-1}: 1170, 1295 (SO_2); 1590 (C=N). ^{1}H NMR spectrum (300 MHz), δ, ppm, *J* (Hz): 1.77 (4H, central m, $C_{(3')}H_2$, $C_{(4')}H_2$); 2.10 (2H, central m, $C_{(2')}H_A$, $C_{(5')}H_A$); 2.42 (2H, central m, $C_{(2')}H_{A'}$, $C_{(5')}H_{A'}$); 5.39 (2H, s, $C_{(12)}H_2$); 7.35-7.55 (4H, m, H arom); 7.60 (1H, td, J_o = 8, J_m = 2.5, $C_{(2)}H$); 7.83-7.96 (3H, m, H arom). Found, %: C 67.50; H 5.50; N 8.32; S 9.57. $C_{19}H_{18}N_2O_2S$. Calculated, %: C 67.43; H 5.36; N 8.28; S 9.47.

B. Anhydrous DMF (30 ml), compound **1** (0.71 g, 2.5 mmol), and 80% emulsion of NaH in vaseline oil (0.20 g, 6.6 mmol) were placed into the device, protected from moisture. A solution of 1,4-dibromobutane (0.30 ml, 2.5 mmol) in DMF (5 ml) was added slowly dropwise to the reaction mixture, with ice cooling and stirring. Stirring was continued for 3-4 h, after which 2-propanol (2 ml) was added and the mixture obtained was poured into water (50 ml). The precipitate was filtered out, washed on the filter with water, and recrystallized from AcOH. Yield 0.76 g (89%) of product **7**, with identical mp and spectral characteristics as the sample obtained by procedure A.

3',4',5',6',7,12-Hexahydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,4'-2H-pyran]-5,5-dioxide (8) was obtained in 80% yield analogously to compound **7** (procedure A), starting from hydrobromide **6**; mp 302°C (DMF). IR spectrum (KBr), ν, cm^{-1}: 1170, 1305 (SO_2); 1590 (C=N). ^{1}H NMR, δ, ppm, *J* (Hz): 2.50 (4H, central m, $C_{(4')}(CH_2)_2$); 4.25 (4H, central m, $O(CH_2)_2$); 5.40 (2H, s, CH_2N); 7.40-7.80 (6H, m, H arom); 7.95 (1H, td, J_o = 8, J_m = 2.5, $C_{(2)}H$); 8.15 (1H, dd, J_o = 8, J_m = 2.5, $C_{(4)}H$). Found, %: C 64.50; H 5.20; N 8.08; S 9.27. $C_{19}H_{18}N_2O_3S$. Calculated, %: C 64.39; H 5.12; N 7.90; S 9.05.

6,6a,7,12-Tetrahydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,1'-cyclopentane]-5,5-dioxide (9). $NaBH_4$ (0.46 g, 12 mmol) was added in portions to a suspension of compound **7** (0.68 g, 2 mmol) in methanol (10 ml) and DMF (1 ml). The reaction mixture was boiled for 2.5 h, cooled, diluted with water; the precipitate of product **9** was filtered out, washed with water and alcohol. Yield 0.58 g (85%); mp 186°C (MeOH). IR spectrum (KBr), ν, cm^{-1}: 1160, 1310 (SO_2); 3230 (N–H). ^{1}H NMR spectrum, δ, ppm, *J* (Hz):

* Exchanges with D_2O.

1.60-2.50 (8H, m, $(CH_2)_4$); 4.65 (2H, s, $C_{(12)}H_2$); 4.80 (1H, d,* J_{vic} = 12, $C_{(6a)}H$); 6.90 (1H, t, J_o = 8, $C_{(1)}H$); 7.10-7.70 (8H, m, H arom, SO_2NH). Found, %: C 67.15; H 6.08; N 8.58; S 9.66. $C_{19}H_{20}N_2O_2S$. Calculated, %: C 67.03; H 5.92; N 8.23; S 9.42.

Using the described procedure, we also obtained product **9** from compound **5** in 80% yield.

3',4',5',6,6',6a,7,12-Octahydrospiro[benzo[5,6][1,2,4]thiadiazino[4,3-*b*]isoquinoline-7,4'-2H-pyran]-5,5-dioxide (10) was obtained analogously to compound **9**, starting from compound **6** or **8** in 83% and 88% yields respectively; mp 210°C (AcOH). IR spectrum (KBr), ν, cm^{-1}: 1160, 1320 (SO_2); 3180 (N–H). ^{1}H NMR spectrum, δ ppm, *J* (Hz): 3.75 (4H, central m, $O(CH_2)_2$); 1.60-2.30 (4H, m, $C_{(4')}(CH_2)_2$); 4.45 (1H, d, J_{gem} = 15, $C_{(12)}H_B$); 4.80 (1H, d, J_{gem} = 15, $C_{(12)}H_A$); 5.20 (1H, d,* *J* = 12, $C_{(6a)}H$); 7.00 (1H, t, J_o = 8, $C_{(1)}H$); 7.15-7.70 (8H, m, H arom., SO_2NH). Found, %: C 64.15; H 5.78; N 7.88; S 9.02. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 64.02; H 5.66; N 7.86; S 8.99.

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* Changes to a singlet in the presence of D_2O.