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7,12-DIHYDROISOQUINO[3,2-*c*]-1,2,4-BENZOTHIADIAZINE, A NEW HETEROCYCLIC SYSTEM

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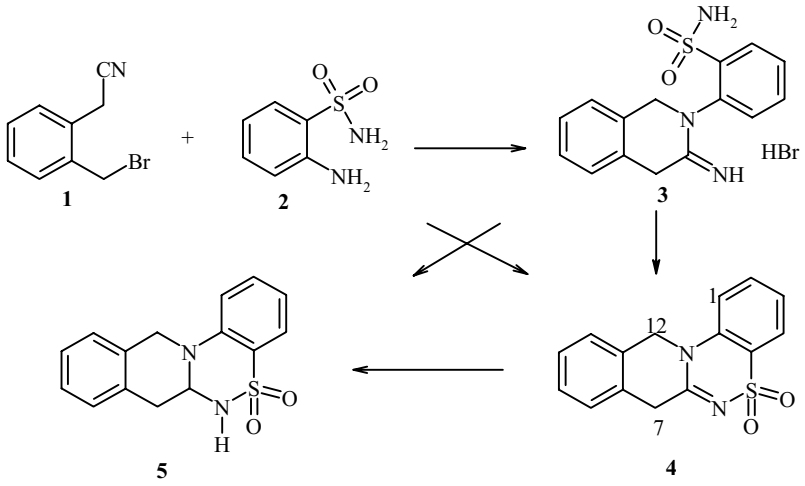
Of all the theoretically possible isoquinobenzothiadiazine systems, only derivatives of the isoquino[1,2-*c*]-1,2,4-benzothiazine system have been reported. These compounds hold promise in pharmacological research [1]. We propose a convenient method for the synthesis of derivatives of the previously unreported 7,12-dihydroisoquino[3,2-*c*]-1,2,4-benzothiadiazine system starting from *o*-bromomethylphenylacetonitrile (**1**) and *o*-aminobenzosulfamide (**2**).



Heating equimolar amounts of **1** and **2** in 2-propanol leads to hydrobromide salt of 3-imino-2-sulfanoylphenyl-1,2,3,4-tetrahydroisoquinoline (**3**) in high yield. The structure of this product was supported by its spectral data, which are in good accord with the data for hydrobromide salts of 2-aryl-3-imino-1,2,3,4-tetrahydroisoquinolines [2]. The IR spectra show a set of N–H bands for the sulfamide and salt imine groups, imine C=N group, and sulfamide S=O group. The protons of the methylene group at $C_{(4)}$ in the ^{1}H NMR spectrum give an AB spin system. The lack of magnetic equivalence of these protons is a consequence of hindered rotation about the N–C_{Ar} single bond and presence of a magnetically-anisotropic sulfamide group in the *ortho* position to the 2-aryl substituent. Such spectral behavior is characteristic for salts of 2-aryl-1,2,3,4-tetrahydroisoquinoline-3-imines with asymmetrical substitution in the 2-aryl group [3].

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Carrying out the reactions of **1** and **2** by heating these compounds in acetonitrile or dioxane for 5 h or by heating salt **3** in dimethylformamide for 0.5 h leads to 7,12-dihydroisoquino[3,2-*c*]-1,2,4-benzothiadiazine 5,5-dioxide (**4**) in high yields. The IR spectrum of this compound lacks N–H stretching bands but retains the S=O bands, while its ^{1}H NMR spectrum has two singlets for the protons of the methylene groups and two aromatic proton multiplets.

Heating **4** in methanol in the presence of a five-fold excess of sodium borohydride leads to reduction of the C=N bond and formation of 6,6a,7,12-tetrahydroisoquino[3,2-*c*]-1,2,4-benzothiadiazine 5,5-dioxide (**5**). This compound may be obtained under the same conditions from salt **3**. Cyclization to give tetracyclic derivative **4** probably precedes the reduction. As expected [4], the sulfonyl group is not altered under these conditions, as indicated by retention of the S=O bands in the IR spectrum of the reduction product. The finding of an A_2MX spin system in the ^{1}H NMR spectrum of **4** for the protons of the $C_{(7)}H_{(2)}$–$C_{(6a)}H$–$N_{(6)}H$ structural fragment is in good accord with the proposed structure.

Compound 3; mp 249°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.65 (1H, s, N^+–H); 8.35 (1H, s, N^+–H); 7.3-8.15 (10H, m, C_{Ar}–H, SO_2NH_2, the broad singlet at 7.76 ppm disappears in the presence of D_2O); 4.92 (2H, s, $C_{(1)}H_2$); 4.23 (1H, d, J_{AB} = 18 Hz, $C_{(4)}H_A$); 4.01 (1H, d, J_{AB} = 18 Hz, $C_{(4)}H_B$). IR spectrum (KBr), cm^{-1}: 3000-3400 (N–H), 1660 (C=N^+), 1240, 1160 (SO_2). Found, %: Br 21.05; N 10.77; S 8.40. $C_{15}H_{15}N_3O_2S$. Calculated, %: Br 20.90; N 10.99; S 8.39.

Compound 4; mp 263°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.8-8.0 (3H, m, C_{Ar}–H); 7.3-7.7 (5H, m, C_{Ar}–H); 5.28 (2H, s, $C_{(12)}H_2$); 4.08 (2H, s, $C_{(7)}H$). IR spectrum (KBr), cm^{-1}: 1280, 1160 (SO_2). Found, %: C 63.18; H 4.35; N 10.02; S 11.44. $C_{16}H_{12}N_2O_2S$. Calculated, %: C 63.36; H 4.25; N 9.85; S 11.28.

Compound 5; mp 208°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.15 (1H, d, $^3J_{6,6a}$ = 11 Hz, $N_{(6)}$–H); 7.15-7.8 (7H, m, C_{Ar}–H); 6.88 (1H, m, C_{Ar}–H); 4.95 (1H, dt, $^3J_{6a,7}$ = 6.5 Hz, $^3J_{6,6a}$ = 11 Hz, $C_{(6a)}$–H); 4.86 (1H, d, $^2J_{AB}$ = 16 Hz, $C_{(12)}$–H_A); 4.46 (1H, d, $^2J_{AB}$ = 16 Hz, $C_{(12)}$–H_B); 3.19 (2H, d, $^3J_{6a,7}$ = 6.5 Hz, $C_{(7)}H_2$). IR spectrum (KBr), cm^{-1}: 3210 (N–H), 1305, 1160 (S=O). Found, %: C 62.78; H 4.77; N 9.89; S 11.41. $C_{16}H_{14}N_2O_2S$. Calculated, %: C 62.92; H 4.93; N 9.78; S 11.20.

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