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A synthetic pathway for obtaining arylamino, alkylamino 3,4-disubstituted 1,2,5-thiadiazole dioxide derivatives has been developed. This methodology could be applied to obtain potential biologically active molecules.

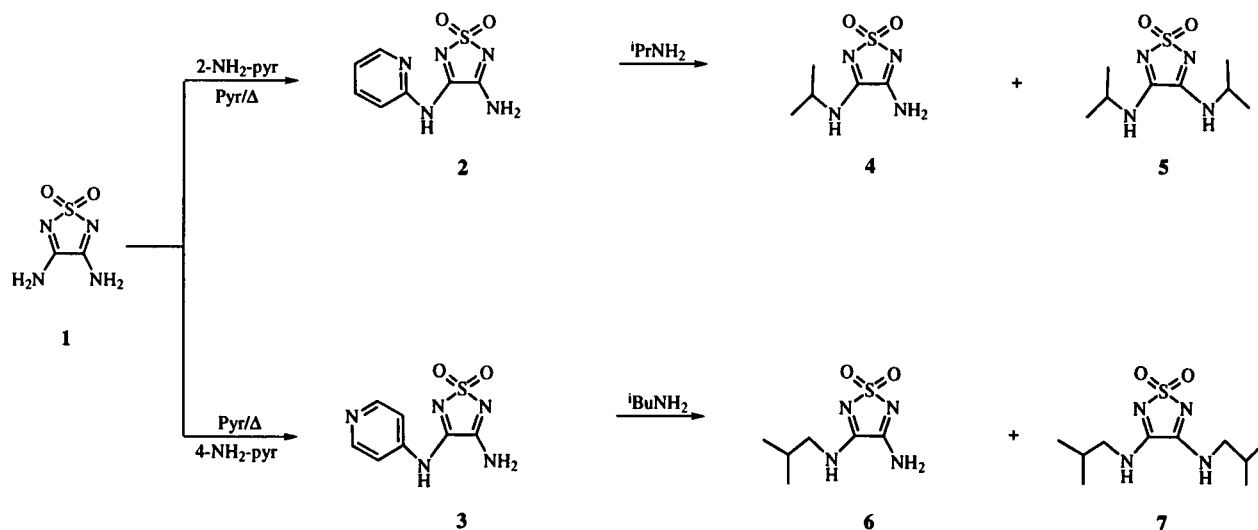
J. Heterocyclic Chem., 35, 297 (1998).

During recent years considerable interest has developed in the 3,4-disubstituted 1,2,5-thiadiazole 1,1-dioxides as antihypertensive and vasodilating agents [1], as histamine H₂-receptor antagonists [2-4], and more recently, as agonists for the 5-HT_{1D} [5] receptor and as specific HIV-1 reverse transcriptase inhibitors [6]. In many cases this kind of heterocyclic functionality was selected as a bioisosteric replacement for the cyanoguanidine moiety which is a major structural constituent of several drug discovery efforts [7]. Continuing with our work in this field [8,9], we report here the synthesis of nonsymmetrically disubstituted 1,2,5-thiadiazoles. The substituents introduced in the 3 and 4 positions of the thiadiazole ring were arylamino and alkylamino fragments.

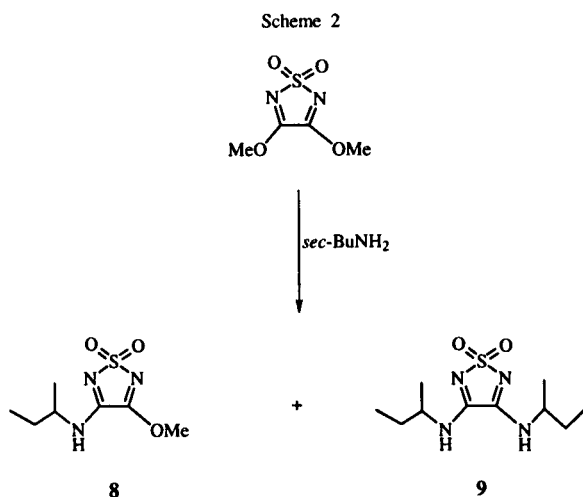
Initially, the synthetic pathway chosen for deriving the target molecules was based on the transamination reactions of amino derivatives of 1,2,5-thiadiazole dioxide [10,11]. Thus the 3,4-diamino compound **1** was obtained in one step in high yield, following a method discovered in our laboratories, by acid-catalyzed cycloaddition of sul-

famide and cyanogen [11]. Whilst transaminations with alkyl amines have been well studied [11] and were smoothly carried out such as at room temperature with 25% ammonium hydroxide, reactions with aryl and heteroarylamines has not been described before. Treatment of compound **1** with an excess of heteroarylamines such as 2- and 4-aminopyridine in pyridine at reflux temperature afforded, after a long reaction time, the monoarylamino derivatives **2** and **3**. No reaction was observed under other attempted conditions, such as 25% ammonium hydroxide or pyridine both at room temperature. Subsequent treatment of these compounds with primary alkylamines in order to introduce the second ring substituent yielded a mixture of mono- and disubstituted alkylamino compounds **4-7** which could be separated by column chromatography (Scheme 1). Under all conditions used, this transamination reaction begins with nucleophilic substitution of the secondary nitrogen attached to the thiadiazole moiety with subsequent elimination of the pyridylamino fragment introduced earlier.

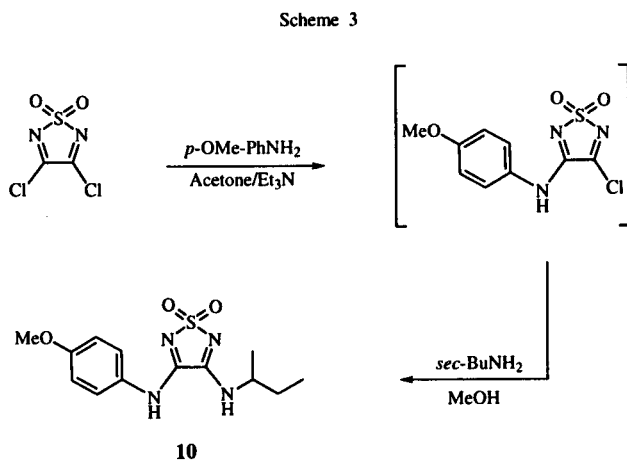
Scheme 1



The nucleophilic displacement of heteroatomic substituents in the 3 and 4 positions of the 1,2,5-thiadiazole dioxide moiety is well known [12,13]. Therefore 3,4-dimethoxy-1,2,5-thiadiazole dioxide was used as the starting material. Treatment with *sec*-butylamine in refluxing methanol yielded a mixture of mono- and disubstituted derivatives **8** and **9** (Scheme 2). However, reaction with aryl or heteroarylamines did not take place. The nucleophilic difference between aliphatic and aromatic amines plays a decisive role in this heteroatomic substitution.

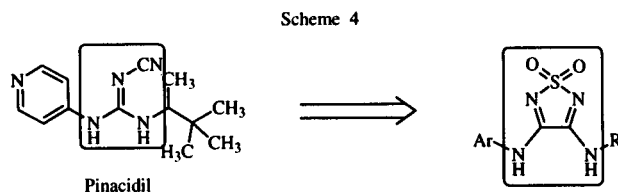


The nonsymmetrically arylamino, alkylamino disubstituted compounds were finally obtained starting from the reactive 3,4-dichlorothiadiazoole derivative. Thus, sequential treatment with an arylamine such as *p*-anisidine and an aliphatic one amine such as *sec*-butylamine gave the nonsymmetrically substituted derivative **10** (Scheme 3).



The structures of all compounds synthesized have been established on the basis of analytical, ^1H and ^{13}C nmr spectroscopic data which are reported in the Experimental.

Compounds obtained in this way may be considered in a general sense as conformationally restricted pinacidil-related derivatives in which the *N*-cyanoguanidine moiety is replaced by the thiadiazole dioxide heterocycle (Scheme 4).



The vasorelaxant properties of the new compounds were examined by measuring the inhibitory effect on the 20 mM and 80 mM potassium chloride-induced contractions of the rat portal vein at two different concentrations, following the procedure described by Weston [14]. None of the compounds provided significant effect as smooth muscle relaxants in the isolated rat portal vein compared with pinacidil as the standard.

A synthetic pathway to obtain nonsymmetrically arylamino, alkylamino-3,4-disubstituted 1,2,5-thiadiazole dioxides starting from the 3,4-dichloro derivative is reported. It may be useful in new drug synthesis.

EXPERIMENTAL

Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. Reagents and solvents were purchased from common commercial suppliers and used without further purification. Flash column chromatography was carried out at medium pressure using silica gel (E. Merck, Grade 60, particle size 0.040-0.063 mm, 230-240 mesh ASTM) with the indicated solvent as the eluent. The nmr spectra were recorded on Bruker AM-200 or Varian Gemini-200 spectrometers working at 200 and 50 MHz for ^1H and ^{13}C , respectively. Chemical shifts are reported in δ values (ppm) relative to internal tetramethylsilane and *J* values are reported in Hertz. Elemental analyses were performed by the analytical department at C.N.Q.O. (CSIC).

4-Amino-3-(2-pyridylamino)-1,2,5-thiadiazole 1,1-Dioxide (**2**).

A solution of compound **1** (444 mg, 3 mmoles) and 2-aminopyridine (282 mg, 3 mmoles) in pyridine (10 ml) was refluxed for 72 hours and the solid was collected by filtration. The compound was purified by recrystallization from methanol,

mp 280-282°, yield 509 mg (75%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 7.70 (d, $J = 5.2$ Hz, 1H, 3-Hpyr), 8.37 (t, $J = 8.4$ Hz, 1H, 5-Hpyr), 8.55 (t, $J = 8.4$ Hz, 1H, 4-Hpyr), 8.87 (d, $J = 5.2$ Hz, 1H, 6-Hpyr), 9.02 (bs, 1H, NH), 9.60 (bs, 2H, NH_2); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 157.3 (C-3), 152.6 (C-4), 151.3, 147.6, 139.7, 120.8, 115.2 (C-pyr).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{N}_5\text{SO}_2$: C, 37.33; H, 3.13; N, 31.10; S, 14.24. Found: C, 37.04; H, 2.90; N, 31.29; S, 14.61.

4-Amino-3-(4-pyridylamino)-1,2,5-thiadiazole 1,1-Dioxide (3).

4-Aminopyridine (188 mg, 2 mmoles) was added to a solution of compound 1 (296 mg, 2 mmoles) in pyridine (10 ml). The reaction mixture was refluxed for 72 hours. After cooling, the solid was collected by filtration and crystallized from ethanol, mp 212-213°, yield 291 mg (64%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 7.96 (d, $J = 7.2$ Hz, 2H, 3-H and 5-Hpyr), 8.09 (d, $J = 7.2$ Hz, 2H, 2-H and 6-Hpyr), 8.20 (bs, 1H, NH), 8.40 (bs, 2H, NH_2); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 161.6 (C-3), 159.7 (C-4), 158.6, 140.0, 108.8 (C-pyr).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{N}_5\text{SO}_2$: C, 37.33; H, 3.13; N, 31.10; S, 14.24. Found: C, 37.06; H, 3.21; N, 30.86; S, 14.40.

3,4-Bis(isopropylamino)-1,2,5-thiadiazole 1,1-Dioxide (5).

Compound 2 (122 mg, 0.5 mmole) and isopropylamine (3 ml) was stirred at room temperature for 40 hours. After this time, the amine was eliminated under reduced pressure. The residue was purified by silica gel column chromatography using dichloromethane:methanol 20:1 as the eluent, mp 165-166°, yield 105 mg (90%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.22 (d, $J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 3.86 (m, $J = 6.8$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 8.50 (bs, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 154.0 (C-3 and C-4), 46.4 (CH), 21.23 (CH_3).

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{N}_4\text{SO}_2$: C, 41.36; H, 6.94; N, 24.12; S, 13.80. Found: C, 41.15; H, 6.56; N, 24.38; S, 14.18.

4-Amino-3-(isopropylamino)-1,2,5-thiadiazole 1,1-Dioxide (4) and 3,4-Bis(isopropylamino)-1,2,5-thiadiazole 1,1-Dioxide (5).

Isopropylamine (15 mg, 0.25 mmole) was added to a solution of compound 2 (56 mg, 0.25 mmole) in ethanol (15 ml). The reaction mixture was refluxed for 5 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane:methanol 20:1 as the eluent. From the first fraction was isolated a derivative whose analytical and spectroscopic data were identical to those obtained for compound 5 (8 mg, 14%). From the second fraction was isolated derivative 4, mp 178-180°, yield 23 mg (48%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 1.22 (d, $J = 7.1$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$), 3.37 (m, $J = 7.1$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 8.04 (bs, 1H, NH), 8.90 (bs, 2H, NH_2); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 159.3 (C-3), 154.4 (C-4), 46.0 (CH), 21.8 (CH_3).

Anal. Calcd. for $\text{C}_5\text{H}_{10}\text{N}_4\text{SO}_2$: C, 31.57; H, 5.30; N, 29.46; S, 16.86. Found: C, 31.73; H, 5.02; N, 29.79; S, 16.76.

4-Amino-3-(isobutylamino)-1,2,5-thiadiazole 1,1-Dioxide (6) and 3,4-Bis(isobutylamino)-1,2,5-thiadiazole 1,1-Dioxide (7).

Isobutylamine (37 mg, 0.5 mmole) was added to a solution of compound 3 (112 mg, 0.5 mmole) in ethanol (15 ml). The reac-

tion mixture was refluxed for 8 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane:methanol 20:1 as the eluent. From the first fraction was isolated the disubstituted derivative 7, mp 176-177°, yield 13 mg (10%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.91 (d, $J = 6.7$ Hz, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.90 (m, $J = 6.7$ Hz, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.13 (t, $J = 6.7$ Hz, 2H, $\text{NCH}_2\text{CH}-$), 8.60 (s, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 156.2 (C-3 and C-4), 51.3 (CH_2), 27.2 (CH), 20.0 (CH_3).

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{N}_4\text{SO}_2$: C, 46.13; H, 7.74; N, 21.52; S, 12.32. Found: C, 46.40; H, 7.89; N, 21.19; S, 12.35.

From the second fraction, the monosubstituted derivative 6 was isolated, mp 180-182°, yield 54 mg (53%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.92 (d, $J = 7.1$ Hz, 6H, $-\text{CH}(\text{CH}_3)_2$), 1.91 (m, $J = 7.1$ Hz, 1H, $-\text{CH}(\text{CH}_3)_2$), 3.17 (t, $J = 7.1$ Hz, 2H, $\text{NCH}_2\text{CH}-$), 8.00 (bs, 1H, NH), 8.90 (bs, 2H, NH_2); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 159.2 (C-3), 156.8 (C-4), 52.3 (CH_2), 25.1 (CH), 19.1 (CH_3).

Anal. Calcd. for $\text{C}_6\text{H}_{12}\text{N}_4\text{SO}_2$: C, 35.28; H, 5.92; N, 27.43; S, 15.70. Found: C, 35.17; H, 6.27; N, 27.78; S, 15.94.

3-Methoxy-4-(*sec*-butylamino)-1,2,5-thiadiazole 1,1-Dioxide (8) and 3,4-Bis(*sec*-butylamino)-1,2,5-thiadiazole 1,1-Dioxide (9).

Sec-butylamine (37 mg, 0.5 mmole) was added to a solution of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide [12] (107 mg, 0.5 mmole) in ethanol (15 ml). The reaction mixture was refluxed for 6 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using dichloromethane:methanol 20:1 as the eluent. From the first fraction was isolated the disubstituted derivative 9, mp 172-174°, yield 10 mg (8%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.92 (t, $J = 6.7$ Hz, 3H, $-\text{CH}_2-\text{CH}_3$), 1.31 (d, $J = 6.7$ Hz, 3H, $-\text{CH}(\text{CH}_3)_2$), 1.66 (m, $J = 6.7$ Hz, 2H, $-\text{CH}_2-\text{CH}_3$), 3.84 (q, $J = 6.7$ Hz, 1H, NCH), 7.68 (s, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 155.6 (C-3 and C-4), 53.5 (CH), 28.3 (CH_2), 18.8 (CH_3), 10.4 (CH_3).

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{N}_4\text{SO}_2$: C, 46.13; H, 7.74; N, 21.52; S, 12.32. Found: C, 46.19; H, 7.35; N, 21.32; S, 12.21.

From the second fraction, derivative 8 was isolated, mp 180-183°, yield 44 mg (42%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.90 (t, $J = 7.1$ Hz, 3H, $-\text{CH}_2-\text{CH}_3$), 1.20 (d, $J = 7.1$ Hz, 3H, $-\text{CH}(\text{CH}_3)_2$), 1.87 (m, $J = 7.1$ Hz, 2H, $-\text{CH}_2-\text{CH}_3$), 3.96 (q, $J = 7.1$ Hz, 1H, NCH), 8.62 (s, 1H, NH), 4.04 (s, 3H, OCH_3); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 157.7 (C-3), 154.3 (C-4), 55.4 (OCH_3), 52.4 (CH), 28.7 (CH_2), 19.0 (CH_3), 10.3 (CH_3).

Anal. Calcd. for $\text{C}_7\text{H}_{13}\text{N}_3\text{SO}_3$: C, 38.34; H, 5.98; N, 19.17; S, 14.62. Found: C, 38.63; H, 6.12; N, 18.89; S, 14.57.

3-(4-Methoxyphenylamino)-4-(*sec*-butylamino)-1,2,5-thiadiazole 1,1-Dioxide (10).

To a solution of 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide [12] (187 mg, 1 mmole) in acetone (15 ml), *p*-anisidine (62 mg, 0.5 mmole) and triethylamine (50 mg, 0.5 mmole) were added. The reaction mixture was stirred at room temperature for 2 hours. The solvent was eliminated under reduced pressure. Then, the residue was dissolved in methanol (15 ml) and refluxed for 30 minutes. After this time, *sec*-butylamine (37 mg, 0.5 mmole) was added to the reaction mixture which was stirred

at room temperature for 12 hours. The solvent was evaporated *in vacuo* and the residue purified by silica gel column chromatography using dichloromethane:methanol 20:1 as the eluent to give the nonsymmetrically derivative **10**, mp 287-288°, yield 60 mg (39%); ^1H nmr (hexadeuterated dimethyl sulfoxide): δ ppm 0.90 (t, J = 5.8 Hz, 3H, $-\text{CH}_2-\text{CH}_3$), 1.20 (d, J = 5.8 Hz, 3H, $-\text{CH}-\text{CH}_3$), 1.66 (m, J = 5.8 Hz, 2H, $-\text{CH}_2-\text{CH}_3$), 3.70 (m, J = 5.8 Hz, 1H, NCH-), 3.76 (s, 3H, OCH_3), 7.04 (m, 2H, H-Ar), 7.66 (m, 2H, H-Ar), 8.62 (s, 1H, NH), 10.52 (s, 1H, NH); ^{13}C nmr (hexadeuterated dimethyl sulfoxide): δ ppm 156.8 (C-3), 155.2 (C-4), 152.4, 151.4, 130.3, 122.4, 114.2 (C-Ar), 55.4 (OCH_3), 52.4 (CH), 28.7 (CH_2), 19.0 (CH_3), 10.3 (CH_3).

Anal. Calcd. for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{SO}_3$: C, 50.30; H, 5.85; N, 18.05; S, 10.33. Found: C, 50.54; H, 5.54; N, 18.23; S, 10.35.

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