4*H*-Thieno[3,4-*e*]- and 4*H*-Pyrazolo[4,3-*e*]-1,2,4-Thiadiazine 1,1-Dioxides. Synthesis, Chemical Properties and Evaluation of their Potential Cardiovascular Activity

Salvador Vega* and María Esther Arranz [1]

Instituto de Química Médica, CSIC, Juan de la Cierva, 3, 28006 Madrid.
Received August 5, 2003

This paper deals with the synthesis of a number of new 4*H*-thieno[3,4-*e*] and 4*H*-pyrazolo[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide derivatives **1**, the study of their chemical behavior in some alkylation reactions and the evaluation of their vasorelaxant effects on spontaneous motility and on tension responses to increased extracellular KCl concentrations in isolated rat portal vein.

J. Heterocyclic Chem., **41**, 45 (2004).

The work, reported in this paper, is a continuation of our research project concerning the synthesis and biological evaluation of novel heterocyclic sulfonamides with possible clinical utility. Within this project we have already described several series of compounds belonging to novel heterocyclic ring systems. Among these latter structures are 1,2,4-benzothiadiazepine 1,1-dioxides, thienoisothiazole 1,1-dioxides, thieno and pyrazolo 2,1-benzothiazepine 1,1 dioxides and thieno and pyrazolo 1,2,4-thiadiazine 1,1-dioxides exhibiting interesting anti-inflammatory, psychotropic, cardiovascular and antiviral activities [2-11].

The compounds **1a-f** (Figure 1) described herein are the first representatives of the new heterocyclic systems 4*H*-thieno[3,4-*e*] and 4*H*-pyrazolo[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides in which one replaces the benzene of a 1,2,4-benzothiadiazine like diazoxide by a thiophene or pyrazole ring. As it is already known, diazoxide (3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide) (Figure 1) is an antihypertensive drug [12] which exerts its action by opening (activating) the adenosine 5'-triphosphate (ATP) sensitive potassium channels (K_{ATP} channels) of vascular smooth muscle [13], and we thought that a thiophene or pyrazole cycle attached to the 1,2,4-thiadiazine ring of this drug could improve its antihypertensive and muscle relaxant activities. This type of bioisosteric replacement was a useful design approach frequently employed in medicinal chemistry to retain or enhance the pharmacological properties of many therapeutic agents. The term bioisosterism refers to the concept in which functional groups that have similar physicochemical properties may be interchangeable, resulting in similar biological activities [14, 15].

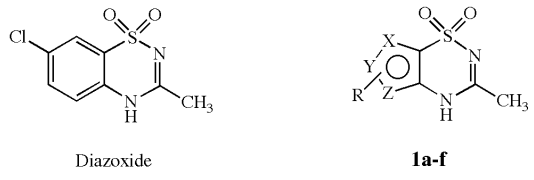


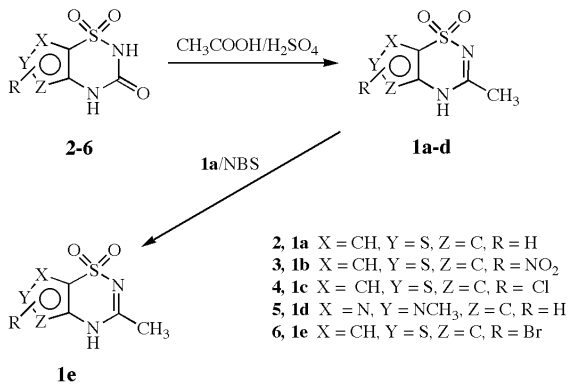
Figure 1

Furthermore, according to Burger [16], a bioisostere may or may not have the same steric or electronic characteristics (nor even the number of atoms) as the substituent for which it is used as a replacement. In this paper, we report the synthesis of the new thieno and pyrazolothiadiazines **1a-f** and their effects on spontaneous motility and on tension responses to increased extracellular KCl concentrations in isolated rat portal vein.

Most of the described synthetic methods of 1,2,4-benzothiadiazines start from anilines [17] which are first converted to *o*-amino-benzensulfonamides, then submitted to cyclization by means of carboxylic acids, acid anhydrides, acid chlorides, amides, esters, ortoesters, iminoesters, amidines or 1,1,1-trihalohegenated compounds [18,19]. However, these methods are not applicable to the formation of their thieno-1,2,4-thiadiazine bioisosteres because of the lack of stability of the required starting aminothiophenes in strong acid media [20]. We therefore attempted two alternative synthetic methods both involving the previous formation of the 1,2,4-thiadiazines **2-6** that we had already prepared through a classical Curtius reaction of appropriate sulfamoylheterocarboxylates [21].

The first one (Scheme 1) consisted of the reaction of **2-6** with a mixture of acetic and sulfuric acids at 120°. Under these conditions the 3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine derivatives **1a**, **1b** and **1c** were respectively

Scheme 1

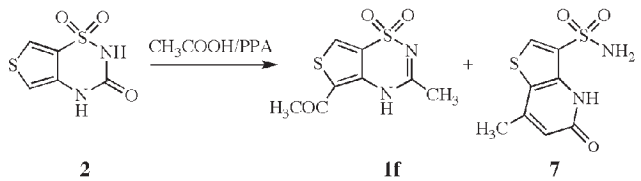


obtained from compounds **2**, **3** and **4** in moderate to good yields, but the pyrazolothiadiazine **1d** was prepared in only 36% yield from compound **5**. Under the same conditions, reaction of **6** did not afford the expected 5-bromo-3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1e**). This latter compound was prepared, in good yield, by bromination of **1a** with *N*-bromosuccinimide. Structural assignments for these new thiadiazines were based on their elemental and spectral analyses. Thus, they exhibited in their ^{1}H nmr spectra (dimethyl sulfoxide-d_6) a broad signal at low field (corresponding to a proton exchangeable by deuterium oxide addition) which was assigned to the NH group, and a singlet at 2.00-2.30 ppm due to the three protons of the methyl group. In the ir spectra (potassium bromide) **1a-e** showed (in addition to the strong bands of the SO_2 group at 1330-1280 and 1165-1140 cm^{-1}) an intense and generally split band at 1625-1565 cm^{-1} corresponding to the C=N bond vibration.

In the second method, the sulfuric acid of the above reaction was replaced by polyphosphoric acid, which has been successfully employed in the related synthesis of some 3-alkyl 1,2,4-benzothiadiazines 1,1-dioxides [22]. This method, however, did not lead to the heterothiadiazines **1** but to other unexpected compounds.

For example, heating of **2** in a mixture of acetic and polyphosphoric acids at 120° led to the formation of two isomeric compounds (Scheme 2) whose structures were established according to their analytical and spectroscopic data. Thus, the first compound, which was isolated as a solid (21%) from the organic extracts of the crude product, exhibited a ^{1}H nmr spectrum (dimethyl sulfoxide-d_6) very similar to that of the starting thiadiazine **2**, but showing only a thiophene proton signal and an additional singlet at 2.50 ppm that integrates for three protons. In addition, its ^{13}C nmr spectrum (dimethyl sulfoxide-d_6) showed a signal at 191.0 ppm (corresponding to a carbonylic carbon atom), and its ir spectrum (KBr) a strong band at 1655 cm^{-1} (typical of stretching frequencies of ketone CO bonds). All these spectroscopic data were consistent with the thienothiadiazine structure **1f** assigned for this first compound. The second compound was isolated in 33% yield after neutralization of the acidic aqueous layer of the final reaction mixture. Its ^{1}H nmr spectrum (dimethyl sulfoxide-d_6) exhibited two signals corresponding to three exchangeable protons, a low field signal due to an only thiophene proton and two singlets at 6.11 and 2.43 ppm corresponding to one and three protons, respectively. These data and the study of its ^{13}C nmr and mass spectra allowed the assignment of the thienopyridone structure **7** to this compound.

Scheme 2

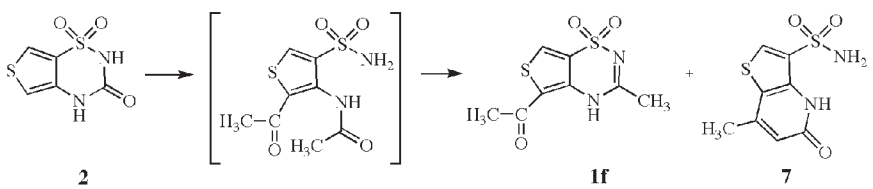


2 **1f** **7**

The latter compound **7** seems to have been formed from an intermediate product (Scheme 3), generated by a Friedel-Crafts reaction of the thiophene ring with acetic acid and a simultaneous opening of the thiadiazine ring with subsequent acylation of the resulting amino group. This intermediate would give rise to the thienothiadiazine **1f** (by reaction of the amide with the sulfonamide group) and to the thienopyridone **7** (by intramolecular ring closure with the $COCH_3$ group). Related formation of 4-aryl-2-pyridones from aroylacetonitriles and ketones in the presence of polyphosphoric acid is well documented in the scientific literature [23]; in this process the cyclization reaction also takes place through an intermediate amide. Table 1 lists the yields obtained and the main physical and analytical characteristics of the compounds prepared.

With these compounds, as observed with other 1,2,4-thiadiazines, there is the possibility of prototropic changes that are important to elucidate (for instance, to determine the receiving nitrogen atom of the alkyl group in an alkylation reaction). To gain insight in this matter, thienothiadiazine **1a** was reacted with methyl iodide in the presence of potassium carbonate and dimethylformamide to give a single product in 75 % yield (Scheme 4). Its structure was established by NOESY experiments that evidenced a positive NOE between the signals assigned to one of the methyl groups and those corresponding to the thiophenic proton in the 5-position. The structure of 3,4-dimethyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1 dioxide (**8**) was therefore assigned for the new alkylated compound (Figure 2). On the other hand, reaction of thienothiadiazine **1a** with benzyl bromide and sodium hydride under the same conditions led to the formation of a mixture of 2H and 4H benzyl regioisomers in different proportions. Regioisomeric assignments of these compounds were also made by NOESY experiments on the

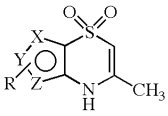
Scheme 3



2 **1f** **7**

Table 1

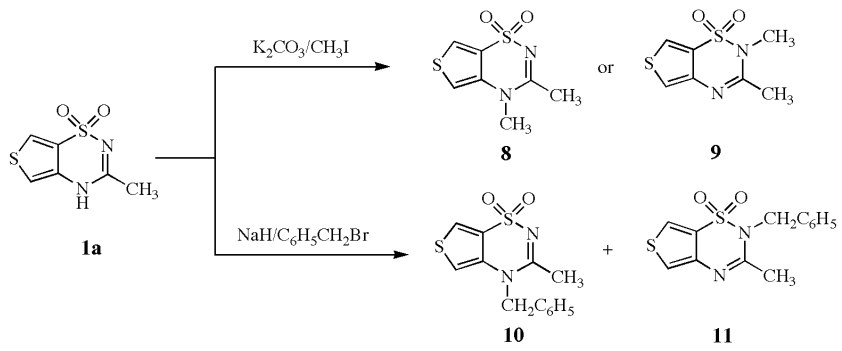
Compounds **1a-f** Synthesized



Comp.	X	Y	Z	R	Mp (°C)*	Yield	Formula	Analysis Calc./Found (%) C	H	N	S
1a	CH	S	C	H	309-310[a]	71	$C_6H_6N_2O_2S_2$	35.63	2.99	13.85	31.71
								35.90	2.88	13.72	32.02
1b	CH	S	C	NO_2	319-321 [b]	82	$C_6H_5N_3O_4S_2$	29.29	2.04	16.99	25.94
								29.21	1.90	16.89	26.62
1c	CH	S	C	Cl	273-275 [b]	56	$C_6H_5ClN_2O_2S_2$	30.44	2.13	11.84	27.09
								30.23	1.98	11.60	27.31
1d	N	NCH_3	C	H	269-271 [c]	36	$C_6H_8N_4O_2S$	35.99	4.03	27.98	16.01
								35.75	3.93	27.78	16.30
1e	CH	S	C	Br	244-246[a]	50	$C_6H_5BrN_2O_2S_2$	25.63	1.79	9.97	22.81
								25.80	1.68	9.84	22.58
1f	CH	S	C	$COCH_3$	233-235 [d]	21	$C_8H_8N_2O_3S_2$	39.33	3.30	11.47	26.25
								39.12	3.39	11.18	26.45

* Recrystallization solvent: [a] Ethanol; [b] Acetonitrile; [c] n-Propanol-Water; [d] Ethanol-Water.

Scheme 4



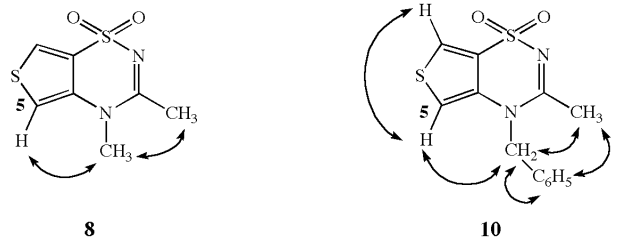


Figure 2

major isomer. The observed correlation signals between the thiophenic H-5 and the methylene protons of the benzyl group (Figure 2) are only consistent with the thiadiazinic structure bearing the benzyl group on the N-4 position. Consequently, the structure of 3-methyl-4-benzyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1 dioxide (**10**) was assigned to the main regioisomer in the mixture.

The compounds synthesized were originally evaluated for their possible activity as agonists of K_{ATP} channels using diazoxide (Figure 1) as reference standard. Vasorelaxant effects on spontaneous motility (K^+ 20 mM) and on tension responses to increased extracellular KCl concentrations motility (K^+ 80 mM) in isolated rat portal vein were first studied [3,24]. Diazoxide and other potassium channel agonists (cromakalin, pinacidil, *etc.*), antagonize the spontaneous motility but do not inhibit contractions induced by KCl at concentrations greater than about 30 mM in vascular smooth muscle. Table 2 summarizes the results obtained. The data clearly indicate that none of the compounds tested presented the pharmacological profile exhibited by diazoxide.

Table 2

Inhibitory Effects of Thiadiazines **1a-f** on KCl (20 mM)- Induced Spontaneous Mechanical Activity/KCl (80 mM)-Induced Contractions in Isolated Rat Portal Vein

Compound	Concentration μM	KCl (20 mM) induced spontaneous motility (%) [a]	KCl (20 mM) induced contraction (%) [b]
1a	10	2 ± 1	
	100	1 ± 0	-5 ± 3
1b	10	6 ± 1	
	100	12 ± 6	2 ± 2
1c	10	2 ± 6	
	100	1 ± 7	4 ± 7
1d	10	2 ± 5	
	100	9 ± 3	-5 ± 5
1e	10	6 ± 9	
	100	3 ± 9	4 ± 2
1f	10	9 ± 3	
	100	9 ± 3	-12 ± 3
Diazoxide	10	16 ± 1	
	100	78 ± 1	7 ± 2

[a] % of inhibition produced by the concentration indicated of each compound on KCl (20 mM)-induced spontaneous motility; [b] KCl (80 mM)-induced contractions.

EXPERIMENTAL

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Ir spectra were recorded using a Shimadzu IR-435 instrument. ^{1}H nmr spectra (300 MHz) and ^{13}C nmr spectra (75 MHz) were measured with a Varian XL-300 spectrometer in the indicated solvent. Chemical shift values are expressed in δ units relative to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Hewlett-Packard 5973 MSD instrument. Silica gel/tlc cards (Fluka, silica gel-precoated aluminium cards with fluorescent indicator 254 nm) were used for thin-layer chromatography (tlc) which were run with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v respectively) as eluents. Medium-pressure chromatography was performed on columns packed with silica gel 60 with (230-400 mesh) purchased from E. Merck, Inc. Elemental analysis were performed on a Heraeus CHN-RAPID instrument. Analytical results, which are only indicated by symbols, were found to be within ± 0.4% of the theoretical values.

Synthesis of Hetero-1,2,4-thiadiazine 1,1-dioxides **1a-d**.

To a mixture of 96% sulfuric acid and glacial acetic acid (1:8 v/v) was added the hetero-1,2,4-thadiazines **2-6** (1 equivalent) [21]. The mixture was heated at 120° with stirring for 7 hours. After cooling, the precipitate was isolated by filtration, washed with water, dried *in vacuo* over phosphorus pentoxide at room temperature, and recrystallized from the appropriate solvent.

3-Methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1a**).

This compound was synthesized from the 2,3-dihydro-3-oxo-4*H*-thieno[3,4-*e*]-1,2.4-thiadiazine 1,1-dioxide (**2**) as a brown crystalline solid; ir (potassium bromide): NH 3255, C=N 1605, 1575, SO_2 1280, 1140 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.24 (s, 3H, CH_3), 7.27 (d, J = 3.3 Hz, 1H, thiophene), 8.45 (d, J = 3.3 Hz, 1H, thiophene), 12.20 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.0 (CH_3), 108,1 (5-C), 124.6 (7a-C), 125.5 (7–C), 134.0 (4a-C), 155.7 (3–C); ms: m/z 201.9 (M^+), 160.8 ($C_4H_3NO_2S_2^+$), 97 ($C_4H_3NS^+$).

3-Methyl-5-nitro-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1b**).

This compound was synthesized from the 2,3-dihydro-5-nitro-3-oxo-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**3**) as a colorless crystalline solid; ir (potassium bromide): NH 3295, C=N 1615, NO_2 1560, 1340, SO_2 1300, 1165 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.47 (s, 3H, CH_3), 8.95 (s, 1H, thiophene), 11.68 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.9 (CH_3), 123.4 (7a-C), 132,1 (5-C), 133.5 (4a-C), 133.8 (7–C), 158.3 (3–C); ms: m/z 247.1 (M^+), 206.1 (M^+-C_2H_3N), 52.1 ($C_4H_4^+$).

5-Chloro-3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1c**).

This compound was synthesized from the 5-chloro-2,3-dihydro-3-oxo-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**4**) as a white crystalline solid; ir (potassium bromide): NH 3310, C=N 1610, 1580, SO_2 1300, 1157 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.31 (s, 3H, CH_3), 8.38 (s, 1H, thiophene), 11.89 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.1 (CH_3), 109,7 (5-C), 123.6 (7–C), 124.6 (7a-C), 130.9 (4a-C), 156.9 (3–C); ms: m/z 236 (M^+), 131 ($C_4H_2ClNS^+$), 52.1 ($C_4H_4^+$).

3,6-Dimethyl-4*H*-pyrazolo[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1d**).

This compound was obtained from the 2,3-dihydro-6-methyl-3-oxo-4*H*-pyrazolo[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**5**) after 17 hours of heating. After cooling, the reaction mixture was concentrated *in vacuo* to give **1d** as a yellow crystalline solid; ir (potassium bromide): NH 3250, 3200, C=N 1625, SO_2 1280, 1160 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.01 (s, 3H, CH_3), 3.97 (s, 3H, CH_3), 7.90 (s, 1H, pyrazole), 12.00 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 21.9 (CH_3), 39.9 (CH_3N), 118.3 (5-C), 122.3 (4a–C), 133.8 (7a-C), 154.4 (C=N); ms: m/z 200 (M^+), 159 ($C_4H_5N_3O_2S^+$), 94.1 ($C_4H_4N_3^+$), 42.2 ($C_3H_6^+$).

Synthesis of 5-Bromo-3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1e**).

To a solution of 3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1a**) (0.5 g, 2.47 mmol) in tetrahydrofuran (10 ml) was added *N*-bromosuccinimide (0.44 g, 2.47 mmol). The reaction mixture was stirred for 3 hours at room temperature. After evaporation of solvent, the solid residue was filtered, washed with water and dried. It was recrystallized from ethanol (brown needles); ir (potassium bromide): NH 3260, C=N 1605, 1565, SO_2 1305, 1155 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.31 (s, 3H, CH_3), 8.54 (s, 1H, thiophene), 11.23 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.1 (CH_3), 93.6 (5-C), 125.0 (7a-C), 126.5 (7–C), 133.1 (4a-C), 157.1 (3–C); ms: m/z 281.8 (M^++2), 279.8 (M^+), 240.9 ($C_4H_2BrNO_2S_2^+$), 238.8 ($C_4H_2BrNO_2S_2^+$), 176.8 ($C_4H_2BrNS^+$), 174.9 ($C_4H_2BrNS^+$), 52.1 ($C_4H_4^+$).

Synthesis of 5-Acetyl-3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**1f**) and 4-Methyl-2-oxo-7-sulfamoyl-1*H*-thieno[3,2-*e*]pyridine (**7**).

To a mixture of polyphosphoric acid (13.6 g) and 2,3-dihydro-3-oxo-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1-dioxide (**2**) (1.0 g, 4.9 mmol), was added glacial acetic acid (2 mL). The reaction mixture was stirred at 120° for 20 hours. After cooling, water (10 mL) was added and the mixture was extracted several times with ethyl acetate. The organic extracts were collected and dried (magnesium sulfate). Evaporation of the solvent *in vacuo* gave an oily residue from which compound **1f** (0.25 g, 21%) precipitated by treatment with ethanol; ir (potassium bromide): NH 3200, C=O 1655, C=N 1560, SO_2 1315, 1160 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.42 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 8.87 (s, 1H, thiophene), 11.18 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.8, 22.9 (CH_3), 120.6 (5-C), 124.5 (7a-C), 132.2 (7–C), 137.2 (4a-C), 157.6 (3–C), 191.0 (CO); ms: m/z 244 (M^+), 203 (M^+-C_2H_3N), 52.3 ($C_4H_4^+$), 43.3 ($C_2H_3O^+$).

By neutralization of the aqueous layer until pH 7 with 5 *N* sodium hydroxide, compound **7** (0.4 g, 33%) precipitated as a brown crystalline solid of mp 315-317° (ethanol-water); ir (potassium bromide): NH 3310, C=O 1610, SO_2 1330, 1155 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.43 (s, 3H, CH_3), 6.11 (s, 1H, CH=), 7.70 (broad s, 2H, NH_2, deuterium oxide exchangeable) 8.51 (s, 1H, thiophene), 11.00 (broad s, 1H, NH, deuterium oxide exchangeable with D_2O); ^{13}C nmr (deuterium oxide, potassium deuterium oxide): δ 24.5, (CH_3), 109.9 (CH), 127.3 (quaternary), 130.5 (CH), 141.5, 151.7, 160.9, (quaternaries), 170.9 (CO); ms: m/z 243.9 (M^+), 226.9 (M^+-NH_3), 180 (M^+-SO_2), 135 ($C_7H_5NS^+$).

Anal. Calcd. For $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.18; H, 3.37; N, 11.39; S, 25.99.

Synthesis of 3,4-Dimethyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1 dioxide (**8**).

Thienothiadiazine **1a** (0.2 g, 0.99 mmol) was dissolved in *N*,*N*-dimethylformamide (8 ml) and cooled to 0°. Then, potassium carbonate (0.082 g, 0.59 mmol) and methyl iodide (0.074 ml, 1.12 mmol) was added. The reaction mixture was stirred for 3 h at 0° and then allowed to warm to room temperature and stirred for an additional 17 hours. The solvent was evaporated to dryness and the residue was treated with water and dichloromethane. The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo* to give compound **8** (0.16 g, 75%) as a white solid of mp 257-259° (ethanol); ir (potassium bromide): C=N 1570, 1540 SO_2 1285, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.41 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.53 (d, J = 3.3 Hz, 1H, thiophene), 8.49 (d, J = 3.3 Hz, 1H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 23.0 (CH_3), 36.5 (CH_3N), 109.3 (5-C), 125.9 (7-C), 126.5 (7a–C), 137.2 (4a-C), 157.5 (3-C=N); ms: m/z 216.1 (M^+), 175.0 (M^+-C_2H_3N), 109.8 ($C_5H_4NS^+$), 65.9 ($C_4H_4N^+$).

Anal. Calcd. For $C_7H_8N_2O_2S_2$: C, 38.87; H, 3.73; N, 12.95; S, 29.65. Found: C, 38.59; H, 3.48; N, 12.88; S, 29.91.

Synthesis of 3-Methyl-4-benzyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1 dioxide (**10**) and 2-Benzyl-3-methyl-4*H*-thieno[3,4-*e*]-1,2,4-thiadiazine 1,1 dioxide (**11**).

To a solution of the thienothiadiazine **1a** (0.2 g, 0.99 mmol) in dry *N*,*N*-dimethylformamide (6 ml), under an inert atmosphere, was added slowly sodium hydride (60% dispersion in mineral oil, 0.042 g, 1.05 mmol) maintaining the temperature below 10°. After 15 minutes, benzyl bromide (0.17 g, 0.99 mmol) was added and the reaction mixture was stirred at 70° for 24 hours. The solvent was evaporated to dryness and the crude solid was treated with water and extracted with ethyl acetate. The organic layer was separated, dried (magnesium sulfate) and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography using hexane/ethyl acetate 1:1 (v/v) as eluent. Compound **10** was isolated as white crystals (0.11 g, 38%) of mp 105-107° (methanol); ir (potassium bromide): C=N 1570, 1540 SO_2 1285, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.41 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 7.53-7.65 (m, 6H, benzene and thiophene), 8.23 (d, J = 3.3 Hz, 1H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.1 (CH_3), 48.2 (CH_2), 110.4 (5-C), 126.7 (7-C), 125.9 (7a–C), 135.0 (4a-C), 157.3 (3-C=N).

Anal. Calcd. For $C_{13}H_{12}N_2O_2S_2$: C, 53.40; H, 4.14; N, 9.58; S, 21.93. Found: C, 53.21; H, 3.98; N, 9.65; S, 21.77.

The slowest moving fractions gave compound **11** as a white solid (0.05 g, 17%) of mp 151-153° (ethanol); ir (potassium bromide): C=N 1568, 1537 SO_2 1305, 1135 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.48 (s, 3H, CH_3), 5.31 (s, 2H, CH_2), 7.50-7.63 (m, 6H, benzene and thiophene), 8.28 (d, J = 3.3 Hz, 1H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 22.9 (CH_3), 48.8 (CH_2), 120.0 (5-C), 124.6 (7-C), 126.5 (7a–C), 142.2 (4a-C), 152.1 (3-C=N).

Anal. Calcd. For $C_{13}H_{12}N_2O_2S_2$: C, 53.40; H, 4.14; N, 9.58; S, 21.93. Found: C, 53.45; H, 4.01; N, 9.50; S, 22.14.

Acknowledgements.

The financial support of this work by the "Comisión Interministerial de Ciencia y Tecnología (CICYT) Madrid" (research grant SAF 99-0061) and "Consejería de Educación de la Comunidad Autónoma de Madrid", (research grant CAM 082/0025/1999.1), Madrid, Spain, is gratefully acknowledged. We also thank Ignasi Cardelús, Jesús Llenas and Almirall Prodesfarma, Barcelona, Spain, for the pharmacological evaluations.

REFERENCES AND NOTES

[1] Present address: Myriad Pharmaceuticals, Inc. 320 Wakara Way, Salt Lake City, Utah 84108. U. S. A.

[2] S. Vega, J. A. Díaz, V. Darias, and C. C. Sánchez Mateo, *J. Heterocyclic Chem*., **37**, 389-393 (2000).

[3] M. E. Arranz, J. A. Díaz, S. Vega, M. Campos –Toimil, F. Orallo, I. Cardelús, J. Llenas and A. G. Fernández, *Eur. J. Med. Chem*., **35**, 751 (2000).

[4] M. E. Arranz, J. A. Díaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clerq and S. Vega, *J. Med. Chem*., **41**, 4109 (1999).

[5] M. E. Arranz, J. A. Díaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clerq and S. Vega, *Bioorg. Med. Chem*., **7**, 2811 (1999).

[6] S. Vega, J. A. Díaz, V. Darias, C. C. Sánchez Mateo and L. M. Albertos, *Pharmazie*, **53**, 130 (1998).

[7] M. E. Arranz, J. A. Díaz, E. Morante, C. Pérez, and S. Vega, *J. Heterocyclic Chem*., **33**, 151 (1996)

[8] J. A. Díaz, S. Vega, M. A. Expósito, C. C. Sánchez Mateo and V. Darias, *Arch. Pharm. Pharm. Med. Chem*., **329**, 352 (1996).

[9] J. A. Díaz, E. Montero, S. Vega, V. Darias, M. L. Tello and S. S. Abdalah, *Arch. Pharm*. **327**, 157 (1994).

[10] J. A. Díaz, and S. Vega, *J. Heterocyclic Chem*., **31**, 93 (1994).
[11] S. Vega, R. Madroñero, J. A. Díaz, F. Junquera, J. Alonso, V. Darias, L. Bravo and S. Abdalah, *Eur. J. Med. Chem.,* **23** 329 (1988).
[12] J. R. Empfield, and K. Russell, *Annu. Rep. Med. Chem*., **30**, 81 (1995).
[13] M. J. Coghlan, and W. A. Carroll, *J. Med. Chem*., **44**, 1627 (2001).
[14] G. A. Patani, and E. J. LaVoie, *Chem. Rev.*, **96**, 3147 (1996).
[15] J. G. Cannon, in Burger's Medicinal Chemistry and Drug Discovery, Vol. **1**, M. E. Wolf, ed, John Wiley & Sons, New York, NY, 1995, pp 783.
[16] A. Burger, *Prog. Drug Res.,* **37**, 287 (1991).
[17] R. E. Busby, in Advances in Heterocyclic Chemistry, Vol. **50**, A. R. Katritzky, ed, Academic Press, San Diego, CA, 1990, p 255.
[18] J. H. Freeman and E. C. Wagner, *J. Org Chem.,* **16**, 815 (1951).
[19] E. C. Wagner, *J. Org Chem.,* **5**, 133 (1940).
[20] R. K. Norris, in The Chemistry of Heterocyclic Compounds, Vol. **44**, S. Gronowitz, ed, , John Wiley & Sons, New York, NY, 1986, p 631.
[21] M. E. Arranz, S. Vega and J. A. Díaz, *Heterocycles*, **45**, 1767 (1997).
[22] Y. Girard, J. G. Atkinson, D. R. Haubrich, M. Williams and G. Yarbrough, *J. Med. Chem*., **25**, 113 (1982).
[23] R. E. Smith, G. F. Morris and C. R. Hauser, *J. Org. Chem*., **33**, 2562 (1968).
[24] M. Jetley and A. H. Weston, *Br. J. Pharmacol.,* **68**, 311 (1980).