Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 2, pp. 179–185, 1995

0968-0896/95 $9.50 + .00

0968-0896(95)00012-7

Dioxides of Bicyclic Thiadiazines: a New Family of Smooth Muscle Relaxants

Ana Castro,[a] Ana Martínez,*[a] Ignasi Cardelús[b] and Jesús Llenas[b]

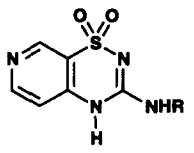
[a]*Instituto de Química Médica (C.S.I.C.), Juan de la Cierva, 3. 28006 Madrid, Spain*
[b]*Laboratorios Almirall S.A., Cardener 68–74, 08024 Barcelona, Spain*

Abstract—The synthesis of dioxides of bicyclic thiadiazine related to diazoxide has been achieved. In a preliminary test, some of these compounds show smooth muscle relaxation similar to that obtained with the reference standard diazoxide.

Introduction

The search for new potassium channel openers has been a very active field in medicinal chemistry over the last few years.[1–5] The recent finding that the biological action of diazoxide (*in vitro* it has an important smooth muscle relaxant effect and *in vivo* a hyperglycemic effect) can be associated with the opening of ATP-dependent potassium channels,[6] has greatly increased interest in the benzothiadiazine family.[7]

Diazoxide



Pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide

Figure 1.

It is known that the sulfate oxidation state is necessary to achieve biological response,[8] but until now, the basic thiadiazine skeleton is normally left unchanged. Only recently, modifications in the benzene ring have been described. Thus, pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides[9] bearing different aminoalkyl side chains in the 3-position show interesting biological results (Fig. 1).

In this context we report the synthesis and the preliminary data for the biological evaluation of diazoxide related bicyclic thiadiazine dioxides. The modifications introduced in this new kind of compound concern the order of the heteroatoms in the thiadiazine moiety as well as the nature and size of the ring fused to the heterocycle[10] (Fig. 2).

Results and Discussion

The synthesis of the bicyclic thiadiazines was achieved by two different pathways: condensation of sulfamide and *N*-alkylsulfamides in acidic media with 2-acetylcyclopentanone and 2-acetylcyclo-hexanone, and alkylation of the NH bicyclic thiadiazines in basic medium. Compounds **1–14** are obtained in good yields (Scheme 1).

The NH-thiadiazines **1** and **2** can exist as two different tautomers. A detailed study of the prototropic exchange in these compounds has been performed.[11] The most stable forms are depicted in Scheme 1. The reaction of alkyl and benzyl halides with bicyclic thiadiazines yields a mixture of isomers whose ratio mainly depends on steric effects. The ratio was experimentally determined by ^{1}H NMR of the reaction crude mixture. The major isomer is the one that results from the attack of the reagent to the less steric congested position of the thiadiazine, i.e. the N-1 substituted one (Table 1). The other synthetic pathway, condensation of *N*-alkyl and *N*-benzyl sulfamides with acetylcycloalkanones, yields a mixture of different composition whose ratios are collected in Table 2. The differences can be explained assuming that *N*-benzylsulfamide reacts almost quantitatively (100%, 90%) by the terminal

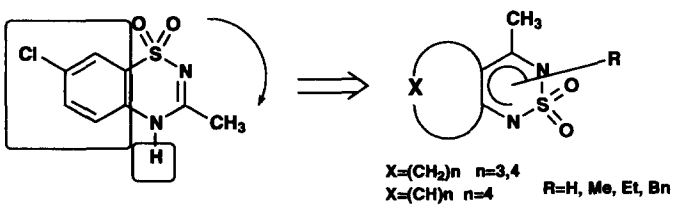
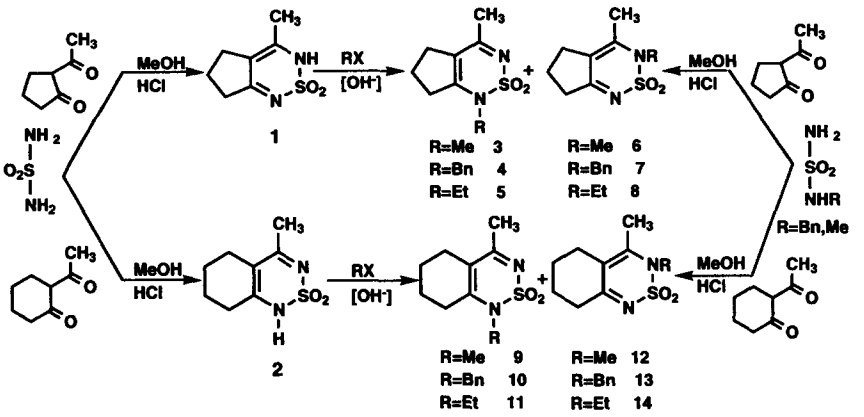


Figure 2.



Scheme 1.

Table 1. Percentage of isomers obtained from N-substitution of bicyclic thiadiazines

Compound	IMe	IEt	BrBn
1	88% 3	70% 5	80% 4
	12% 6	30% 8	20% 7
2	92% 9	70% 11	70% 10
	8% 12	30% 14	30% 13

Table 2. Percentages of isomers obtained from 2-acetylcycloalkanones and sulfamides

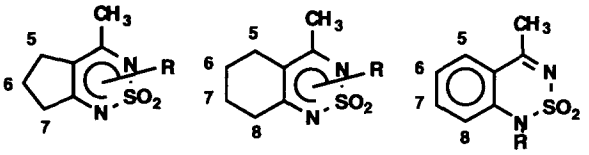
	N-methyl sulfamide	*N*-benzyl sulfamide
2-acetyl	33% 3	-
cyclopentanone	67% 6	100% 7
2-acetyl	45% 9	10% 10
cyclohexanone	55% 12	90% 13

NH_2 in the first step (yielding N-3 isomers), whereas in *N*-methylsulfamide, both nitrogen atoms compete in the first step althought the NH_2 (yielding the N-3 isomer) is still the most reactive (67%, 55%). The same behaviour was found in the synthesis of bicyclic pyrazoles from acetylcycloalkanones.[12]If we compare the results obtained for the two synthetic routes, regioselective synthesis of *N*-alkyl bicyclic thiadiazines can be obtained.

The structures of the new compounds were established according to their analytical, ^1H and ^{13}C NMR spectroscopic data which are collected in Tables 3 and 4. The determination of the alkylation position has been made by NOE experiments. Thus, irradiation on the signal corresponding to the alkyl group directly joined to the nitrogen atom of the thiadiazine moiety, produces a positive NOE effect on the heterocycle methyl group if the substitution has taken place on N(3). When the alkyl group is located on N(1), the signal affected by the NOE effect is the one corresponding to a methylene group of the cycloalkyl chain. Quaternary carbons linked to nitrogen atoms in the thiadiazine moiety could be unequivocally assigned by comparison of the coupled ^{13}C spectra registered with and without irradiation on the protons of the heterocyclic methyl group. Unambiguous assignments of the rest of the proton and carbon atoms have been made by means of COSY and HETCOR experiments. It is worth mentioning that N-substitution at the 3-position of the bicyclic thiadiazine ring system produces a down shift of 6 ppm on the C-CH_3 signal, as can be observed in ^{13}C NMR. This fact was previously observed for the methyl derivatives[11] and can be used for future elucidations.

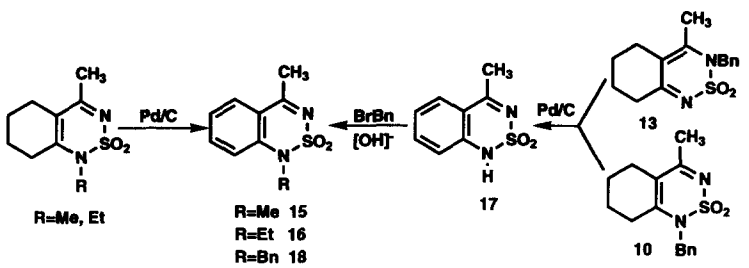
In order to obtain thiadiazines closely related to diazoxide, aromatization of some bicyclic thiadiazines was carried out. The methodology employed was the dehydrogenation over palladium at high temperatures. Thus, compounds **15** and **16** were obtained in good yields. When benzyl derivatives **10** and **13** were treated under these conditions, the benzothiadiazine **17** was obtained. In these cases, aromatization is simultaneous with the hydrogenolysis of the benzyl group. It is worth mentioning that compound **17** was previously obtained

Table 3.- ^{1}H NMR Parameters (chemical shifts and coupling constants) of bicyclic thiadiazine dioxides



Compound	H-5	H-6	H-7	H-8	C-CH_3	N-R
R = Bn **4**[a]	2.54(t)	1.87(q)	2.55(t)	-	2.14(s)	4.90(s)(CH_2)
						7.20(m)(Ar)
7[b]	2.63(t)	2.05(q)	2.80(t)	-	2.08(s)	5.08(s)(CH_2)
						7.30(m)(Ar)
10	2.30(m)		.....1.63(m).....	2.40(m)	2.20(s)	5.05(s)(CH_2)
						7.20-7.30(m)(Ar)
13	2.36(m)		.....1.70(m).....	2.67(m)	2.08(s)	5.01(s)(CH_2)
						7.27-7.31(m)(Ar)
18[c]	7.18(d)	7.51(t)	7.22(t)	7.80(d)	2.72(s)	5.22(s)(CH_2)
						7.40-7.60(m)(Ar)
R = Et **5**[b]	2.67(t)	2.10(q)	2.83(t)	-	2.19(s)	3.83(q)(CH_2)
						1.40(t)(CH_3)
8[d]	2.74(t)	2.00(q)	2.74(t)	-	2.24(s)	3.92(q)(CH_2)
						1.39(t)(CH_3)
11[c]	2.34(t)	1.66(q)	1.77(q)	2.56(m)	2.20(s)	3.85(q)(CH_2)
						1.31(t)(CH_3)
14	2.37(m)		.....1.73(m).....	2.61(m)	2.21(s)	3.95(q)(CH_2)
						1.41(t)(CH_3)
16[c]	7.13(m)	7.60(t)	7.13(m)	7.70(m)	2.62(s)	4.02(q)(CH_2)
						1.38(t)(CH_3)
R = Me **15**[c]	7.22(d)	7.66(t)	7.14(t)	7.80(d)	2.68(s)	3.51(s)(NMe)
R = H **17**[c]	7.21(d)	7.66(t)	7.19(t)	7.94(d)	2.65(s)	

[a] $J_{H6,H6} = J_{H6,H7} = 8$ Hz; [b] $J_{H5,H6} = J_{H6,H7} = 7$ Hz; [c] $J_{H5,H6} = J_{H6,H7} = J_{H7,H8} = 6$ Hz; [d] $J_{H5,H6} = J_{H6,H7} = 8$ Hz.



Scheme 2.

by reaction of 2-aminoacetophenone with sulfamide in lower yields.[13] Further alkylation of benzothiadiazine **17** in basic medium yields derivative **18** (Scheme 2). The analytical and spectroscopic data of these new benzothiadiazines are collected in Tables 3 and 4.

The smooth muscle relaxant activity of compounds **1–18** were evaluated by measuring two biological responses: the effect on isolated rat portal vein spontaneous motility and the relaxant activity on guinea pig isolated trachea. These two methods have

been described by the groups of Weston[14] and Allen[15] respectively. Diazoxide was considered the standard reference in all experiments. The results are summarized in Table 5.

As can be seen, some of the tested compounds show relaxations similar to those of the reference on the portal vein at K^+ 20 mM, whilst the relaxation power on tracheal muscle is not significant. In the cases with relaxant activity similar to those of the standard, the IC_{50} values were calculated, giving 36, 57 and 28 μM for compounds **4**, **10** and diazoxide respectively.

The inhibitory effect produced by some bicyclic thiadiazines on portal vein contractions induced by an 80 mM potassium solution is in contrast with the lack of activity found with the reference compound (diazoxide). Other compounds classified as potassium channel openers are not able to inhibit these kind of contractions.[16] For this reason, it can be concluded that the relaxation effect of the bicyclic thiadiazines on portal vein preparations is not an agonist effect on potassium channels.

Further efforts are being carried out in order to determine the precise pharmacological profile of these new compounds and to increase the biological response and the tissue selectivity of the bicyclic thiadiazine dioxides.

Experimental

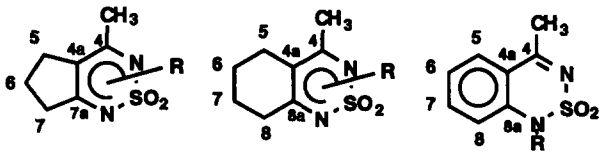
Melting points were determined with a Reichert–Jung Thermovar and are uncorrected. IR Spectra: Shimadzu IR-435. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). ^1H NMR spectra were obtained at 298 K using TMS as internal standard on a Varian-Gemini 200 and a Varian XL-300, operating at 200 MHz and 300 MHz, respectively. ^{13}C NMR spectra were recorded with a Varian-Gemini 200 and a Bruker AM-200, operating at 50 MHz and using TMS as internal reference.

Compounds **1–3**, **6**, **9** and **12** were prepared following described procedures.[11]

1-Ethyl-4-methyl-1,5,6,7-tetrahydrocyclopenta[c]-[1,2,6]thiadiazine 2,2-dioxide (5) and 3-ethyl-4-methyl-3,5,6,7-tetrahydrocyclopenta[c][1,2,6]thiadiazine 2,2-dioxide (8)

To a solution of the NH-derivative **1**[11] (1.0 g, 5 mmol) n acetone (30 mL), potassium carbonate (0.3 g, 5 mmol) and ethyl iodide (1.0 g, 6 mmol) were added. The reaction mixture was refluxed for 6 h. After cooling, the solid was filtered off and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate:hexane 1:3 as eluent. From the first fraction was isolated derivative **5** (0.34 g, 32%) as white crystals; mp: 106 °C; ν_{max}

Table 4. ^{13}C NMR Parameters (chemical shift) of bicyclic thiadiazines dioxides



Compound	C-4	C-4a	C-5	C-6	C-7	C-7a	C-8	C-8a	C-Me	Others
R=Bn **4**	170.79	113.66	29.47	21.66	33.30	162.02	-	-	24.29	50.65(CH_2),127.92, 128.68, 129.47, 135.89 (C-Ar)
7	152.43	113.99	28.26	21.61	36.01	180.87	-	-	17.68	49.10(CH_2), 127.93,128.99,129.32, 135.55 (C-Ar)
10	174.48	111.68	24.89	21.13	21.37	-	27.49	153.58	23.91	48.14(CH_2), 126.54, 127.76, 128.90, 135.32 (C-Ar)
13	155.78	110.86	25.68	21.18	22.11	-	34.41	171.32	16.51	49.51(CH_2), 126.67, 127.84, 128.91,135.26 (C-Ar)
18	174.76	118.49	122.19	122.18	116.61	-	135.63	142.46	24.29	49.63(CH_2), 126.79, 127.84, 128.91, 135.21 (C-Ar)
R=Et **5**	170.08	112.52	29.05	21.29	32.19	161.44	-	-	23.66	42.70(CH_2), 15.96 (CH_3)
8	152.32	113.57	28.28	22.16	36.52	180.86	-	-	17.61	41.66(CH_2), 16.51 (CH_3)
11	173.91	110.61	24.94	21.29	21.59	-	25.82	152.95	23.84	40.05(CH_2), 15.82 (CH_3)
14	155.87	109.88	25.86	21.57	22.57	-	34.39	173.73	15.87	41.66(CH_2), 15.87 (CH_3)
16	174.63	118.45	129.63	122.03	115.64	-	135.98	142.42	24.45	41.16(CH_2), 14.32 (CH_3)
R=Me **15**	174.56	117.74	129.20	121.92	117.74	-	135.97	143.25	24.15	31.06(NMe)
R=H **17**	174.36	115.42	129.24	122.61	117.02	-	135.77	141.36	23.70	

Table 5. Comparative study of the effect over the spontaneous motility in the rat portal vein and the relaxant effect in the smooth tracheal muscle of guinea pig at a concentration of 100 μM

Comp.	Rat Portal Vein K^+ 20mM % inhibition of the spontaneous movement	Rat Portal Vein K+ 80mM % inhibition of the spontaneous movement	Guinea Pig Trachea % relaxation to isoprenaline
Diazoxide	65±4	12±3	61±7
1	-4±5	-7±6	15±15
2	2±3	-3±6	20±0
3	-2±5	-10±7	9±1
4	73±5	100±0	-
5	2±7	11±2	5±2
7	11±5	19±4	-
8	16±5	24±5	0±3
9	5±3	2±2	12±4
10	72±5	100±0	-
11	26±8	23±4	-
12	3±4	13±2	6±2
13	50±1	61±2	0±0
14	13±4	6±5	-
15	17±4	7±5	24±12
16	32±3	31±13	-
17	24±8	26±7	-
18	32±6	58±10	-

(nujol): 1400, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_9H_{14}N_2O_2S$: C, 50.47; H, 6.54; N, 13.08; S, 14.95. Found: C, 50.68; H, 6.37; N, 13.21; S, 14.63.

From the second fraction was isolated derivative **8** (0.06, 6%); mp: 68 °C, ν_{max} (nujol): 1320, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_9H_{14}N_2O_2S$: C, 50.47; H, 6.54; N, 13.08; S, 14.95. Found: C, 50.47; H, 6.68; N, 13.31; S, 14.72.

3-Benzyl-4-methyl-3,5,6,7-tetrahydrocyclopenta[c]-[1,2,6]thiadiazine 2,2-dioxide (7)

A mixture of *N*-benzylsulfamide (1.5 g, 8 mmol) and 2-acetylcyclopentanone (1.0 g, 8 mmol) in methanol (25 mL) was saturated with hydrogen chloride at 0 °C and stirred at room temperature for 3 days. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography using ethyl acetate:hexane 1:5

as eluent to give 0.08 g (4%) of compound **7**; mp 112 °C; ν_{max} (KBr): 1380, 1150 (SO_2) cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_2S$: C, 60.87; H, 5.80; N, 10.14; S, 11.59. Found: C, 60.84; H, 6.08; N, 10.09; S, 11.22.

1-Benzyl-4-methyl-1,5,6,7-tetrahydrocyclopenta[c]-[1,2,6]thiadiazine 2,2-dioxide (4)

Benzyl bromide (1.0 g, 6 mmol) was added to a solution of thiadiazine **1** (1.1 g, 6 mmol) in acetone (30 mL) and potassium carbonate (0.4 g, 3 mmol). The reaction mixture was refluxed for 6 h. After cooling, the solid was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from water/methanol to give **4** as white needles (1.2 g, 72%); mp 97 °C ; ν_{max} (nujol): 1380, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_{14}H_{16}N_2O_2S$: C, 60.87; H, 5.80; N, 10.14; S, 11.59. Found: C, 61.08; H, 5.62; N, 10.27; S, 11.87.

3-Benzyl-4-methyl-5,6,7,8-tetrahydro-3H-[2,1,3]-benzothiadiazine 2,2-dioxide (13)

A solution of *N*-benzylsulfamide (6.0 g, 0.03 mol) and 2-acetylcyclohexanone (4.5 g, 0.03 mol) in methanol (50 mL) was saturated with hydrogen chloride at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue crystallized from methanol yielding compound **13** (5.0 g, 57%) as white needles; mp: 103–104 °C; ν_{max} (KBr): 1320, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_{15}H_{18}N_2O_2S$: C, 62.07; H, 6.20; N, 9.65; S, 11.03. Found: C, 61.90; H, 6.28; N, 9.64; S, 10.82.

1-Benzyl-4-methyl-5,6,7,8-tetrahydro-1H-[2,1,3]-benzothiadiazine 2,2-dioxide (10)

Benzyl bromide (2.5 g, 0.01 mol) was added to a solution of thiadiazine **2**[17] (3 g, 0.01 mol) in acetone (30 mL) and potassium carbonate (0.7 g, 5 mmol). The reaction mixture was refluxed for 6 h. After cooling, the solid was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue,which was a mixture of two compounds, was purified by column chromatography using ethyl acetate:hexane (5:1) as eluent.

From the first fraction was isolated derivative **10** (2.6 g, 60%); mp: 112–113 °C; ν_{max} (KBr): 1310, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_{15}H_{18}N_2O_2S$: C, 62.07; H, 6.20; N, 9.65; S, 11.03. Found: C, 62.37; H, 6.28; N, 9.65; S, 11.10.

From the second fraction was isolated a derivative whose analytical and spectroscopic data were identical to those obtained for compound **13** (1.1 g, 25%).

1-Ethyl-4-methyl-5,6,7,8-tetrahydro-1H-[2,1,3]-benzothiadiazine 2,2-dioxide (11) and 3-ethyl-4-methyl-5,6,7,8-tetrahydro-3H-[2,1,3]-benzothiadiazine 2,2-dioxide (**14**)

To a solution of thiadiazine **2**[11] (2.5 g, 0.01 mmol) in acetone (30 mL), potassium carbonate (0.7 g, 5 mmol) and ethyl iodide (1.9 g, 0.01 mmol) were added. The reaction mixture was refluxed for 6 h. After cooling, the solid was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue, which was a mixture of two compounds, was purified by preparative thin layer chromato-graphy, using ethyl acetate:hexane (1:1) as eluent.

From the faster running band, 1.4 g (51%) of derivative **11** was isolated; mp: 89–91 °C; ν_{max} (nujol): 1380, 1140 (SO_2) cm^{-1}. Anal. calcd for $C_{10}H_{16}N_2O_2S$: C, 52.63; H, 7.02; N, 12.28; S, 14.03. Found: C, 52.62; H, 7.01; N, 12.46; S, 14.04.

The lower running band gave 0.6 g (22%) of compound **14**; mp: 98 °C, ν_{max} (nujol): 1360, 1160 (SO_2) cm^{-1}. Anal. calcd for $C_{10}H_{16}N_2O_2S$: C, 52.63; H, 7.02; N, 12.28; S, 14.03. Found: C, 52.36; H, 6.97; N, 11.99; S, 13.85.

1,4-Dimethyl-[2,1,3]-benzothiadiazine 2,2-dioxide (15)

A solution of dimethylthiadiazine **9**[11] (0.15 g, 0.7 mmol) and Pd/C (10% weight) in diglyme (20 mL) was refluxed for 40 h. After cooling, the catalyst was removed by filtration. The solvent was eliminated under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate:hexane 1:3 as eluent to give **15** (0.1 g, 68%); mp: 185 °C. Anal. calcd for $C_9H_{10}N_2O_2S$: C, 51.42; H, 4.76; N, 13.33; S, 15.23. Found: C, 51.15; H, 4.99; N, 13.07; S, 15.07.

1-Ethyl-4-methyl-[2,1,3]-benzothiadiazine 2,2-dioxide (16)

Following the above procedure, 0.15 g (0.65 mmol) of compound **11** was dehydrogenated. The eluent used in the chromatography purification was ethyl acetate: hexane 4:1. In these conditions, 0.01 g (41%) of compound **16** was obtained as a yellow oil. Anal. calcd for $C_{10}H_{12}N_2O_2S$: C, 53.57; H, 5.35; N, 12.50; S, 14.28. Found: C, 53.97; H, 5.30; N, 12.92; S, 14.07.

1-Benzyl-4-methyl-[2,1,3]-benzothiadiazine 2,2-dioxide (18)

To a solution of the derivative **17** (0.04 g, 0.20 mmol) in acetone (15 mL), potassium carbonate (0.01 g, 0.10 mmol) and benzyl iodide (0.03 g, 0.20 mmol) were added. The reaction mixture was refluxed for 6 h. After cooling, the solid was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue was purified by preparative thin layer chroma-tography, using ethyl acetate:hexane (1:3) as eluent to give **18** (0.029 g, 50%); mp 170–172 °C. Anal. calcd for $C_{14}H_{12}N_2O_2S$: C, 61.76; H, 4.41; N, 10.29; S, 11.76. Found: C, 62.07; H, 4.03; N, 10.52; S, 11.96.

Biological methods

Reagents and solutions. All compounds tested were prepared in this work, except diazoxide which was

purchased from Impex Química (Mollet del Vallés, Spain). All drugs were dissolved in 10 to 50% of polyethylene glycol 300 in distilled water and diluted with Krebs–Henseleit physiological solution when necessary. The composition of Krebs–Henseleit solution was as follows (in mM): NaCl 118, KCl 4.7, $MgCl_2$ 1.2, $CaCl_2$ 2.55, NaH_2PO_4 1.0, $NaHCO_3$ 25.0 and glucose 11.0.

Relaxant activity in the guinea pig isolated trachea. Guinea pigs (male Dunkin–Hartley) of weight range 400–600 g were fasted overnight with free access to water. Animals were then killed by cranial percussion, and the trachea dissected free of connective tissue was placed into Krebs solution at 20 °C. The trachea was cut into preparations consisting of 2 cartilaginous rings which were then cut through the cartilaginous zones. The preparations were suspended in 30 mL organ baths containing Krebs solution at 37 °C gassed with 5% CO_2 in O_2. These were allowed at least 1 h to equilibrate during which time the resting tension was maintained at 1 g. A control response to isoprenaline (1×10^{-7} M) was then obtained, to indicate the maximum relaxation possible. The tissues were then washed and allowed 30 min to re-equilibrate before adding the drugs under study using a cumulative concentration procedure. Tension responses were allowed to stabilize (usually within 15 min of drug addition). Tension was recorded using an isometric transducer (Letica TR1 010) onto a Letica polygraph (model 4000).

Isolated rat portal vein. Male Wistar rats weighing 290–310 g were killed by cervical dislocation and the hepatic portal vein excised and placed in an oxygenated Krebs–Henseleit solution maintained at room temperature. Portal veins were dissected free of adhering connective tissue and cut longitudinally. One end of each portal vein was tied to a stainless-steel rod and placed into an organ bath containing the same solution at 37 °C and continuously oxygenated with a mixture of 5% CO_2 in O_2. Contractions were recorded with a Letica polygraph (model 4000) and stored into a PC computer for further analysis. The muscle preparations were equilibrated in normal Krebs solution for at least 30 min while resting tension was adjusted to 1 g. During the equilibration period, tissues were washed twice with fresh solution. Afterwards, the bath solution was changed to a modified one containing 20 mM K^+ and the experimental procedure was started when a stable spontaneous motility had been achieved. Compounds under study were added cumulatively and usually 20 min were enough to reach maximal inhibitory responses. Another group of preparations was used to assess the relaxant activity of these compounds on K^+ 80 mM-induced contractions. Spontaneous motility was measured by using a specific designed software (Letica) which calculates the AUC (area under the curve) every 3 min.

Acknowledgment

The financial support from CICYT (project no. SAF 93/710) is gratefully acknowledged.

References and Notes

1. Roberston, D. W.; Steinberg, M. I. *Ann. Rep. Med. Chem.* **1989**, *24*, 91.

2. Roberston, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, *33*, 1529.

3. Evans, J. M.; Longman, S. D. *Ann. Rep. Med. Chem.* **1991**, *26*, 73.

4. Atwal, K. S. *Med. Res. Rev.* **1992**, *12*, 569.

5. Harvey, A. L. *Med. Res. Rev.* **1993**, *13*, 81.

6. Quast, U.; Cook, N. S. *Trends Pharmacol. Sci.* **1989**, *10*, 431.

7. Edwards, G.; Weston, A. H. *Trends Pharmacol. Sci.* **1990**, *11*, 417.

8. Ros, D. D; Lednicer, D. *J. Heterocyclic Chem.* **1982**, *19*, 975.

9. Pirotte, B.; Tullio, P.; Lebrun, P.; Antoine, M. H.; Fontaine, J.; Maseree, B.; Schynts, M.; Dupont, L.; Herchuelz, A.; Delarge, J. *J. Med. Chem.* **1993**, *36*, 3211.

10. Castro, A.; Martínez, A.; Cardelús, I.; Llenas, J. Presented at the VIII Spanish Symposium on Therapeutical Chemistry, Salamanca, 1993.

11. Castro, A.; Martinez, A. *J. Chem. Soc. Perkin Trans. 2* **1994**, 1561.

12. Elguero, J.; Martinez, A.; Singh, S. P.; Kumar, D. *J. Heterocyclic Chem.* **1991**, *28*, 647.

13. Wright, J. B. *J. Org. Chem.* **1965**, 30, 3960.

14. Jetley, M.; Weston, A. H. *Br. J. Pharmacol.* **1980**, *68*, 311.

15. Allen, S. L.; Boyle, J. P.; Cortijo, J.; Foster, R. W.; Morgan, G. P.; Small, R. C. *Br. J. Pharmacol.* **1986**, *89*, 395.

16. Hamilton, T. C.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1986**, *88*, 103.

17. Wright, J. B. *J. Org Chem.* **1964**, *29*, 1905.

(*Received in U.S.A.* 19 *July* 1994; *accepted* 25 *November* 1994)