Chad E. Stephens and J. Walter Sowell, Sr.*

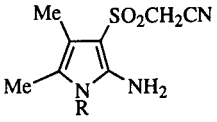
University of South Carolina, College of Pharmacy,
Department of Basic Pharmaceutical Sciences,
Division of Medicinal Chemistry,
Columbia, SC 29208

Received November 20, 1995

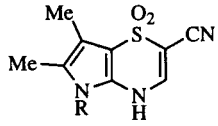
A series of substituted pyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-dioxides is synthesized from 1-substituted-2-amino-3-cyanomethylsulfonyl-4,5-dimethylpyrroles.

J. Heterocyclic Chem., **33**, 1615 (1996).

Previous work in our laboratory has involved the synthesis of 1-substituted-2-amino-3-cyanomethylsulfonyl-4,5-dimethylpyrroles **I** *via* the condensation of acetoin, a primary amine, and sulfonyldiacetonitrile [1,2]. From these pyrroles, a number of substituted pyrrolo[3,2-*b*]-[1,4]thiazine 1,1-dioxides **II** were prepared by cyclization with triethyl orthoformate [2].



I



II

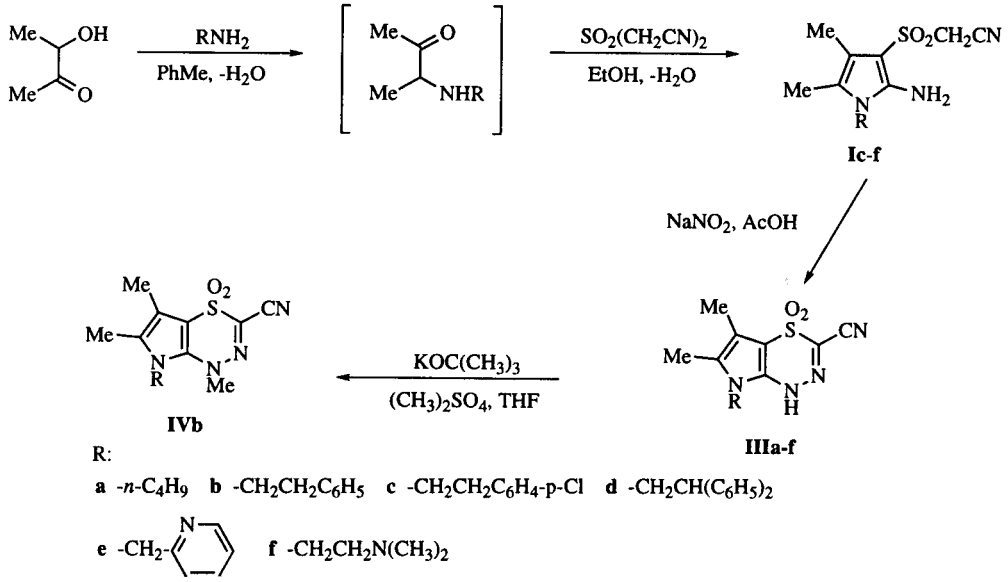
We now wish to report the synthesis of a series of substituted pyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-dioxides **IIIa-f**, novel aza-isosteres of **II**. Upon review of *Chemical Abstracts*, this is only the second reported pyrrolothiadiazine system in which the pyrrole nitrogen is not part of the thiadiazine ring, the other being a pyrrolo[2,3-*c*]-[1,2,6]thiadiazine [3].

In this facile procedure (Scheme 1), derivatives of **I** in acetic acid were cyclized to the title compounds by treatment with sodium nitrite at room temperature. After stirring 15-20 minutes, the pyrrolo[2,3-*e*]thiadiazines were isolated by filtration either directly from the reaction mixture, or following dilution with water or diethyl ether (see Experimental). Recrystallization afforded analytically pure samples.

Compound **IIIb** was subsequently *N*-alkylated using potassium *t*-butoxide and dimethyl sulfate in refluxing tetrahydrofuran to yield **IVb**.

As precursors to these pyrrolo[2,3-*e*]thiadiazines, we have also synthesized four new 1-substituted-2-amino-3-cyanomethylsulfonyl-4,5-dimethylpyrroles **Ic-f** *via* a modification of our original procedure. This modification

Scheme 1



R:

a -*n*-C_4H_9 **b** -$CH_2CH_2C_6H_5$ **c** -$CH_2CH_2C_6H_4$-p-Cl **d** -$CH_2CH(C_6H_5)_2$

e -CH_2- **f** -$CH_2CH_2N(CH_3)_2$

Table 1

Compound No.	Yield (%)	Mp (°C)	R_f [a]	Recrystallization Solvent	Formula		Analysis (%) Calcd.	Found
Ic	70	144-145	0.45 [b]	Methanol	$C_{16}H_{18}ClN_3O_2S$	C	54.61	54.51
						H	5.16	5.21
						Cl	10.08	10.01
						N	11.94	11.91
						S	9.09	9.04
Id	61	159-160 dec	0.58 [b]	Methanol	$C_{22}H_{23}N_3O_2S$	C	67.15	67.22
						H	5.89	5.93
						N	10.68	10.73
						S	8.15	8.24
Ie	56	119-120	0.59	Methanol	$C_{14}H_{16}N_4O_2S$	C	55.24	55.10
						H	5.30	5.35
						N	18.41	18.49
						S	10.53	10.46
If	68	87.5-88	0.48 [c]	Methanol/Water (1:1)	$C_{12}H_{20}N_4O_2S$	C	50.68	50.66
						H	7.09	7.11
						N	19.70	19.66
						S	11.28	11.22
IIIa	67	200 dec	0.65	EtOAc/Hexane	$C_{12}H_{16}N_4O_2S$	C	51.41	51.43
						H	5.75	5.75
						N	19.99	19.84
						S	11.44	11.33
IIIb	100	212 dec	0.60	Methanol	$C_{16}H_{16}N_4O_2S$	C	58.52	58.25
						H	4.91	4.93
						N	17.06	16.87
						S	9.76	9.56
IIIc	50	270 dec	0.60	Methanol	$C_{16}H_{15}ClN_4O_2S$	C	52.96	53.04
						H	4.17	4.13
						Cl	9.77	9.77
						N	15.44	15.34
						S	8.84	8.93
IIId	96	245-246 dec	0.50 [b]	Methanol	$C_{22}H_{20}N_4O_2S \cdot 0.75\ H_2O$	C	63.21	63.22
						H	5.18	5.21
						N	13.40	13.44
						S	7.67	7.58
IIIe	78	189-190	0.28	Methanol	$C_{14}H_{13}N_5O_2S \cdot 0.9\ CH_3OH$	C	51.99	51.64
						H	4.85	4.68
						N	20.35	20.70
						S	9.32	9.57
IIIf	57	238-240 dec	0.27 [c]	2-Propanol/Acetone (5:1)	$C_{12}H_{17}N_5O_2S$	C	48.79	48.60
						H	5.80	5.99
						N	23.71	23.60
						S	10.86	10.71
IVb	51	199-202	0.72	Methanol	$C_{17}H_{18}N_4O_2S$	C	59.63	59.48
						H	5.30	5.28
						N	16.36	16.29
						S	9.36	9.25

[a] Ethyl acetate unless otherwise indicated. [b] Ethyl acetate/Hexane (1:1). [c] Ethyl acetate/MeOH (2:1).

(Scheme 1 and Experimental) eliminates the use of benzene and reduces the approximate reaction time from 3 hours to 30 minutes while maintaining comparable yields (Table 1).

Structural assignments of all new compounds were made on the basis of elemental analysis, nmr and infrared spectra. This data is presented in Table 1 and the Experimental.

EXPERIMENTAL

Melting points were determined on an Electrothermal melting point apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Brucker WH-400 spectrometer. Infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analysis were performed by Atlantic Microlab, Inc., Norcross, Georgia. Tlc were performed on Baker Si250F silica plates and visualized under UV light. Sulfonyldiacetonitrile was synthesized according to a literature procedure [4]. Compounds **Ia-b** have been previously synthesized and reported [2].

The procedure given for the synthesis of **Ie** was utilized in the preparation of **Ic-f**.

2-Amino-3-cyanomethylsulfonyl-4,5-dimethyl-1-(2-pyridylmethyl)pyrrole (**Ie**).

A mixture of acetoin (1.04 g of an 85% aqueous solution, 0.01 mole) and 2-(aminomethyl)pyridine (1.08 g, 0.01 mole) in toluene (20 ml) was refluxed under a Dean-Stark trap until the evolution of water ceased (10-20 minutes). The toluene was removed *in vacuo* and replaced with ethanol. Sulfonyldiacetonitrile (1.44 g, 0.01 mole) was added and the mixture was refluxed for 10 minutes. Concentration *in vacuo* yielded a dark red oil

which was diluted with methanol (15 ml) and stirred in an ice bath. Addition of water (5 ml) gave a light brown solid (1.69 g, 56%). The product was suspended in methanol (10 ml) and recollected. A sample (0.5 g) was then dissolved in boiling methanol (10 ml), treated with charcoal, filtered and chilled to give light tan crystals, mp 119-120°; ir: ν 3435 and 3275 (NH_2), 2240 (CN), 1300 and 1095 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.92 and 2.01 (2s, 6H, $-CH_3$ at C_4 and C_5), 4.69 (s, 2H, SO_2-CH_2), 5.09 (s, 2H, $N-CH_2$), 5.89 (s, 2H, $-NH_2$), 6.96 (d, 1H, ArH), 7.29-7.32 (m, 1H, ArH), 7.75-7.79 (m, 1H, ArH), 8.54 (d, 1H, ArH).

2-Amino-1-[2-(4-chlorophenyl)ethyl]-3-cyanomethylsulfonyl-4,5-dimethylpyrrole (**Ic**).

This compound had ir: ν 3465 and 3365 (NH_2), 2240 (CN), 1290 and 1085 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.89 and 2.06 (2s, 6H, $-CH_3$ at C_4 and C_5), 2.87 (t, 2H, $-CH_2-Ph$), 3.84 (t, 2H, $N-CH_2$), 3.91 (s, 2H, SO_2-CH_2), 6.99 (d, 2H, ArH), 7.25 (d, 2H, ArH).

2-Amino-3-cyanomethylsulfonyl-1-(2,2-diphenylethyl)-4,5-dimethylpyrrole (**Id**).

Compound **Id** was isolated by filtration from the cooled reaction mixture. This compound had ir: ν 3435 and 3350 (NH_2), 2245 (CN), 1305 and 1100 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.88 and 2.09 (2s, 6H, $-CH_3$ at C_4 and C_5), 3.85 (s, 2H, SO_2-CH_2), 4.20-4.28 (m, 3H, $N-CH_2-CH$ overlapping) 7.13-7.17 (m, 4H, ArH), 7.25-7.35 (m, 6H, ArH).

2-Amino-3-cyanomethylsulfonyl-1-(2-dimethylaminoethyl)-4,5-dimethylpyrrole (**If**).

This compound had ir: ν 3460, 3415 and 3360 (NH_2), 2240 (CN), 1295 and 1095 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.98 and 2.01 (2s, 6H, $-CH_3$ at C_4 and C_5), 2.18 (s, 6H, $N-(CH_3)_2$), 2.39 (t, 2H, $N-CH_2-CH_2$), 3.77 (t, 2H, $N-CH_2$), 4.63 (s, 2H, SO_2-CH_2), 5.78 (s, 2H, NH_2)

The procedure given for the synthesis of **IIIb** was utilized in the synthesis of **IIIa-f**.

3-Cyano-1,7-dihydro-5,6-dimethyl-7-(2-phenylethyl)pyrrolo-[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IIIb**).

A solution of **Ib** (1.90 g, 6 mmoles) in acetic acid (50 ml) was prepared by warming. At room temperature, sodium nitrite (0.46 g, 6.6 mmoles) in water (2 ml) was added dropwise and the solution was stirred for 15-20 minutes, diluted with ice/water, and the insoluble product was collected and air dried. The orange solid (2.0 g, 100%) was dissolved in boiling methanol, treated with charcoal, filtered and chilled to give a yellow/orange powder, mp 212° dec; ir: ν 3220 (NH), 2205 (CN), 1250 and 1080 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.03 and 2.12 (2s, 6H, $-CH_3$ at C_5 and C_6), 2.90 (t, 2H, $-CH_2-Ph$), 4.25 (t, 2H, $N-CH_2$), 7.16-7.29 (m, 5H, ArH), 14.2 (broad s, 1H, NH).

7-Butyl-3-cyano-1,7-dihydro-5,6-dimethylpyrrolo[2,3-*e*][1,3,4]-thiadiazine 4,4-Dioxide (**IIIa**).

This compound had ir: ν 3235 (NH), 2205 (CN), 1250 and 1080 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.90 (t, 3H, $-CH_2-CH_3$), 1.28 (m, 2H, $-CH_2-CH_3$), 1.55 (m, 2H, $N-CH_2-CH_2$), 2.13 and 2.20 (2s, 6H, $-CH_3$ at C_5 and C_6), 4.00 (t, 2H, $N-CH_2$), 14.2 (broad s, 1H, NH).

7-[2-(4-Chlorophenyl)ethyl]-3-cyano-1,7-dihydro-5,6-dimethylpyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IIIc**).

Compound **IIIc** was isolated directly from the chilled reaction mixture. This compound had ir: ν 3205 (NH), 2205 (CN), 1240 and 1075 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.07 and 2.12 (2s, 6H, $-CH_3$ at C_5 and C_6), 2.91 (t, 2H, $-CH_2-Ph$), 4.23 (t, 2H, $N-CH_2$), 7.21 (d, 2H, ArH), 7.36 (d, 2H, ArH), 14.2 (broad s, 1H, NH).

3-Cyano-7-(2,2-diphenylethyl)-1,7-dihydro-5,6-dimethylpyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IIId**).

This compound had ir: ν 3220 (NH), 2205 (CN), 1240 and 1085 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): 1.90 and 2.07 (2s, 6H, $-CH_3$ at C_5 and C_6), 4.35 (t, 1H, $-CH-Ph_2$), 4.72 (d, 2H, $N-CH_2$), 7.19-7.29 (m, 10H, ArH), 14.1 (broad s, 1H, NH).

3-Cyano-1,7-dihydro-5,6-dimethyl-7-(2-pyridylmethyl)pyrrolo-[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IIIe**).

Compound **IIIe** precipitated during the reaction and was isolated following dilution with ice/water. This compound had ir: ν 3520 (NH), 2210 (CN), 1260 and 1100 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.05 and 2.15 (2s, 6H, $-CH_3$ at C_5 and C_6), 5.43 (s, 2H, $N-CH_2$), 7.26 (d,1H, ArH), 7.32 (t, 1H, ArH), 7.81 (t, 1H, ArH), 8.45 (d, 1H, ArH).

3-Cyano-7-(2-dimethylaminoethyl)-1,7-dihydro-5,6-dimethylpyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IIIf**).

Compound **IIIf** was isolated by diluting with diethyl ether, chilling, and decanting. The oily solid was then crystallized from 2-propanol. This compound had ir: ν 3520 (NH), 2185 (CN), 1220 and 1080 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.12 and 2.20 (2s, 6H, $-CH_3$ at C_5 and C_6), 2.86 (s, 6H, $N-(CH_3)_2$), 3.37 (t, 2H, $N-CH_2-CH_2$), 4.40 (t, 2H, $N-CH_2$).

3-Cyano-1,7-dihydro-1,5,6-trimethyl-7-(2-phenylethyl)pyrrolo-[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**IVb**).

To a solution of **IIIb** (0.70 g, 2.13 mmoles) in dry THF (10 ml) was added potassium *t*-butoxide (0.251 g, 2.24 mmoles). After stirring 15 minutes, dimethyl sulfate (0.296 g, 2.35 mmoles) was added and the mixture was refluxed for 2 hours. Concentration *in vacuo* gave a solid which was dissolved in boiling methanol (100 ml), treated with charcoal, filtered, and chilled to give an orange/brown solid (0.37 g, 51%). A sample (0.1 g) was again recrystallized from methanol (20 ml) to yield fine orange needles, mp 199-202°; ir: ν 2180 (CN), 1270 and 1100 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.02 and 2.27 (2s, 6H, $-CH_3$ at C_5 and C_6), 2.93 (t, 2H, $-CH_2-Ph$), 4.17 (s, 3H, $N-CH_3$), 4.26 (t, 2H, $N-CH_2$), 6.93-6.96 (m, 2H, ArH), 7.22-7.26 (m, 3H, ArH).

REFERENCES AND NOTES

[1] R. J. Mattson, L. C. Wang and J. W. Sowell, Sr., J. *Heterocyclic Chem.*, **17**, 1793 (1980).

[2] D. L. Wang, S. M. Bayomi and J. W. Sowell, Sr., *Pak. J. Sci. Ind. Res.*, **31**, 242 (1988).

[3] W. Offerman, K. Eger and H. J. Roth, *Arch. Pharm.* (Weinheim), **314**, 168 (1981).

[4] J. E. McCormick and R. S. McElhinney, J. *Chem. Soc., Perkin Trans. 1*, **11**, 1335 (1972).