Synthesis and Cyclization Reactions of 2-Amino-3-[(methoxycarbonyl)methylsulfonyl]pyrroles and Thiophene

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The title aminopyrroles and thiophene have been prepared by condensation of methyl (cyanomethylsulfonyl)acetate with various α-amino ketones or 2-mercaptoacetaldehyde, respectively. Subsequent cyclization of these compounds by reaction between the amine and activated methylene has led to various ester-substituted thiazine- and thiadiazine-based bicyclic derivatives. In addition, cyclization of the title compounds by intramolecular coupling of the amine and ester has led to the analogous bicyclic thiazin-3(2*H*)-ones. Attempted hydrolysis of the ester-substituted bicyclics to the corresponding carboxylic acids was unsuccessful.

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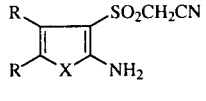
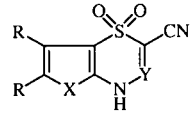
Previously, we have described the synthesis of 1-substituted-2-amino-3-cyanomethylsulfonyl-4,5-dimethylpyrroles **I** and the analogous furan **II** *via* condensation of sulfonyldiacetonitrile with an α-amino ketone or acetoin, respectively [1,2]. Most recently, this methodology has been extended to the preparation of a thiophene analogue **III** using 2-mercaptoacetaldehyde as the carbonyl component [3]. From these amino heterocycles, a variety of thiazine- and thiadiazine-based bicyclic derivatives corresponding to general structure **IV** have been prepared by cyclization between the amine and the activated methylene [2-5].



I X = N-Alkyl, R = Me
II X = O, R = Me
III X = S, R = H



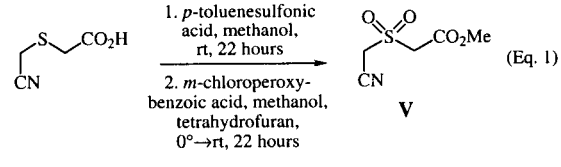
IV Y = CR' or N

For some time now, we have been interested in converting the nitrile group of these bicyclic systems to other functional groups (*i.e.*, carboxamide, carboxylic acid/ester) for the purpose of broad-screen biological evaluation. However, all attempts to hydrolyze the nitrile in these compounds, both under acidic and basic conditions, unfortunately have proven unsuccessful. This includes an exhaustive study by Wang [6] during the course of the original work with the pyrrolothiazines in which attempted hydrolysis under a variety of conditions led to only small traces of the carboxamide, with decomposition or recovery of starting material predominating. It has thus become apparent that a different synthetic route to these aforementioned derivatives is required.

One obvious route involves having the desired functional group in place before formation of the thiazine or thiadiazine ring, thus eliminating the need for subsequent manipulation of the apparently unreactive nitrile. Although this could conceivably be accomplished by hydrolysis of the nitrile in compounds **I-III** to the corresponding amide or carboxylic acid, we envisioned that the most practical route would be to directly prepare the amino heterocycle precursors using an unsymmetrical bis-activated sulfonyl derivative in place of sulfonyldiacetonitrile. Key to the success of this approach, however, is the requirement for condensation of such a bis-activated sulfone to take place preferentially at the acetonitrile methylene rather than at the alternative acetate or acetamido methylene.

Herein, we report on our initial investigation into this approach using methyl (cyanomethylsulfonyl)acetate as the bis-activated sulfonyl component. To our gratification, this route has indeed led to the title aminopyrroles and thiophene, which have been cyclized to the various bicyclic derivatives corresponding to **IV** containing an ester moiety in place of the nitrile. In addition, the title compounds have also served as precursors in the synthesis of the analogous pyrrolo- and thienothiazin-3(2*H*)-ones *via* intramolecular coupling of the amine and ester.

Methyl (cyanomethylsulfonyl)acetate (**V**, Equation 1) was synthesized starting with (cyanomethylthio)acetic acid [7] by way of Fischer esterification (*p*-toluenesulfonic acid, methanol), followed by oxidation of the sulfide with excess *m*-chloroperoxybenzoic acid.



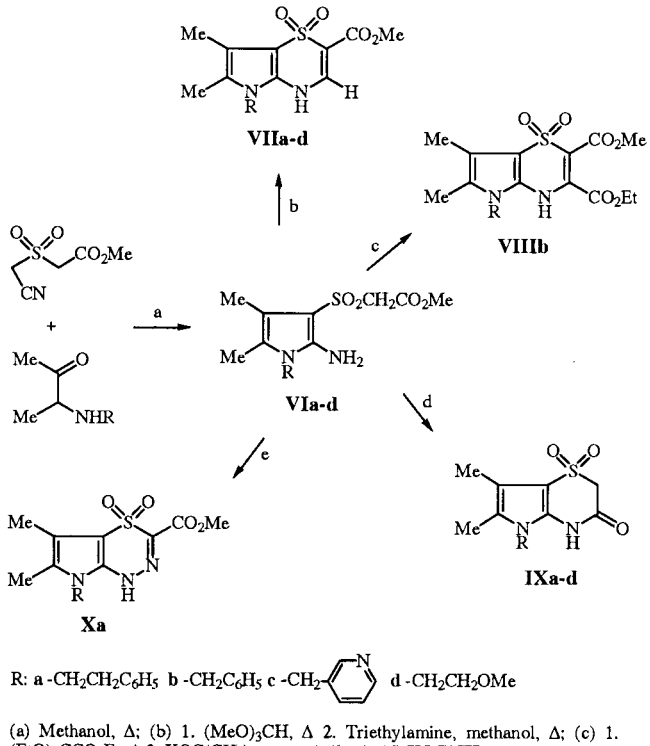
V (Eq. 1)

As shown in Scheme 1, reaction of sulfone **V** with various α-amino ketones (prepared *in situ* by condensation of acetoin with a primary amine) in methanol at 70-75° for 1.25 hours gave aminopyrroles **VIa-d** in 76-41% yield following crystallization or chromatography. In general, this

reaction proceeded rather cleanly for pyrroles **VIa-c** (R = aryl-containing group) as judged by tlc and crude proton nmr, with no evidence of by-products occurring by way of reaction of **V** at the acetate methylene. As a single exception, the synthesis of **VId** (R = 2-methoxyethyl) under identical conditions proceeded noticeably less cleanly, thus giving the pyrrole in a reduced yield of 34%. Owing this lower yield to perhaps loss of the 2-methoxyethylamine (bp 95°) during formation of the amino ketone, we repeated the reaction using for this step the lower boiling cyclohexane in place of toluene; this modification, however, resulted in only a modest increase of the yield to 41%.

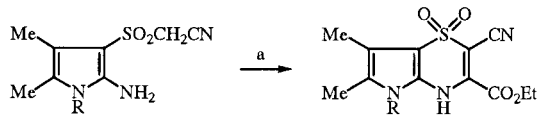
Also shown in Scheme 1 is the cyclization of pyrroles **VIa-d** to the various bicyclic derivatives. First, reaction with trimethyl orthoformate at 100-110° for 0.5-2.5 hours followed by treatment of the intermediate imino ether with triethylamine in methanol gave ester-substituted pyrrolothiazines **VIIa-d** in 86-66% yield. Next, this same reaction sequence was explored using ethyl triethoxyacetate as the *ortho* ester. In this case, treatment of the intermediate imino ether derived from pyrrole **VIb** with triethylamine failed to result in cyclization to pyrrolothiazine **VIIIb**; however, the use of potassium *t*-butoxide in hot acetonitrile was found to give the cyclized product in 60% yield. Interestingly, this requirement for a stronger base to promote cyclization to the bis-ester pyrrolothiazine is in contrast to that observed for the analogous cyano-substituted

Scheme 1



(a) Methanol, Δ; (b) 1. $(MeO)_3CH$, Δ 2. Triethylamine, methanol, Δ; (c) 1. $(EtO)_3CCO_2Et$, Δ 2. $KOC(CH_3)_3$, acetonitrile, Δ; (d) $KOC(CH_3)_3$, acetonitrile, Δ, (e) $NaNO_2$, acetic acid.

Scheme 2



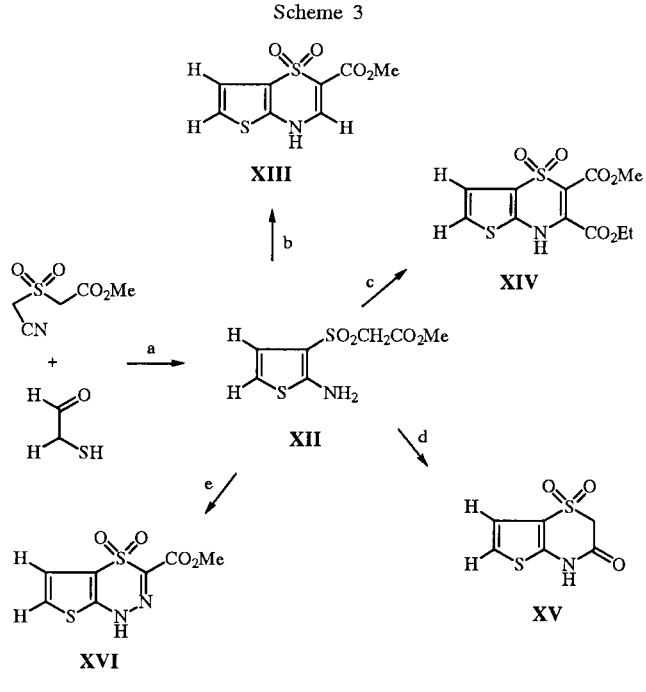
R: **a** -$CH_2CH_2C_6H_4$-*p*-Cl **b** -$CH_2C_6H_5$

a) 1. $(EtO)_3CCO_2Et$, Δ 2. Triethylamine, ethanol, Δ.

pyrrolothiazines **XIa-b** (Scheme 2), which were prepared using triethylamine. Continuing in Scheme 1, treatment of pyrroles **VIa-d** with potassium *t*-butoxide in refluxing methanol for 2 hours resulted in intramolecular cyclization to pyrrolothiazin-3(2*H*)-ones **IXa-d** in yields ranging from 89-43%. Finally, treatment of pyrrole **VIa** in acetic acid with sodium nitrite gave ester-substituted pyrrolothiadiazine **Xa** in 42% yield.

As shown in Scheme 3, title aminothiophene **XII** was prepared by reaction of sulfone **V** with 2-mercaptoacetaldehyde [8] in methanol using triethylamine as base (63% yield following chromatography). Subsequent cyclization of this compound under conditions identical to that described for pyrroles **VIa-d** gave the corresponding thienothiazines and thienothiadiazine. Thus, reaction of **XII** with trimethyl orthoformate or ethyl triethoxyacetate gave thienothiazines **XIII** (96% yield) and **XIV** (45% yield), respectively, while reaction with potassium *t*-butoxide or sodium nitrite/acetic acid gave thienothiazin-3(2*H*)-

Scheme 3



(a) Triethylamine, methanol; (b) 1. $(MeO)_3CH$, Δ 2. Triethylamine, methanol, Δ; (c) 1. $(EtO)_3CCO_2Et$, Δ 2. $KOC(CH_3)_3$, acetonitrile, Δ; (d) $KOC(CH_3)_3$, methanol, Δ, (e) $NaNO_2$, acetic acid.

one **XV** (66% yield) and thienothiadiazine **XVI** (72% yield), respectively.

In contrast to the success found with the preparation of the title pyrroles and thiophene, attempted synthesis of the analogous 4,5-dimethylfuran by reaction of sulfone **V** with acetoin using either triethylamine or 4-dimethylaminopyridine as base proceeded quite sluggishly and resulted in a complex mixture of products and starting material after prolonged heating. Interestingly, this result is also in contrast to that previously found with sulfonyldiacetonitrile, which readily and selectively condenses with acetoin using 4-dimethylaminopyridine as catalyst to give furan **II** [2].

Finally, with the ester-substituted bicyclic derivatives within the pyrrole and thiophene series in hand, we explored the hydrolysis of these compounds to the corresponding carboxylic acids [9]. Unfortunately, as with the cyano-substituted derivatives, attempted hydrolysis under a variety of acidic (hydrochloric or sulfuric acid) or basic (sodium hydroxide) conditions resulted in only recovery of starting material or decomposition depending on the concentration/temperature employed. We have previously observed that certain thienothiazines are susceptible to nucleophilic addition at the 3-position by hydrazine [3], and this type of chemistry may indeed account for the decomposition of the thiazines prepared here. It thus appears that an ester group which can be cleaved under mild and non-hydrolytic conditions, *i.e.*, benzyl, *tert*-butyl, or allyl ester [10], is required as precursor to the carboxylic acids. Based on the success found here in preparing the methyl esters, such alternative ester derivatives should be available using the appropriate ester of (cyanomethylsulfonyl)acetate, and efforts to develop this chemistry, as well as that of the analogous carboxamides, are currently underway in our laboratory.

EXPERIMENTAL

General analytical details are as previously described [2,3]. Infrared spectra were obtained using the potassium bromide technique unless otherwise indicated. Proton nmr spectra were recorded at 300 MHz unless otherwise indicated. Reaction temperatures given are indicative of the oil bath. Column chromatography was conducted on Fisher Selecto 60 (230-400 mesh) silica gel. (Cyanomethylthio)acetic acid was synthesized as described in the literature [7] with exception that the final extraction following acidification was performed using ether:THF (9:1) due to difficulty in completely removing ethyl acetate. Ethyl triethoxyacetate was synthesized as a 66% mixture with diethyl oxalate following simple distillation and used as such [11].

Methyl (Cyanomethylsulfonyl)acetate (**V**).

To a solution of (cyanomethylthio)acetic acid (3.93 g, 0.03 mole) in methanol (60 ml) was added *p*-toluenesulfonic acid (0.29 g) and the mixture was stirred at room temperature for 22 hours. The solvent was removed *in vacuo* and the remaining oil was diluted with saturated sodium bicarbonate solution and extracted with ether. The organic layer was washed with brine, dried (magnesium sulfate), and concentrated to give the sulfide ester as a pale yellow thin oil (3.55 g, 82%) which exhibited nmr data identical to that previously reported [12].

A solution of the sulfide ester (3.55 g, 0.0245 mole) in methanol (5 ml) was stirred in an ice/water bath as a solution of *m*-chloroperbenzoic acid (Aldrich, 57-86%) (14.06 g) in tetrahydrofuran (50-55 ml) was added dropwise over 15 minutes. The ice bath was then removed and the mixture was stirred at ambient temperature, recooling if necessary to control the mild exotherm. After 22 hours, approximately one-half of the solvent was removed *in vacuo* and the mixture was diluted with saturated sodium bicarbonate solution (50 ml) and extracted twice with ethyl acetate (50 ml each). The organic layer was washed with saturated sodium bicarbonate solution, brine, and dried (magnesium sulfate). Following concentration *in vacuo,* the sulfone ester was obtained as a pale yellow oil (3.50 g, 81%) which was used without further purification; tlc R_f, hexanes:ethyl acetate (3:2), 0.48 (single spot by iodine); ir: ν 2250 (CN), 1715 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.82 (s, 3H, OMe), 4.27 (s, 2H, $-CH_2$), 4.40 (s, 2H, $-CH_2$); ms: (ei) m/z 177 (M^+), 146, 137.

The procedure given for **VIa** was utilized in the preparation of **VIb-d**.

2-Amino-3-(methoxycarbonyl)methylsulfonyl-4,5-dimethyl-1-(2-phenylethyl)pyrrole (**VIa**).

A mixture of acetoin (0.68 g, 7.7 mmoles) and phenethylamine (0.93 g, 7.7 mmoles) in toluene (10 ml) was refluxed under a Dean-Stark trap until the evolution of water ceased (10-20 minutes). After removal of the toluene *in vacuo,* methyl (cyanomethylsulfonyl)acetate (**V**) (1.24 g, 7.0 mmoles) and methanol (10 ml) were added and the mixture was heated at gentle reflux (70-75°) for 1.25 hours. The methanol was then removed and the residue was diluted with ethyl acetate and washed with hydrochloric acid (1*N*), brine, and dried (magnesium sulfate). Following concentration, the dark oil was diluted with methanol (8 ml) and stored in the freezer to give a yellow/tan solid (1.72 g, 70%). Recrystallization from methanol:water gave a tan crystalline solid, mp 94-95°; tlc R_f, hexanes:ethyl acetate (1:1), 0.52; ir: ν 3470 and 3375 (NH_2), 1740 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95 and 2.05 (2s, 6H, $-CH_3$ at C_4 and C_5), 2.88 (t, 2H, $-CH_2Ph$), 3.71 (s, 3H, OMe), 3.84 (t, 2H, N-CH_2), 3.95 (s, 2H, SO_2CH_2), 3.99 (br s, 2H, NH_2) 7.04 (d, 2H, ArH), 7.26-7.31 (m, 3H, ArH).

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.26; H, 6.33; N, 8.00; S, 9.15. Found: C, 58.42; H, 6.35; N, 8.07; S, 9.09.

2-Amino-1-benzyl-3-(methoxycarbonyl)methylsulfonyl-4,5-dimethylpyrrole (**VIb**).

Following workup, this compound was isolated by column chromatography eluting with hexanes:ethyl acetate (3:2 to 1:1) to give an amber colored viscous oil (1.79 g, 76%); tlc R_f, hexanes:ethyl acetate (3:2), 0.38; ir (neat firm): ν 3455 and 3360 (NH_2), 1730 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.01 and 2.02 (2s, 6H, $-CH_3$ at C-4 and C-5), 3.67 (s, 3H, OMe), 4.03 (s, 2H, SO_2-CH_2), 4.43 (br s, 2H, NH_2), 4.89 (s, 2H, N-CH_2), 7.02 (d, 2H, ArH), 7.27-7.36 (m, 3H, ArH).

Anal. Calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.12; H, 5.99; N, 8.33; S, 9.53. Found:C, 57.34; H, 5.89; N, 8.10; S, 9.77.

2-Amino-3-(methoxycarbonyl)methylsulfonyl-4,5-dimethyl-1-(3-pyridylmethyl)pyrrole (**VIc**).

Following workup, this compound was isolated by concentrating the ethyl acetate solution *in vacuo* to <10 ml and chilling to give a

tan crystalline solid (1.17 g, 61%), mp 172-173° dec; tlc R_f, ethyl acetate, 0.27; ir: ν 3440 and 3320 (NH_2), 1735 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.88 and 1.96 (2s, 6H, -CH_3 at C-4 and C-5), 3.59 (s, 3H, OMe), 4.15 (s, 2H, SO_2-CH_2), 5.07 (s, 2H, N-CH_2), 5.71 (s, 2H, NH_2), 7.36-7.38 (m, 2H, ArH), 8.30 (s, 1H, ArH), 8.47 (t,1H, ArH).

Anal. Calcd. for $C_{15}H_{19}N_3O_4S$: C, 53.40; H, 5.68; N, 12.45; S, 9.50. Found: C, 53.42; H, 5.74; N, 12.36; S, 9.59.

2-Amino-3-(methoxycarbonyl)methylsulfonyl-1-(2-methoxyethyl)-4,5-dimethylpyrrole (**VId**).

This compound was prepared using cyclohexane in place of toluene. Following workup, the dark oil was purified by column chromatography eluting with hexanes:ethyl acetate (1:1 to 1 :2) to give an amber colored oil (0.62 g, 41%); tlc R_f, hexanes:ethyl acetate (1:1), 0.40; ir (neat film): ν 3420 and 3330 (NH_2), 1730 (CO) cm^{-1}; ^1H nmr: δ 1.99 and 2.05 (2s, 6H, -CH_3 at C-4 and C-5), 3.31 (s, 3H, OMe), 3.53 (t, 2H, O-CH_2), 3.70 (s, 3H, OMe), 3.80 (t, 2H, N-CH_2), 3.98 (s, 2H, SO_2-CH_2), 5.02 (br s, 2H, NH_2).

Anal. Calcd. for $C_{12}H_{20}N_2O_5S$: C, 47.35; H, 6.62; N, 9.21; S, 10.53. Found: C, 47.40; H, 6.61; N, 9.11; S, 10.55.

The procedure given for **VIIa** was utilized in the preparation of **VIIb-d**.

4,5-Dihydro-2-methoxycarbonyl-6,7-dimethyl-5-(2-phenylethyl)-pyrrolo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIa**).

A mixture of pyrrole **VIa** (0.46 g, 1.31 mmoles) and trimethyl orthoformate (1.0 g) was heated at 100-110° until tlc analysis (hexanes:ethyl acetate, 3:2) showed complete conversion to a more lipophilic product (30-60 minutes). After cooling, triethylamine (0.26 g, 2.6 mmoles) in methanol (3 ml) was added and heating was continued at 80-90° for 1.5 hours. The methanol was removed *in vacuo,* and the dark oil was dissolved in a small amount of aqueous sodium hydroxide (1*N*) and extracted with ethyl acetate. The aqueous solution was acidified with concentrated hydrochloric acid/ice to give a tan solid which was collected, rinsed with water, and air dried (0.36 g, 76%). Recrystalization from methanol gave tan crystals, mp 261-263° dec; ir: ν 3265 (NH), 1670 (CO) cm^{-1}; ^1H nmr (400 MHz, dimethyl-d_6 sulfoxide): δ 1.97 and 2.07 (2s, 6H, -CH_3 at C-6 and C-7), 2.85 (t, 2H, -CH_2-Ar), 3.75 (s, 3H, OMe), 4.13 (t, 2H, N-CH_2), 7.18-7.30 (m, 5H, ArH), 7.69 (s, 1H, 3-H), 11.82 (br s, 1H, NH).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$: C, 59,98; H, 5.59; N, 7.77; S, 8.90. Found: C, 60.08; H, 5.63; N, 7.76; S, 8.96.

5-Benzyl-4,5-dihydro-2-methoxycarbonyl-6,7-dimethylpyrrolo-[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIb**).

This compound was obtained as a tan solid (0.30 g, 66%). Recrystallization from methanol gave fluffy tan needles, mp 292-295° dec; ir: ν 3200 (NH), 1695 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.00 and 2.11 (2s, 6H, -CH_3 at C-6 and C-7), 3.74 (s, 3H, OMe), 5.25 (s, 2H, N-CH_2), 6.96 (d, 2H, ArH), 7.28-7.38 (m, 3H, ArH), 7.73 (s, 1H, 3-H).

Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; S, 9.26. Found: C, 58.87; H, 5.33; N, 8.02; S, 9.37.

4,5-Dihydro-2-methoxycarbonyl-6,7-dimethyl-5-(3-pyridyl-methyl)pyrrolo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIc**).

This compound was prepared with a reaction time with trimethyl orthoformate of 2.5 hours due to initial insolubility. Acidification with acetic acid gave a tan solid (0.33 g, 86%). Recrystallization from methanol gave tan crystals, mp 232-233° dec; ir: ν 3220 (NH), 1690 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.03 and 2.12 (2s, 6H, -CH_3 at C-6 and C-7), 3.75 (s, 3H, OMe), 5.31 (s, 2H, N-CH_2), 7.29 (d, 1H, ArH), 7.38 (t, 1H, ArH), 7.75 (s, 1H, 3-H), 8.31 (s, 1H, ArH), 8.50 (d, 1H, ArH), 11.97 (br s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3O_4S$: C, 55.32; H, 4.93; N, 12.10; S, 9.23. Found: C, 55.21; H, 5.01; N, 11.99; S, 9.31.

4,5-Dihydro-2-methoxycarbonyl-5-(2-methoxyethyl)-6,7-dimethylpyrrolo[3,2-b][1,4]thiazine 1,1-Dioxide (**VIId**).

This compound was obtained as a tan solid (0.47 g, 75%). Recrystallization from a small amount of methanol gave grey/tan scales, mp 240-241°; ir: ν 3290 and 3215 (NH), 1690 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.08 and 2.13 (2s, 6H, -CH_3 at C-6 and C-7), 3.22 (s, 3H, OMe), 3.50 (t, 2H, O-CH_2), 3.74 (s, 3H, OMe), 4.09 (t, 2H, N-CH_2), 7.71 (s, 1H, 3H), 11.71 (br s, 1H, NH).

Anal. Calcd. for $C_{13}H_{18}N_2O_5S$: C, 49.67; H, 5.77; N, 8.91; S, 10.20. Found: C, 49.78; H, 5.85; N, 8.86; S, 10.11.

5-Benzyl-3-ethoxycarbonyl-4,5-dihydro-2-methoxycarbonyl-6,7-dimethylpyrrolo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**VIIIb**).

A mixture of pyrrole **VIb** (0.60 g, 1.78 mmoles) and ethyl triethoxyacetate (66%) (0.82 g, 1.4 equivalents) was heated at 90-100° until tlc analysis (hexanes:ethyl acetate, 3:2) showed complete conversion to a more lipophilic product (1 hour). Following removal of the produced ethanol *in vacuo,* the dark oil was dissolved in dry acetonitrile (3 ml), treated with potassium *t*-butoxide (0.22 g, 1.96 mmoles), and heated again at 90° for 1.25 hours. The mixture was then diluted with water and extracted with ethyl acetate. The aqueous layer was acidified with concentrated hydrochloric acid/ice to give an oil which quickly solidified with stiring to a tan solid (0.45 g, 60%). Recrystallization from ethanol (with partial concentration after filtering) gave golden brown crystals, mp 222-223°; ir: ν 3240 (NH), 1725 (CO), 1705 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.27 (t, 3H, -CH_3), 1.99 and 2.12 (2s, 6H, -CH_3 at C-6 and C-7), 3.74 (s, 3H, OMe), 4.28 (q, 2H, O-CH_2), 5.31 (s, 2H, N-CH_2), 6.93 (d, 2H, ArH), 7.297.40 (m, 3H, ArH), 12.25 (br s, 1H, NH).

Anal. Calcd. for $C_{20}H_{22}N_2O_6S$: C, 57.40; H, 5.30; N, 6.70; S, 7.66. Found: C, 57.33; H, 5.35; N, 6.63; S, 7.55.

The procedure given for **IXa** was utilized in the preparation of **IXb-d**.

4,5-Dihydro-6,7-dimethyl-5-(2-phenylethyl)pyrrolo[3,2-*b*][1,4]-thiazin-3(2*H*)-one 1,1-Dioxide (**IXa**).

To a solution of pyrrole **VIa** (0.50 g, 1.43 mmoles) in methanol (10 ml) was added potassium *t*-butoxide (0.19 g, 1.72 mmoles) and the mixture was heated at 75-80° for 2 hours. Following concentration *in vacuo,* the residue was dissolved in a small amount of water and extracted with ethyl acetate. The aqueous layer was then acidified with concentrated hydrochloric acid/ice to give a tan solid which was collected, rinsed with water, and air dried (0.35 g, 77%). Recrystallization from methanol gave tan scale-like crystals, mp 206-207°; ir: ν 3220 and 3120 (NH), 1665 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.07 and 2.20 (2s, 6H, -CH_3 at C-6 and C-7), 2.87 (t, 2H, -CH_2Ph), 3.91 (s, 2H, SO_2-CH_2), 4.02 (t, 2H, N-CH_2), 6.99 (d, 2H, ArH), 7.20-7.27 (m, 3H, ArH), 9.76 (br s,1H, NH).

Anal. Calcd. for $C_{16}H_{18}N_2O_3S$: C, 60.35; H, 5.70; N, 8.80; S, 10.07. Found: C, 60.24; H, 5.65; N, 8.75; S, 9.96.

5-Benzyl-4,5-dihydro-6,7-dimethylpyrrolo[3,2-*b*][1,4]thiazin-3(2*H*)-one 1,1-Dioxide (**IXb**).

This compound was obtained as a tan solid (0.28 g, 64%). Recrystallization from methanol gave fine golden/brown prisms, mp 240-241°; ir: ν 3230 and 3140 (NH), 1670 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04 and 2.22 (2s, 6H, $-CH_3$ at C-6 and C-7), 4.02 (s, 2H, SO_2-CH_2), 5.02 (s, 2H, $N-CH_2$), 6.92 (d, 2H, ArH), 7.31-7.33 (m, 3H, ArH), 9.39 (s,1H, NH).

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.21; S, 10.53. Found: C, 59.04; H, 5.26; N, 9.10; S, 10.63.

4,5-Dihydro-6,7-dimethyl-5-(3-pyridylmethyl)pyrrolo[3,2-*b*][1,4]-thiazin-3(2*H*)-one 1,1-Dioxide (**IXc**).

Following acidification with acetic acid, this compound was obtained as a tan solid (0.38 g, 89%). Recrystallization from methanol (with partial concentration after filtering) gave a tan crystalline powder, mp 263-264°; ir: ν 3230 and 3110 (NH), 1670 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.95 and 2.09 (2s, 6H, $-CH_3$ at C-6 and C-7), 4.47 (s, 2H, SO_2-CH_2), 5.25 (s, 2H, $N-CH_2$), 7.37 (t, 2H, ArH), 8.34 (s, 1H, ArH), 8.50 (t, 1H, ArH), 11.43 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 54.99; H, 4,97; N, 13.72; S, 10.42.

4,5-Dihydro-5-(2-methoxyethyl)-6,7-dimethylpyrrolo[3,2-*b*][1,4]-thiazin3(2*H*)-one 1,1-Dioxide (**IXd**).

This compound was obtained as a tan/orange solid (0.20 g, 43%). Recrystallization from methanol:water (4:1) gave a burnt orange crystalline solid, mp 167-168°; ir: ν 3230 and 3160 (NH), 1665 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.06 and 2.07 (2s, 6H, $-CH_3$ at C-6 and C-7), 3.23 (s, 3H, OMe), 3.45 (t, 2H, $O-CH_2$), 4.04 (t, 2H, $N-CH_2$), 4.37 (s, 2H, SO_2CH_2), 11.11 (s, 1H, NH).

Anal. Calcd. for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.56; H, 5.99; N, 10.19; S, 11.67.

1,7-Dihydro-3-methoxycarbonyl-5,6-dimethyl-7-(2-phenylethyl)-pyrrolo[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**Xa**).

To a solution of pyrrole **VIa** (0.70 g, 2.0 mmoles) in acetic acid (10 ml) was added dropwise a solution of sodium nitrite (0.15 g, 2.2 mmoles) in water (2 ml) and the mixture was stirred at room temperature for 30 minutes producing a yellow solid. After chilling for 1 hour, the solid was collected, rinsed with water, and air dried (0.30 g, 42%). Recrystallization from methanol:water (*ca.* 9:1) gave fine orange needles, mp 212-213° dec; ir: ν 3245 (NH), 1700 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.02 and 2.10 (2s, 6H, $-CH_3$ at C-5 and C-6), 2.89 (t, 2H, $-CH_2-Ph$), 3.83 (s, 3H, OMe), 4.19 (t, 2H, $N-CH_2$), 7.19-7.31 (m, 5H, ArH), 13.63 (br s, 1H, NH).

Anal. Calcd. for $C_{17}H_{19}N_3O_4S$: C, 56.49; H, 5.30; N, 11.63; S, 8.87. Found: C, 56.57; H, 5.35; N, 11.66; S, 8.91.

5-[2-(4-Chlorophenyl)ethyl]-2-cyano-3-ethoxycarbonyl-4,5-dihydro-6,7-dimethylpyrrolo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**XIa**).

A mixture of 2-amino-1-[2-(4-chlorophenyl)ethyl]-3-cyanomethylsulfonyl-4,5-dimethylpyrrole [5] (0.35 g, 1.0 mmole) and ethyl triethoxyacetate (66%) (1.0 g, 3.0 equivalents) was heated at 100-110° for 1 hour. The dark mixture was cooled, and triethylamine (0.15 g, 1.5 mmoles) in ethanol (2-3 ml) was added and heating was continued at 95° for 1.5 hours. The mixture was then diluted with a small amount of ice/water and acidified with concentrated hydrochloric acid to give a yellow/brown solid (0.40 g, 92%). Recrystallization from a large volume of ethanol (with partial concentration after filtering) gave fine yellow needles, mp 240° dec; ir: ν 3280 (NH), 2200 (CN), 1740 (CO) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.45 (t, 3H, $-CH_3$), 2.14 and 2.16 (2s, 6H, $-CH_3$ at C-6 and C-7), 2.84 (t, 2H, $-CH_2-Ar$), 4.17 (t, 2H, $N-CH_2$), 4.44 (q, 2H, OCH_2), 6.79 (d, 2H, ArH), 7.16 (d, 2H, ArH), 7.88 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{20}ClN_3O_4S$: C, 55.36; H, 4.65; Cl, 8.17; N, 9.68; S, 7.39. Found: C, 55.43; H, 4.68; Cl, 8.24; N, 9.58; S, 7.30.

5-Benzyl-2-cyano-3-ethoxycarbonyl-4,5-dihydro-6,7-dimethyl-pyrrolo[3,2-*b*][1,4]thiazine 1,1-Dioxide (**XIb**).

This compound was prepared from 2-amino-1-benzyl-3-cyanomethylsulfonyl-4,5-dimethylpyrrole [1] according to the above procedure for **XIa** using 1.0 equivalent of triethylamine. An oily solid was obtained following acidification which was isolated by decanting, stirred with a small amount of *ca.* 75% aqueous ethanol, and chilled to give a yellow solid (0.60 g, 52%). Recrystallization from ethanol gave mustard yellow crystals, mp 214°; ir: ν 3310 (NH), 2200 (CN), 1725 (CO) cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.40 (t, 3H, $-CH_3$), 2.20 and 2.23 (2s, 6H, $-CH_3$ at C-6 and C-7), 4.40 (q, 2H, $O-CH_2$), 5.26 (s, 2H, $N-CH_2$), 7.05 (d, 2H, ArH), 7.32-7.38 (m, 3H, ArH), 8.61 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.90; S, 8.32. Found: C, 59.28; H, 5.06; N, 10.88; S, 8.32.

2-Amino-3-[(methoxycarbonyl)methylsulfonyl]thiophene (**XII**).

To a suspension of methyl (cyanomethylsulfonyl)acetate (**V**) (0.62 g, 3.5 mmole) and 1,4-dithiane-2,5-diol (0.28 g, 1.84 mmoles) in methanol (5 ml) was added triethylamine (0.071 g, 0.2 equivalent) and the mixture was stirred at room temperature for 3-4 hours. The resulting solution was then filtered to clarify and concentrated *in vacuo* to near dryness. The solution was diluted with ethyl acetate and washed with hydrochloric acid (1*N*), brine, and dried (magnesium sulfate). Following concentration, the pale orange oil was chromatographed eluting with hexanes:ethyl acetate (3:2 to 1:1) to give, following concentration of the homogenous fractions, a near colorless oil which slowly solidified under high vacuum (0.52 g, 63%), mp 72-73°; ir: ν 3450 and 3350 (NH_2), 1735 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, OMe), 4.06 (s, 2H, SO_2-CH_2), 6.30 and 6.79 (2d, 2H, 4-H and 5-H).

Anal. Calcd. for $C_7H_9NO_4S_2$: C, 35.73; H, 3.86; N, 5.95; S, 27.25. Found: C, 35.80; H, 3.89; N, 5.89; S, 27.33.

2-Methoxycarbonyl-4*H*-thieno[3,2-*b*][1,4]thiazine 1,1-Dioxide (**XIII**).

Prepared from thiophene **XII** (0.48 g) according to the procedure described for **VIIa** using 1.0 g of trimethyl orthoformate to give a cream colored solid (0.48 g, 96%). Recrystallization from methanol gave fine white needles, mp 274-276° dec; ir: ν 3200 (NH), 1695 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.78 (s, 3H, OMe), 7.32 and 7.37 (2d, 2H, 6-H and 7-H), 8.17 (s, 1H, 3-H), 12.40 (brs, 1H, NH).

Anal. Calcd. for $C_8H_7NO_4S_2$: C, 39.17; H, 2.88; N, 5.71; S, 26.14. Found: C, 39.25; H, 2.89; N, 5.64; S, 26.11.

3-Ethoxycarbonyl-2-methoxycarbonyl-4*H*-thieno[3,2-*b*][1,4]-thiazine 1,1-Dioxide (**XIV**).

Prepared from thiophene **XII** (0.82 g, 3.5 mmoles) according to the procedure described for **VIIIb** using 1.46 g (1.25 equivalents)

of ethyl triethoxyacetate (66%). The resulting oil following acidification was extracted into ethyl acetate, washed with brine, and dried (magnesium sulfate). The solution was concentrated *in vacuo* to near dryness and passed over a short silica plug eluting with ethyl acetate (50 ml) to give, following removal of the solvent, a tan solid (0.50 g, 45%). Recrystallization from ethyl acetate gave a golden/brown crystalline solid, mp 160-161°; ir: ν 3215 (NH), 1740 (CO), 1690 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.31 (t, 3H, $-CH_3$), 3.78 (s, 3H, OMe), 4 35 (q, 2H, $O-CH_2$), 7.36 and 7.46 (2d, 2H, 6-H and 7-H), 13.08 (broad s, 1H, NH).

Anal. Calcd. for $C_{11}H_{11}NO_6S_2$: C, 41.63; H, 3.49; N, 4.41; S, 20.21. Found: C, 41.90; H, 3.57; N, 4.31; S, 20.05.

4*H*-Thieno[3,2-*b*][1,4]thiazin-3(2*H*)-one 1,1-Dioxide (**XV**).

This compound was prepared from thiophene **XII** (0.49 g, 2.08 mmoles) according to the procedure described for **IXa** to give a tan/orange solid (0.28 g, 66%). Recrystallization from water followed by drying under vacuum at 75° gave fine tan needles, mp 181-182°; ir: ν 3120 (NH), 1690 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 4.68 (s, 2H, SO_2-CH_2), 7.22 and 7.27 (2d, 2H, 6-H and 7-H), 11.85 (s, 1H, NH).

Anal. Calcd. for $C_6H_5NO_3S_2$: C, 35.46; H, 2.48; N, 6.89; S, 31.55. Found: C, 35.39; H, 2.45; N, 6.83; S, 31.45.

3-Methoxycarbonyl-1*H*-thieno[2,3-*e*][1,3,4]thiadiazine 4,4-Dioxide (**XVI**).

Prepared from thiophene **XII** (0.78 g, 3.32 mmoles) according to the procedure described for **Xa** using 7 ml of acetic acid. The product precipitated during the reaction and was collected after diluting with water (2 ml) and chilling to give a fine orange colored crystalline solid which was rinsed well with water and air dried (0.59 g, 72%). The solid was dissolved in boiling methanol (75 ml) and the solution was filtered, concentrated on a hotplate to *ca.* 30 ml, and then chilled to give fine orange needles, mp 254-255° dec, with darkening >225°; ir: ν 3225 (NH), 1735 (CO) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide): δ 3.86 (s, 3H, OMe), 7.48 and 7.56 (2d, 2H, 5-H and 6-H), 13.90 (br s, 1H, NH).

Anal. Calcd. for $C_7H_6N_2O_4S_2$: C, 34.14; H, 2.46; N, 11.38; S, 26.04. Found: C, 34.26; H, 2.43; N, 11.29; S, 25.92.

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