Preparation and Alkylation of 1,5-Dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxides

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1,5-Dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-dioxides (**3**) are prepared by reaction of isatoic anhydrides with methyl *N*-(chloromethanesulfonyl)carbamimidothioate (**6**). The sodium salt of **3a**, generated with sodium hydride in *N,N*-dimethylformamide, is alkylated excusively on N-10. An improved preparation of **6** is described, utilizing a two-phase sulfonylation.

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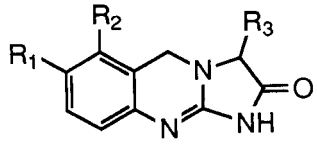
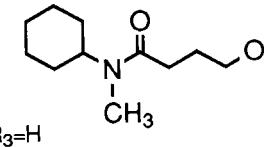
Although the 1,2,4-thiadiazole system is well known [1], there have been few reports on the corresponding 2,2-dioxides [2a-i], and fewer still on fused ring systems containing this heterocycle [3a-b]. We were thus interested in the preparation of a variety of structures, resembling known pharmacologically active agents, which would incorporate the 1,2,4-thiadiazole 2,2-dioxide moiety. Among the compounds selected for analogue preparation were the 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline-2-ones **1**, which are potent cAMP phosphodiesterase inhibitors and potentially useful as cardiotonic or antithrombotic agents. Three examples are anagrelide (**1a**) [4], quazinone (RO 13-6438, **1b**) [5], and RS 82856 (**1c**) [6].

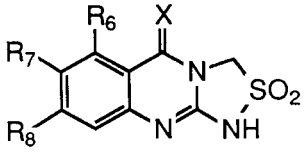


1a: R_1=R_2=Cl, R_3=H
1b: R_1=H, R_2=Cl, R_3=CH_3

1c: R_1=

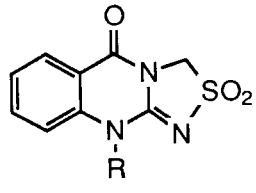


R_2=R_3=H



2: X=H_2

3a-g: X=O



4a-g

We wished to replace the amide carbonyl in these structures with a sulfonyl group, to determine if the resulting novel ring system **2** retained the biological activity of structures **1**. We report here the first examples of this ring system, represented by the corresponding 5-oxo derivatives **3**, and describe the results of alkylation of the sodium salt of **3a**, to provide the 10-alkyl derivatives **4**.

The tricyclic systems **3** are prepared by reacting the corresponding 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride) **5** with methyl *N*-(chloromethanesulfonyl)carbamimidothioate (**6**) [2c,3b] in a polar solvent, in the presence of a base (Scheme 1). The reaction has been carried out in a limited number of solvents (acetonitrile, dioxane, *N*-methylpyrrolidinone) with various bases (4-(dimethylamino)pyridine, 1,5-diazabicyclo[4.3.0]non-5-ene, sodium hydride), and consistently gives low (10-30%) yields of compound **3** as the only identifiable product (Table 1).

The possibility of cyclization in an alternate fashion (path b), giving the isomeric 1,5-dihydro-2*H*-1,2,4-thiadiazolo[3,2-*b*]quinazolin-5-ones **7**, is ruled out by the ready solubility of the products in aqueous sodium hydroxide, consistent with an acidic sulfonamide. The acylation of compound **6** is known to occur on the nitrogen *gamma* to sulfur [2c]; this is also consistent with our assignment of path a to the reaction and structure **3** to the products.

Compounds **3** can be *N*-alkylated *via* their sodium salts, generated by sodium hydride in *N,N*-dimethylformamide. Alkylation occurs exculsively on N-10 in good yield (Table 2). The position of alkylation was verified by a second synthesis of the 10-methyl derivative **4a** *via* the unambiguous route from *N*-methylisatoic anhydride (Scheme 1).

The movement of the double bond from the 10 position in **3** to the 10a position in **4** is also revealed by the infrared spectra: the carbonyl stretching frequency consistently moves *ca.* 20 cm^{-1} to lower wavenumber upon alkylation, more consistent with a perturbation of the π system than with a remote alkylation at N-1.

The compounds **2** exhibited moderate activity against cAMP phosphodiesterase fraction III, with IC_{50}'s ranging from 35 to 150 micromolar.

Scheme 1:

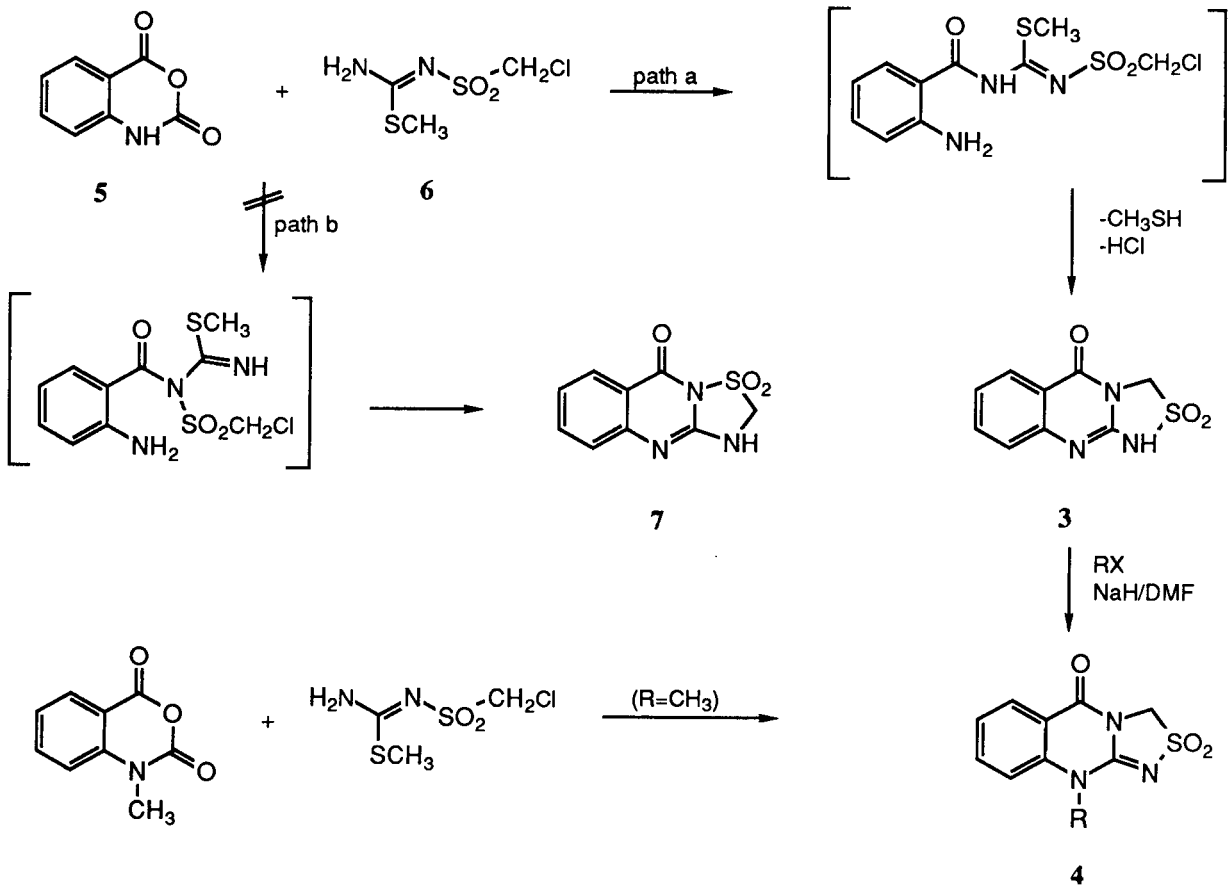


Table 1

Compound	R_6	R_7	R_8	Reaction Solvent [a]	Base [b]	% Yield	mp	Recrystallization Solvent
3a	H	H	H	MeCN	DMAP	29	>330	DMF
3b	H	NO_2	H	MeCN	DMAP	16	>300	DMSO
3c	H	OMe	OMe	dioxane	DBN	7.5	>330	DMSO
3d	OMe	OMe	H	NMP	NaH	21	>300	DMF/H_2O
3e	H	Cl	Cl	NMP	NaH	31	>300	DMF
3f	H	Cl	H	dioxane	DMAP	15	>330	DMF
3g	H	H	Cl	MeCN	DMAP	24	>330	DMF

[a] DMF = *N,N*-dimethylformamide, NMP = *N*-methylpyrrolidinone, DMSO = dimethyl sulfoxide, MeCN = acetonitrile.
[b] DMAP = 4-(dimethylamino)pyridine, DBN = 1,5-diazabicyclo[4.3.0]nonane.

Table 2

Compound	R	Reaction Solvent [a]	% Yield	mp	Recrystallization Solvent
4a	Me	DMF	75	>330	DMF/H_2O
4b	$CH_2C{\equiv}CH$	DMF	88	273-275	DMF/H_2O
4c	CH_2CO_2Et	DMF	78	185-186	CH_2Cl_2/Et_2O
4d	CH_2CO_2H	dioxane [b]	91 [b]	284-286	DMF
4e	$CH_2CH{=}CH_2$	DMF	82	214-216	EtOH
4f	CH_2CH_2Br	NMP	55	275-280	CH_2Cl_2/Et_2O
4g	4-F-$C_6H_4CH_2$	DMF	81	>300	DMF/H_2O

[a] DMF = *N,N*-dimethylformamide, NMP = *N*-methylpyrrolidinone.
[b] For saponification of **4c**.

EXPERIMENTAL

Melting points were determined in capillary tubes, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer spectrometer, and proton nmr spectra were recorded on a Varian EM-390 spectrometer and are referenced to internal tetramethylsilane. Electron impact (20 eV) and chemical ionization (ammonia-methane ionizing gas) mass spectra were obtained on a Finnigan MAT 8230 mass spectrometer. Isatoic anhydrides not commercially available were synthesized from the corresponding anthranilic acids by known methods [7]. Chloromethanesulfonyl chloride was obtained from Alfa or from Fairfield Chemical Co; all other materials were obtained from Aldrich Chemical Co.

Methyl *N*-(Chloromethanesulfonyl)carbamimidothioate (**6**).

The following is an improvement over the published procedure [3b], which in our hands failed to provide useful quantities of **6**. To a stirred slurry of *S*-methylisothiourea sulfate (77.3 g, 0.556 mole), sodium carbonate (273 g, 2.56 mole) and methylene chloride (1100 ml) at 20° was added water (250 ml). The temperature rose to 30°. Chloromethanesulfonyl chloride [8] (85% pure, 94.8 g, 0.542 mole) was added dropwise at such a rate as to maintain gentle reflux (45 minutes). The mixture was stirred at room temperature for 16 hours, and the supernatant liquid was decanted. The remaining solids were washed with methylene chloride (500 ml), and the combined organic solutions were washed with 10% aqueous citric acid, dried (magnesium sulfate), filtered, and concentrated to provide crude **6** as a yellow oil (99.5 g). Chromatography on silica (Merck silica gel 60, 1.2 kg) with 2.5% ether in methylene chloride provided pure **6** as a colorless, foul-smelling solid (71.6 g, 65%), mp 60-62° (lit 58° [2c]).

1,5-Dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**3a**).

To a stirred slurry of isatoic anhydride (3.10 g, 19 mmoles) and **6** (3.85 g, 19 mmoles) in acetonitrile (30 ml) under nitrogen was added 4-(dimethylamino)pyridine (2.32 g, 19 mmoles). The mixture was stirred at reflux for 16 hours, concentrated, and stirred with 0.5 *N* aqueous hydrochloric acid (75 ml). The precipitate was collected by filtration, washed with water and ether, and recrystallized from *N,N*-dimethylformamide to provide **3a** as a white solid (1.32 g, 29%), mp >330°; ir (potassium bromide): 1720, 1660, 1600, 1320, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13 (br s, 1H), 8.0 (d, 1H), 7.4 (dd, 1H), 7.3 (s, 1H), 4.9 (s, 2H).

Anal. Calcd. for $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71. Found: C, 45.92; H, 3.10; N, 18.05.

1,5-Dihydro-7-nitro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**3b**).

To a stirred solution of 5-nitroisatoic anhydride (1.04 g, 5.00 mmoles) and **6** (1.01 g, 6.00 mmoles) in acetonitrile (10 ml) under nitrogen was added 4-(dimethylamino)pyridine (0.61 g, 5.00 mmoles). The mixture was stirred at reflux for 16 hours, cooled, and poured into 10% aqueous citric acid. The precipitate was collected by filtration, washed with water, and recrystallized twice from 2-propanol/*N,N*-dimethylformamide and once from dimethyl sulfoxide to provide **3b** as a pale yellow solid (225 mg, 16%), mp >300°; ir (potassium bromide): 1700, 1650, 1600, 1330, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13 (br s, 1H), 8.6 (s, 1H), 8.5 (d, 1H), 7.5 (d, 1H), 4.9 (s, 2H); ms: m/z 282 (M+), 218, 190 (base), 164, 144, 90.

Anal. Calcd. for $C_9H_6N_4O_5S$: C, 38.30; H, 2.14; N, 19.85. Found: C, 38.66; H, 2.24; N, 19.48.

1,5-Dihydro-7,8-dimethoxy-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**3c**).

To a stirred slurry of 4,5-dimethoxyisatoic anhydride (4.46 g, 20.0 mmoles) and **6** (4.06 g, 20 mmoles) in dioxane (30 ml) under nitrogen was added 1,5-diazabicyclo[4.3.0]non-5-ene (2.5 ml, 20.2 mmoles). The mixture was stirred at reflux for 4 hours, cooled, and poured into 0.3 *N* aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water, and recrystallized from dimethyl sulfoxide to provide **3c** as a pale yellow solid (445 mg, 7.5%), mp >330°; ir (potassium bromide): 1710, 1660, 1580, 1330, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13 (br s, 1H), 7.3 (s, 1H), 6.8 (s, 1H), 4.9 (s, 2H), 3.75 (s, 3H), 3.70 (s, 3H); ms: (ci) m/z 298 (M+1), 234, 138, 121.

Anal. Calcd. for $C_{11}H_{11}N_3O_5S$: C, 44.44; H, 3.73; N, 14.13. Found: C, 44.22; H, 3.67; N, 13.75.

1,5-Dihydro-6,7-dimethoxy-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**3d**).

To a stirred slurry of 5,6-dimethoxyisatoic anhydride (8.93 g, 40.0 mmoles) and **6** (90% purity, not chromatographed, 9.73 g, 44 mmoles) in *N*-methyl-2-pyrrolidinone (50 ml) under nitrogen was added sodium hydride (60 % in oil, 1.65 g, 41 mmoles). The mixture was stirred at 20° for 15 minutes, then at 80° for 16 hours, cooled, and poured into 0.5 *N* aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water and ether, and recrystallized from 5% water in *N,N*-dimethylformamide to provide **3d** as a tan solid (2.55 g, 21%), mp >300°; ir (potassium bromide): 1720, 1650, 1580, 1330, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 12.5 (br s, 1H), 7.5 (d, 1H), 7.0 (d, 1H), 4.8 (s, 2H), 3.75 (s, 3H), 3.65 (s, 3H).

Anal. Calcd. for $C_{11}H_{11}N_3O_5S$: C, 44.44; H, 3.73; N, 14.13. Found: C, 44.70; H, 3.79; N, 13.77.

7,8-Dichloro-1,5-dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one, 2,2-Dioxide (**3e**).

To a stirred slurry of 4,5-dichloroisatoic anhydride (11.54 g, 50.0 mmoles) in *N*-methyl-2-pyrrolidinone (50 ml) under nitrogen was added sodium hydride (60% in oil, 2.05 g , 52 mmoles). The mixture was stirred at 20° for 30 minutes (the anhydride dissolves). To the resulting solution was added **6** (11.0 g, 55 mmoles), and the mixture is stirred at 80° for 18 hours. The mixture was poured into 0.3 *N* aqueous hydrochloric acid, and the precipitate was collected by filtration, washed with water and ether, and recrystallized from *N,N*-dimethylformamide to provide **3e** as a white solid (4.69 g, 31%), mp >300°; ir (potassium bromide): 1710, 1640, 1580, 1320, 1170 cm^{-1}; ^1H nmr (DMSO-d_6): δ 12 (br s, 1H), 8.1 (s, 1H), 7.5 (s, 1H), 4.9 (s, 2H); ms: (ci) m/z 306 (M + 1), 242, 135.

Anal. Calcd. for $C_9H_5Cl_2N_3O_3S$: C, 35.31; H, 1.65; N, 13.73. Found: C, 35.63; H, 1.65; N, 14.17.

7-Chloro-1,5-dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**3f**).

To a stirred slurry of 5-chloroisatoic anhydride (5.93 g, 30.0 mmoles) and **6** (6.08 g, 30.0 mmoles) in dioxane (50 ml) under nitrogen was added 4-(dimethylamino)pyridine (3.67 g, 30.0 mmoles). The mixture was stirred at reflux for 24 hours, cooled, and poured into 0.5 *N* aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water and ether, and recrystallized from *N,N*-dimethylformamide to provide **3f** as a white solid (1.24 g, 15%), mp >330°; ir (potassium bromide): 1700, 1640, 1580, 1300, 1140 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13 (br s, 1H), 7.9 (s, 1H), 7.8 (dd, 1H), 7.3 (d, 1H), 4.9 (s, 2H); ms (ci) m/z 272 (M + 1).

Anal. Calcd. for $C_9H_6ClN_3O_3S$: C, 39.79; H, 2.23; N, 15.47. Found: C, 39.45; H, 2.14; N, 15.69.

8-Chloro-1,5-dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2 Dioxide (**3g**).

To a stirred slurry of 4-chloroisatoic anhydride (4.95 g, 25.0 mmoles) and **6** (5.07 g, 25.0 mmoles) in acetonitrile (25 ml) under nitrogen was added 4-(dimethylamino)pyridine (3.97 g, 33.0 mmoles). The mixture was stirred at reflux for 24 hours, cooled, and poured into 0.5 *N* aqueous hydrochloric acid. The precipitate was collected by filtration, washed with water and ether, and triturated with hot ethanol, then recrystallized from *N,N*-dimethylformamide to provide **3g** as a white solid (1.65 g, 24%), mp >300°; ir (potassium bromide): 1730, 1640, 1580, 1330, 1170 cm^{-1}; ^1H nmr (DMSO-d_6): δ 13 (br s, 1H), 8.0 (d, 1H), 7.4 (dd, 1H), 7.3 (s, 1H), 4.9 (s, 2H); ms: (ci) m/z 272 (M + 1).

Anal. Calcd. for $C_9H_6ClN_3O_3S$: C, 39.79; H, 2.23; N, 15.47. Found: C, 39.78; H, 2.15; N, 15.29.

5,10-Dihydro-10-methyl-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**4a**).

A. To a stirred slurry of *N*-methylisatoic anhydride (2.35 g, 13.3 mmoles) and **6** (2.69 g, 13.3 mmoles) in acetonitrile (25 ml) under nitrogen was added 4-(dimethylamino)pyridine (1.62 g, 13.3 mmoles). The mixture was stirred at reflux for 16 hours, cooled, and the precipitate was collected by filtration, washed with water and ethanol, and dried to provide **4a** as a tan solid (1.06 g, 32%), mp >330°; ir (potassium bromide): 1700, 1620, 1570, 1320, 1160 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 7.5-8.4 (m, 4H), 5.3 (s, 2H), 3.9 (s, 3H); ms: m/z 251 (M+), 222, 159, 104, 77 (base).

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.80; H, 3.61; N, 16.72. Found: C, 48.00; H, 3.49; N, 16.91.

B. A small sample of **4a**, prepared in 75% yield by alkylation of **3a** with methyl iodide and sodium hydride in *N,N*-dimethylformamide (*vide infra*), was identical by ir, nmr, tlc and reverse-phase hplc to material prepared as above.

5,10-Dihydro-10-(3-propynyl)-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**4b**).

To a stirred slurry of **3a** (3.00 g, 12.6 mmoles) in *N,N*-dimethylformamide (25 ml) under nitrogen was added sodium hydride (60% in oil, 0.53 g, 13.2 mmoles). The mixture was stirred at 40° for 30 minutes, propargyl bromide (80% in toluene, 2.06 g, 13.9 mmoles) was added, and the mixture was stirred 24 hours at 40°. The mixture was cooled and poured into water. The precipitate was collected by filtration, washed with water and methanol, and recrystallized from water/*N,N*-dimethylformamide to provide **4b** as a white solid (3.06 g, 88%), mp 273-275°; ir (potassium bromide): 3290, 2140, 1690, 1600, 1580, 1320, 1150 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.4-8.2 (m, 4H), 5.1 (s, 2H), 5.0 (d, 2H, J = 1.5 Hz), 3.5 (t, 1H, J = 1.5 Hz); ms: (ci) m/z 276 (M + 1), 135.

Anal. Calcd. for $C_{12}H_9N_3O_3S$: C, 52.36; H, 3.30; N, 15.26. Found: C, 52.42; H, 3.26; N, 15.28.

5,10-Dihydro-5-oxo-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazoline-10-acetic Acid 2,2-Dioxide Ethyl Ester (**4c**).

To a stirred slurry of **3a** (2.50 g, 10.5 mmoles) in *N,N*-dimethylformamide (20 ml) under nitrogen was added sodium hydride (60% in oil, 0.46 g, 11.6 mmoles). The mixture was stirred at 40° for 30 minutes, ethyl bromoacetate (1.75 ml, 15.7 mmoles) was added, and the mixture was stirred 24 hours at 90°. The mixture was cooled and poured into 10% aqueous citric acid. The precipitate was collected by filtration, washed with water and ether, and dissolved in methylene chloride. The resulting solution was eluted through silica (Merck silica gel 60, 50 g) with 5% ether in methylene chloride, and the eluate was evaporated. Trituration of the residue with hexane provides **4c** as a white solid (2.65 g, 78%), mp 185-186°; ir (potassium bromide): 1740, 1710, 1620, 1580, 1330, 1160 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.1-8.3 (m, 4H), 5.1 (two s, 4H), 4.4 (q, 2H), 1.4 (t, 3H); ms: (ci) m/z 324 (M + 1).

Anal. Calcd. for $C_{13}H_{13}N_3O_5S$: C, 48.29; H, 4.05; N, 13.00. Found: C, 48.22; H, 3.99; N, 12.95.

5,10-Dihydro-5-oxo-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazoline-10-acetic Acid 2,2-Dioxide (**4d**).

To a slurry of **4c** (2.5 g, 8.03 mmoles) in dioxane (10 ml) under nitrogen was added 1.0 *M* aqueous sodium hydroxide (10 ml). After 30 minutes, a clear solution resulted, which was acidified with hydrochloric acid and partially evaporated. The resulting precipitate was collected by filtration, washed with water, and triturated with with hot methylene chloride to provide **4d** as a colorless solid (2.08 g, 91%), mp 284-286 after recrystallization from *N,N*-dimethylformamide; ir (potassium bromide): 3440, 1750, 1690, 1600, 1580, 1330, 1140 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.0 (br s, 1H), 7.4-8.2 (m, 4H), 5.2 (s, 2H), 4.9 (s, 2H).

5,10-Dihydro-10-(3-propenyl)-3*H*-1,2,4-thiadiazolo[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**4e**).

To a stirred slurry of **3a** (2.50 g, 10.5 mmoles) in *N,N*-dimethylformamide (30 ml) under nitrogen was added sodium hydride (60% in oil, 0.46 g, 11.5 mmoles). The mixture was stirred at 40° for 30 minutes, 3-bromopropene (1.91 g, 15.8 mmoles) was added, and the mixture was stirred 24 hours at 70°. The mixture was cooled and poured into 1 *M* aqueous hydrochloric acid (100 ml). The precipitate was collected by filtration, washed with water and ether, and recrystallized from ethanol to provide **4e** as a white solid (2.40 g, 82%), mp 214-216°; ir (potassium bromide): 1690, 1610, 1600, 1580, 1330, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.4-8.2 (m, 4H), 6.0 (m, 1H), 5.2 (m, 2H), 5.0 (s, 2H), 4.8 (m, 2H).

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 4.00; N, 15.15. Found: C, 52.07; H, 4.10; N, 15.55.

10-(2-Bromoethyl)-5,10-dihydro-3*H*-1,2,4-thiadiazolo[3,4-*b*]-quinazolin-5-one 2,2-Dioxide (**4f**).

To a stirred slurry of **3a** (2.37 g, 10.0 mmoles) in *N*-methyl-2-pyrrolidinone (15 ml) under nitrogen was added sodium hydride (60% in oil, 0.42 g, 10.5 mmoles). The mixture was stirred at 40° for 30 minutes and the resulting solution was added dropwise over 30 minutes to a solution of 1,2-dibromoethane (8.6 ml, 100 mmoles) in *N*-methyl-2-pyrrolidinone (10 ml), and the mixture was stirred 24 hours at 70°. The mixture was cooled and poured into 1 *M* aqueous hydrochloric acid (100 ml). The resulting suspension was stirred with 50 ml of ether, and the precipitate was collected by filtration and chromatographed on silica with 3% ether in methylene chloride to provide **4f** as a white solid (1.88 g, 55%), mp 275-280° dec; ir (potassium bromide): 1720, 1620, 1600, 1580, 1320, 1150 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.4-8.2 (m, 4H), 5.0 (s, 2H), 4.8 (t, 2H), 3.7 (t, 2H); ms: (ci) m/z 344 (M + 1), 266, 138, 121.

Anal. Calcd. for $C_{12}H_{10}BrN_3O_3S$: C, 38.39; H, 2.93; N, 12.21. Found: C, 38.64; H, 2.94; N, 11.89.

10-[(4-Fluorophenyl)methyl]-5,10-dihydro-3*H*-1,2,4-thiadiazolo-[3,4-*b*]quinazolin-5-one 2,2-Dioxide (**4g**).

To a stirred slurry of **3a** (2.00 g, 8.43 mmoles) in *N,N*-dimethylformamide (15 ml) under nitrogen was added sodium hydride (60% in oil, 370 mg, 9.25 mmoles). The mixture was stirred at 40° for 30 minutes, 4-fluorobenzyl chloride (1.50 ml, 12.5 mmoles) was added, and the mixture was stirred 16 hours at 90°. The mixture was cooled and poured into 1 *M* aqueous hydrochloric acid (150 ml). The precipitate was collected by filtration, washed with water and ether, and recrystallized from *N,N*-dimethylformamide/water to provide **4g** as a white solid (2.35 g, 81%), mp > 300°; ir (potassium bromide): 1690, 1610, 1600, 1580, 1330, 1160 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.2-8.3 (m, 8H), 5.5 (s, 2H), 5.1 (s, 2H); ms: (ci) m/z 346 (M + 1).

Anal. Calcd. for $C_{16}H_{12}FN_3O_3S$: C, 55.65; H, 3.50; N, 12.17. Found: C, 55.40; H, 3.54; N, 12.05.

REFERENCES AND NOTES

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[8] The purity of chloromethanesulfonyl chloride is most easily determined by nmr integration, using toluene as an internal standard. The 15-20% impurity (present in several commercial samples) is largely dichloromethanesulfonyl chloride (δ 6.6 in deuteriochloroform).