The Synthesis of the 1,2,4-Thiadiazine-1,1-dioxides[1]

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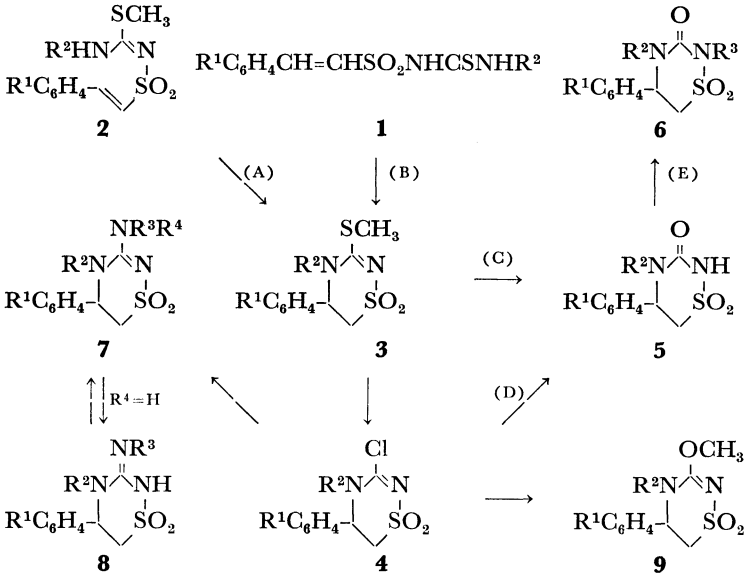
N-(2-Phenylethene-1-sulfonyl)-*N'*-monoalkyl *S*-methylisothioureas, **2**, were ring-closed to yield Michael cycloadducts, 3-methylthio-4-alkyl-5-phenyl-1,1-dioxo-5,6-dihydro-1,2,4-thiadiazines, **3**. Bulky *N'*-alkyl groups hindered the cycloaddition. The base-catalyzed hydrolysis of **3** and 3-chloro-derivatives **4** gave 4-methyl-5-phenyl-2,3,5,6-tetrahydro-1,1,3-trioxo-1,2,4-thiadiazines, **5**, which in turn underwent *N*-alkylation to give **6**. The reaction of **4** with amines or with sodium methoxide yielded 3-amino-, **7**, or 3-methoxy-thiadiazine derivatives, **9**.

Recently we have reported[2,3] the synthesis of a new heterocyclic system, 5,6-dihydro-1,4,2-dithiazine-1,1-dioxide, by the intramolecular Michael cycloaddition of *N*-(2-phenylethene-1-sulfonyl)-*N'*-alkylthioureas, dithiocarbamates, and *O*-alkyl thiocarbamates. This paper will describe a new route to the little-known 1,2,4-thiadiazine-1,1-dioxide derivatives,[4] starting from the substituted isothioureas. The process is outlined below.



Results and Discussion

The reaction of *N*-(2-phenylethene-1-sulfonyl)-*N'*-monoalkylthioureas (**1**) with dimethyl sulfate in DMF afforded *N*-(2-phenylethene-1-sulfonyl)-*N'*-alkyl *S*-methylisothioureas (**2**) (Table 1). They were ring-closed in ethanol containing catalytic amounts of sodium hydroxide to yield intramolecular cycloadducts, 3-methylthio-4-alkyl-5-phenyl-1,1-dioxo-1,2,4-thiadiazines (**3**) (Table 2, Method (A)). The IR spectrum of **3a** displayed a strong band at 1530 cm^{-1} due to the N=C bond, but no absorption due to the NH bond was observed. In the NMR pattern of **3a**, ring protons, $H_AH_CH_B$, showed an ABX pattern consisting of three quartets of H_A centered at δ 3.36, H_C 3.53, and H_B 5.03 (J_{AC}=13.5 Hz, J_{AB}=10.5 Hz, J_{BC}=6.0 Hz) (Fig. 1). The peak at *m/e* 118.066 in the mass spectrum was in complete agreement with the fragment ion, $C_6H_5CN^+CH_3$, derived from only the six-membered heterocycle, **3**. The structures of **3b**—**3h** were inferred because they were analogous with **3a** in their preparations and spectral data.

Cycloaddition is subject to steric hindrance, and it was unsuccessful here when the alkyl group, R^2, in **2** was bulky or branched, like the cyclohexyl, isopropyl, *s*-, and *t*-butyl groups. The amounts of a base required to complete the cycloaddition of **2**'s in 6 hr at 25—30°C were determined. Table 2 shows that only from a sixth to a third equivalent of the base was sufficient to effect the cycloaddition of **2** when R^2 was the methyl group, while more bases were required when R^2 became bulky. The *N'*-dialkylisothiourea could not be ring-closed, presumably because of the lack of a hydrogen atom at the *N'*-position. The reaction of **1** with dimethyl sulfate and sodium hydroxide in ethanol afforded **3** directly (Table 2, Method (B)). The C–N bond in **3** could not be cleaved by a strong base at elevated temperatures, but hydrolytic products, 4-methyl-5-phenyl-2,3,5,6-tetrahydro-1,1,3-trioxo-1,2,4-thiadiazines (**5**) resulted (Table 4, Method (C)). They were identified by

1) Presented in part at the 25th Annual Meeting of the Chemical Society of Japan, Tokyo, October, 1971.

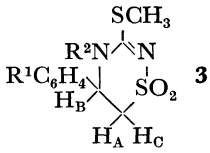
2) K. Hasegawa and S. Hirooka, This Bulletin, **45**, 525 (1972).

3) K. Hasegawa and S. Hirooka, *ibid.*, **45**, 1567 (1972).

4) A. Lawson and R. B. Tinkler, *Chem. Rev.*, **70**, 593 (1970).

Table 1. $R^1C_6H_4CH_B{=}CH_ASO_2N{=}C(NHR^2)(SCH_3)$ **2**

Compd.	R^1	R^2	Yield (%)	Mp (°C)	Found (%)				Calcd (%)			
					C	H	N	S	C	H	N	S
2a	H	CH_3	89	80— 81	49.04	5.33	10.30	23.49	48.89	5.22	10.37	23.68
2b	H	C_2H_5	89	107—108	50.66	5.78	9.63	21.04	50.70	5.67	9.86	22.51
2c	H	*n*-C_3H_7	84	99—100	52.07	5.93	9.41	21.31	52.34	6.08	9.39	21.45
2d	H	*i*-C_3H_7	79	135—136	52.16	5.78	9.48	21.38	52.34	6.08	9.39	21.45
2e	H	*n*-C_4H_9	90	148—149	53.87	6.19	9.07	21.20	53.84	6.45	8.97	20.51
2f	H	*i*-C_4H_9	87	141—142	53.61	5.86	9.07		53.84	6.45	8.97	20.51
2g	H	*s*-C_4H_9	95	112—113	53.47	6.26	9.05	20.37	53.84	6.45	8.97	20.51
2h	H	*t*-C_4H_9	83	139—140	54.02	6.44	9.28	19.92	53.84	6.45	8.97	20.51
2i	H	*n*-C_6H_{13}	67	40— 41	56.37	7.12	8.15		56.46	7.11	8.23	
2j	H		87	152—153	56.36	6.48	8.33	18.65	56.79	6.45	8.28	18.91
2k	*p*-Cl	CH_3	84	168—169	43.30	4.25	9.35	21.35	43.34	4.30	9.19	21.04
2l	*p*-Cl	C_2H_5	91	130—131	45.13	4.67	8.60	20.02	45.21	4.74	8.79	20.11
2m	*p*-Br	CH_3	80	167—168	38.05	3.84	7.95	18.06	37.82	3.75	8.02	18.36
2n	*p*-Br	C_2H_5	81	138—140	39.86	4.44	7.66	17.28	39.67	4.16	7.71	17.65
2o	*p*-CH_3	CH_3	90	152—153	51.00	5.64	10.12	22.50	50.70	5.67	9.86	22.51
2p	*p*-CH_3	C_2H_5	89	103—104	52.07	6.14	9.43	21.39	52.34	6.08	9.39	21.45

Table 2.  **3**

Compd.	R^1	R^2	Moles of base[a] (mol of **2**)	Yield (%) Method (A)	Yield (%) Method (B)	Mp (°C)	Found (%)				Calcd (%)			
							C	H	N	S	C	H	N	S
3a	H	CH_3	1/6	82	69	140—141	48.53	5.58	10.28	23.50	48.89	5.22	10.37	23.68
3b	H	C_2H_5	1/2	82	76	196—197	50.33	5.75	9.79	22.11	50.68	5.67	9.85	22.55
3c	H	*n*-C_3H_7	1.0	83		144—145	52.24	5.98	9.38	21.14	52.34	6.08	9.39	21.45
3d	H	*n*-C_4H_9	2.0	89		93— 95	53.62	6.63	9.20	20.27	53.84	6.45	8.97	20.51
3e	H	*i*-C_4H_9	2.0	81		141—142	53.48	6.36	9.00	20.16	53.84	6.45	8.97	20.51
3f	H	*n*-C_6H_{13}	2.0	71		85— 86	57.14	7.31	8.34		56.46	7.11	8.23	
3g	*p*-Cl	CH_3	1/3	90		210—211	43.29	4.14	9.24	20.75	43.34	4.30	9.19	21.04
3h	*p*-CH_3	CH_3	1/3	78		171—172	50.56	5.75	9.79	22.11	50.68	5.67	9.85	22.55

a) 1 N NaOH solution was used.

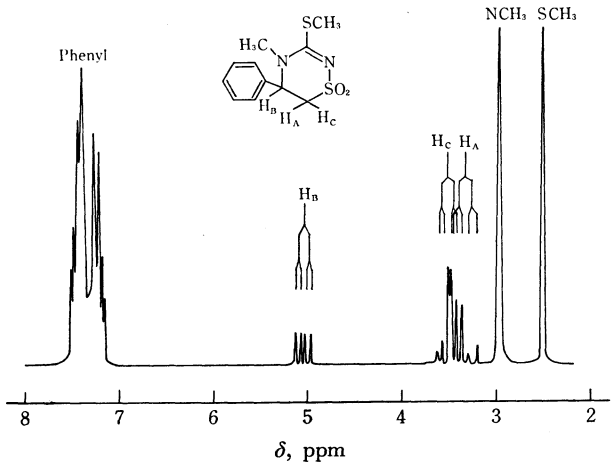
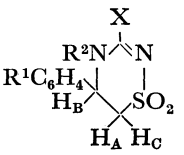
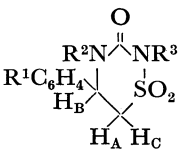


Fig. 1. NMR spectrum of **3a** in $CDCl_3$.

means of the IR (1650 cm^{-1} for C=O, 2960 cm^{-1} for NH), NMR (δ 3.30 for NH) and mass spectra, and also by means of the results of elemental analyses. The methylthio group in **3** was replaced by a chlorine atom to give 3-chloro-derivatives (**4**) (Table 3). The base-catalyzed hydrolysis of **4** gave **5** (Table 4, Method (D)), and **5** was readily methylated to afford 2,4-dimethyl-5-phenyl-2,3,5,6-tetrahydro-1,1,3-trioxo-1,2,4-thiadiazine (**6**) (Table 4, Method (E)). The reaction of **4** with various amines or with sodium methoxide yielded 3-alkylamino- or -hydrazino- (**7**), or 3-methoxy-derivatives (**9**) (Table 3). When the R^4 in **7** is a hydrogen atom, the tautomerism between **7** and **8** can be expected. The possibility that the solid product is an alternative isomer, **8**, was discounted by its insolubility in alkali, thereby demonstrating the absence of the SO_2NH group. The IR

TABLE 3. 

Compd.	R^1	R^2	X	Yield (%)	Mp (°C)	Found (%)				Calcd (%)			
						C	H	N	S	C	H	N	S
4a	H	CH_3	Cl	92	156—157	46.65	4.22	11.06	12.35	46.80	4.25	10.83	12.39
4b	H	C_2H_5	Cl	86	155—156	48.37	4.79	10.46	11.73	48.44	4.80	10.27	11.76
4c	*p*-Cl	CH_3	Cl	81	196—197	40.78	3.38	9.36	10.95	40.97	3.44	9.56	10.94
4d	*p*-CH_3	CH_3	Cl	83	148—149	48.22	4.87	10.00	12.38	48.44	4.80	10.27	11.76
7a	H	CH_3	$NHCH_3$	81	202—203	51.90	5.91	16.40	12.62	52.17	5.97	16.59	12.64
7b	H	CH_3	NHC_2H_5	95	168—169	53.86	6.45	15.79	12.01	53.92	6.41	15.72	11.97
7c	H	CH_3	$N(CH_3)_2$	99	228—229	53.72	6.40	15.66	12.16	53.92	6.41	15.72	11.97
7d	H	CH_3	$N(C_2H_5)_2$	87	170—171	56.93	7.18	14.09	10.98	56.93	7.17	14.23	10.84
7e	H	CH_3	$NHNH_2$	61	212—213	46.98	5.54	21.77	12.26	47.24	5.55	22.04	12.59
7f	H	C_2H_5	NH-⟨H⟩	98	160—161	57.53	7.56	11.92	9.12	57.77	7.70	11.89	9.06
7g	*p*-Cl	CH_3	$NHCH_3$	98	280—282	45.66	4.83	14.33	11.28	45.91	4.90	14.60	11.14
7h	*p*-Cl	CH_3	$NHNH_2$	91	218—220	41.84	4.52	19.26	11.03	41.59	4.54	19.40	11.10
7i	*p*-CH_3	CH_3	$NHCH_3$	87	218—219	54.17	6.51	15.86	12.08	53.92	6.41	15.72	11.97
7j	*p*-CH_3	CH_3	$N(CH_3)_2$	90	196—197	55.78	6.71	15.19	11.63	55.50	6.81	14.94	11.38
9a	H	CH_3	OCH_3	37	155—156	51.96	5.46	10.84	12.51	51.96	5.55	11.02	12.59

TABLE 4. 

Compd.	R^1	R^2	R^3	Yield (%) Method (C) (E)	Yield (%) Method (D)	Mp (°C)	Found (%)				Calcd (%)			
							C	H	N	S	C	H	N	S
5a	H	CH_3	H	82	96	227—229	49.96	5.00	11.78	13.37	50.00	5.04	11.66	13.32
5b	*p*-Cl	CH_3	H	72	78	236—238	43.55	3.95	10.28	11.65	43.72	4.04	10.20	11.67
5c	*p*-CH_3	CH_3	H	77	81	247—249	51.79	5.61	10.81	12.67	51.95	5.55	11.02	12.60
6a	H	CH_3	CH_3	52		123—124	51.68	5.50	11.06	12.63	51.95	5.55	11.02	12.60
6b	*p*-Cl	CH_3	CH_3	58		142—143	45.61	4.36	9.54		45.75	4.54	9.70	

spectra of **7a** and **7b** in KBr tablets displayed absorption peaks in the same region as the N=C group in **7c** and **7d**. However, NMR studies of **7a**, **7g**, and **7i** dissolved in DMSO-d_6 offered evidence for the presence of the **8** isomer in a tautomeric mixture in the solution. In the $NHCH_3$ group in **7a**, methyl protons showed a doublet at δ 2.71 (J=4.0 Hz), and a NH proton, a broad quartet at δ 6.94 (J=4.0 Hz), with a peak area of 0.52H. In addition, there was a sharp singlet at δ 2.70, assignable to the $=NCH_3$ protons in **8** between a doublet methyl signal. However, a sulfonamide NH proton of **8** could not be observed because of overlapping with a signal of water contained in DMSO-d_6 at 3.34. After the treatment with D_2O, the NH proton signal (δ 6.94) was eliminated and only a sharp singlet due to the $=NCH_3$ protons appeared. The relative peak areas of the methyl and NH peaks assignable to the structures of **7** and **8** indicated that **7a** consisted of about a 50 : 50 mixture of **7** and **8** in DMSO-d_6.

Experimental

The melting points were determined on a Yanagimoto micro-melting-point measuring apparatus, MP-S2, and are uncorrected. The IR spectra were recored on a JASCO IRA-1 spectrometer. The NMR spectra were determined with a Varian HA-100 spectrometer, with TMS as the internal standard, and the mass spectra, with a JMS-OlSG spectrometer.

*N-(2-Phenylethene-1-sulfonyl)-N'-methyl S-Methylisothiourea (**2a**).* To a stirred solution of *N*-(2-phenylethene-1-sulfonyl)-*N'*-methylthiourea (1.20 g, 0.0040 mol) in DMF (10 m*l*), we added a 1 N NaOH solution (9.6 m*l*, 0.0096 mol) and dimethyl sulfate (0.61 g, 0.0048 mol), drop by drop, at 0—10°C. After being stirred for 3 hr at room temperature, the reaction mixture was poured into ice water (100 m*l*) and kept overnight. The precipitated white solid was filtered to give 0.96 g (89%) of **2a**. Recrystallization from benzene–petroleum ether gave colorless crystals. IR (KBr): 3330 (NH), 3040 (=CH), 1610 (C=C), 1560 (N=C),

1335, and 1115 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 2.44 (s, 1H, SCH_3), 2.99 (d, J_{NHCH_3}=5.0 Hz, 3H, $NHCH_3$), 6.93 (d, J_{AB}=15.5 Hz, 1H, H_A), 7.54 (d, J_{AB}=15.5 Hz, 1H, H_B), 7.45±0.02 (m, 5H, phenyl), 8.10 (broad, 1H, NH). Mass spectrum *m/e*: 270 (M^+).

*3-Methylthio-4-methyl-5-phenyl-1,1-dioxo-5,6-dihydro-1,2,4-thiadiazine (**3a**).* *Method (A):* To a solution of **2a** (0.54 g, 0.0020 mol) in ethanol (20 ml), we added a 1 N NaOH solution (0.34 ml, 0.00033 mol), after which the mixture was stirred for 6 hr at 25—30°C. An ethanol solution containing white precipitates was concentrated *in vacuo*, water (5 ml) was added, and the precipitates were collected to obtain 0.44 g (82%) of **3a**. Recrystallization from ethanol gave colorless crystals. IR (KBr): 1530 (N=C), 1300, and 1140 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 2.47 (s, 3H, SCH_3), 2.86 (s, 3H, NCH_3), 3.36 (q, J_{AC}=13.5 Hz, J_{AB}=10.5 Hz, 1H, H_A), 3.53 (q, J_{AC}=13.5 Hz, J_{BC}=6.0 Hz, 1H, H_C), 5.03 (q, J_{AB}=10.5 Hz, J_{BC}=6.0 Hz, 1H, H_B), 7.34±0.12 (m, 5H, phenyl). Mass spectrum (75 eV) *m/e* (rel intensity): 77 (17), 78 (13), 91 (10), 104 (100), 105 (10), 118.066 (12), 119 (6), 132 (6), 159 (6), 173 (3), 191 (4), 206 (5), 207 (10), 270.105 (calculated molecular weight, 270.106, 10).

Method (B): Into a solution of *N*-(2-phenylethene-1-sulfonyl)-*N'*-methylthiourea (10.25 g, 0.0400 mol) in a 1 N NaOH solution (80 ml, 0.0800 mol) and ethanol (80 ml), we stirred, drop by drop, dimethyl sulfate (6.40 g, 0.050 mol) at 0—10°C. Stirring was continued for a further 4 hr at room temperature. An ethanol solution containing white precipitates was concentrated *in vacuo*, and the precipitates were collected to afford 7.50 g (69%) of **3a**. The aqueous filtrate was acidified with concentrated hydrochloric acid to give 2.20 g of **5a**.

*3-Chloro-4-methyl-5-phenyl-1,1-dioxo-5,6-dihydro-1,2,4-thiadiazine (**4a**).* Into a solution of **3a** (2.70 g, 0.0100 mol) in chloroform (20 ml) we bubbled excess chlorine at 30—40°C until the colorless solution turned orange. The evaporation of the chloroform left white precipitates, which were recrystallized from methanol to obtain 2.40 g (92%) of colorless crystals. IR (KBr): 1590 and 1575 (N=C), 1330 and 1150 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 3.04 (s, 3H, CH_3), 3.48 (q, J_{AC}=14.0 Hz, J_{AB}=9.5 Hz, 1H, H_A), 3.63 (q, J_{AC}=14.0 Hz, J_{BC}=7.0 Hz, 1H, H_C), 5.18 (q, J_{AB}=9.5 Hz, J_{BC}=7.0 Hz, 1H, H_B), 7.44 (s, 5H, phenyl). Mass spectrum *m/e*: 258.088 (calculated molecular weight, 258.082).

*4-Methyl-5-phenyl-2,3,5,6-tetrahydro-1,1,3-trioxo-1,2,4-thiadiazine (**5a**).* *Method (C)*: To a solution of **3a** (0.54 g, 0.0020 mol) in acetone (10 ml), we added a 1 N NaOH solution (4.0 ml, 0.0040 mol), after which the reaction mixture was refluxed for 2 hr. The acetone was evaporated *in vacuo*, and the solution was acidified with concentrated hydrochloric acid to afford 0.44 g (82%) of **5a**. Recrystallization from ethanol gave colorless crystals. IR (KBr): 2960 (NH), 1650 (C=O), 1340, 1320, and 1140 (SO_2) cm^{-1}. NMR (DMSO-d_6): δ 2.59 (s, 3H, NCH_3), 3.30 (broad, 1H, NH), 3.73 (q, J_{AC}=13.7 Hz, J_{AB}=9.8 Hz, 1H, H_A), 3.94 (q, J_{AC}=13.7 Hz, J_{BC}=5.6 Hz, 1H, H_C), 4.89 (q, J_{AB}=9.8 Hz, J_{BC}=5.6 Hz, 1H, H_B), 7.38 (s, 5H, phenyl). Mass spectrum *m/e*: 240.083 (calculated molecular weight, 240.085).

Method (D): To a solution of **4a** (0.52 g, 0.0020 mol) in acetone (20 ml), we added a 1 N NaOH solution (4.0 ml), 0.0040 mol), after which the reaction mixture was stirred for 1 hr at room temperature. The acetone was evaporated *in vacuo*, and water (10 ml) was added to the residue. The solution was then acidified with concentrated hydrochloric acid to afford 0.46 g (96%) of **5a**.

*2,4-Dimethyl-5-phenyl-2,3,5,6-tetrahydro-1,1,3-trioxo-1,2,4-thiadiazine (**6a**).* Into a solution of **5a** (0.64 g, 0.0027 mol) in a 1 N NaOH solution (5.5 ml, 0.0054 mol) and ethanol (5.5 ml), we stirred, drop by drop, dimethyl sulfate (0.40 g, 0.0032 mol) over a 4-hr period at room temperature. The alkaline solution containing white precipitates was concentrated and collected to obtain 0.35 g (52%) of **6a**. Recrystallization from aqueous methanol gave colorless crystals. IR (KBr): 1650 (C=O), 1350, 1340, and 1145 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 2.77 (s, 3H, $C_6H_5\underset{|}{C}HN(\underline{CH_3})$-), 3.24 (s, 3H, $-N(CH_3)SO_2-$), 3.43 (q, J_{AC}=13.2 Hz, J_{AB}=12.0 Hz, 1H, H_A), 3.65 (q, J_{AC}=13.2 Hz, J_{BC}=6.0 Hz, 1H, H_C), 4.81 (q, J_{AB}=12.0 Hz, J_{BC}=6.0 Hz, 1H, H_B), 7.37±0.1 (m, 5H, phenyl). Mass spectrum *m/e*: 254.075 (calculated molecular weight, 254.073).

*3-Methylamino-4-methyl-5-phenyl-1,1-dioxo-5,6-dihydro-1,2,4-thiadiazine (**7a**).* To a stirred solution of **4a** (1.03 g, 0.0040 mol) in chloroform (10 ml), we added a 30% aqueous methylamine solution (0.83 g, 0.0080 mol) at room temperature, and then the mixture was stirred for 1 hr. The chloroform was evaporated *in vacuo*, and water (10 ml) was added to the residue. The cooled precipitates were collected to obtain 0.82 g (81%) of **7a**. Recrystallization from chloroform–petroleum ether gave colorless crystals. IR (KBr): 3350 (NH), 1560—1530 (N=C), 1340 and 1115 (SO_2) cm^{-1}. NMR (DMSO-d_6): δ 2.65 (s, 3H, NCH_3), 2.71 (d, J_{NHCH_3}=4.0 Hz, $NHCH_3$), 2.70 (s, $=NCH_3$), 3.20 (q, J_{AC}=13.5 Hz, J_{AB}=10.0 Hz, 1H, H_A), 3.45 (q, J_{AC}=13.5 Hz, J_{BC}=6.0 Hz, 1H, H_C), 4.89 (q, J_{AB}=10.0 Hz, J_{BC}=6.0 Hz, 1H, H_B), 6.94 (q, J_{NHCH_3}=4.0 Hz, 0.52H,NH), 3.34 (SO_2NH), 7.34 (s, 5H, phenyl). Mass spectrum *m/e*: 253.116 (calculated molecular weight, 253.118).

*3-Methoxy-4-methyl-5-phenyl-1,1-dioxo-5,6-dihydro-1,2,4-thiadiazine (**9a**).* To a solution containing sodium metal (0.3 g) dissolved in methanol (4 ml), we added **4a** (0.78 g, 0.0030 mol) in portions over a 30-min period at room temperature. The mixture was then allowed to stand for 2 hr, water (10 ml) was added, and the precipitates (0.27 g (37%) of **9a**) were collected. The filtrate was acidified with concentrated hydrochloric acid to afford 0.28 g of a hydrolytic product of **4a**. Recrystallization of **9a** from methanol gave colorless crystals. IR (KBr): 1570 (N=C), 1300, and 1130 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 2.73 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 3.25 (q, J_{AC}=15.0 Hz, J_{AB}=10.4 Hz, 1H, H_A), 3.54 (q, J_{AC}=15.0 Hz, J_{BC}=6.0 Hz, 1H, H_C), 4.97 (q, J_{AB}=10.4 Hz, J_{BC}=6.0 Hz, 1H, H_B), 7.38±0.05 (m, 5H, phenyl). Mass spectrum *m/e:* 254 (M^+).