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The Synthesis of the 3-Substituted 1,4,2-Dithiazine 1,1-Dioxides[1)]

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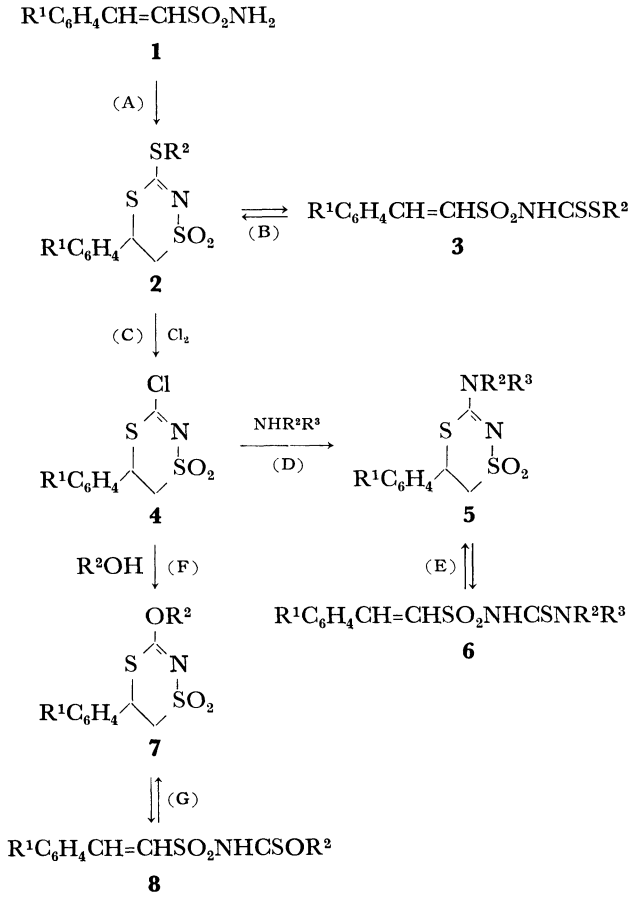
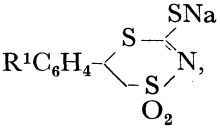
Our previous report[2)] has dealt with the synthesis, cleavage, and structural elucidation of a new heterocycle, 3-monoalkylamino-5-phenyl-1,1-dioxo-5, 6-dihydro-1,4, 2-dithiazine (**5**). This paper will describe the general procedures for the synthesis and cleavage of 3-sub-stituted 1,4,2-dithiazine-1,1-dioxides, which are outlined below:



Results

The reaction of $R^1C_6H_4CH{=}CHSO_2NH_2$ with NaOH, CS_2, and R^2X yielded 3-alkylthio-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazines (**2**). The mechanism is assumed to involve the intermediate of  , which is an intramolecular Michael cycloadduct of $R^1C_6H_4CH{=}CHSO_2N{=}C(SNa)_2$ (Step (A)). The structure of **2** was confirmed by studying its IR, NMR, and mass spectra and by elemental analyses. The C–S bond in **2** could be split to yield *N*-(2-phenylethene-1-sulfonyl) dithiocarbamates, **3**, in strongly basic media (pH≥13.40). They tend to undergo ring-closure to **2** when preserved for long periods. Cycloadducts, **2**, were again obtained from **3** by intramolecular Michael cycloaddition in weakly basic media (pH≤12.55, Step (B)) and also by dissolving it in alcohol, even at room temperature. A mixture of **2** and **3** was obtained when the pH of the solution was between 12.55 and 13.40. The treatment of **2** with chlorine afforded 3-chloro derivatives, **4** (Step (C)). Ammonia, mono-, and dialkylamines attacked **4** at the chlorine atom to form **5** (Step (D)). They were also formed by the Michael cycloaddition of *N*-(2-phenylethene-1-sulfonyl)-*N'*,*N'*-dialkylthioureas, **6**, which are reverse Michael reaction products (Step (E)). *N'*-hydrogen derivatives of **6** are unstable and undergo rapid ring-closure, giving a rather impure product. Thioureas, **6b** and **6c**, were cycloadded upon melting, and **6a**, at 104—106°C before melting. Alcohols reacted with **4** to form 3-alkoxy derivatives, **7** (Step (F)). They were also prepared by the Michael cycloaddition of *O*-alkyl *N*-(2-phenylethene-1-sulfonyl)thiocarbamates, **8**, which are also reverse Michael reaction products of **7** (Step (G)). Solid **8** was stable at room temperature, but was easily cycloadded to give **7** when dissolved in warm alcohol. The results are summarized in Tables 1 and 2.

Experimental

*3-Methylthio-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine (**2a**).* *Step (A)*: To a stirred solution of 2-phenylethene-1-sulfonamide (18.3 g, 0.100 mol) in DMF (180 m*l*), we added NaOH (4.0 g, 0.100 mol) in water (8 m*l*) at room temperature, and then CS_2 (5.7 g, 0.075 mol) was added at 20—30°C. After 10 min, NaOH (4.0 g, 0.100 mol) in water (8 m*l*) and CS_2 (5.7 g, 0.075 mol) were added, and the mixture was stirred for 2 hr; then $(CH_3O)_2SO_2$ (25.2 g, 0.200 mol) was added, portion by portion, at 20—35°C. The yellow reaction mixture was stirred for 2 hr at room temperature, poured into ice water (1000 m*l*), and left to stand overnight. The yellow solid which formed was filtered to give 26.0 g (95%) of **2a**. Recrystallization from methanol gave colorless crystals. IR (KBr): 1535 ($\nu_{N=C}$), 1320 and 1135 cm^{-1} (ν_{SO_2}). NMR ($CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.43 (q, 1H, H_A), 3.80 (q, 1H, H_C), 5.16 (q, 1H, H_B), J_{AC}= 14.0 Hz, J_{AB}=12.0 Hz, J_{BC}=3.6 Hz, 7.41±0.03 (5H, phenyl). MS: *m/e* 121 ($C_6H_5CS^+$), 273 (M^+).

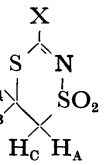
Step (B): When **3a** (1.09 g, 0.004 mol) was dissolved in a warm 0.1M K_2CO_3 solution (40 m*l*, 0.004 mol), the **2a** began to separate out in a few minutes. After the mixture had then been kept overnight, it was filtered to give 0.98 g (90%) of **2a**.

*Methyl N-(2-Phenylethene-1-sulfonyl)dithiocarbamate (**3a**).* To **2a** (6.90 g, 0.025 mol) in acetone (100 m*l*), we added a 1.0N NaOH solution (50 m*l*, 0.050 mol), and then the mixture was stirred for 1 hr at room temperature. The acetone was

1) Presented 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).

TABLE I.



Compd	R^1	X	Yield (%) Method A, C D, F	Yield (%) Method B, E G	Mp (°C)	Calcd (%) C	Calcd (%) H	Calcd (%) N	Calcd (%) S	Found (%) C	Found (%) H	Found (%) N	Found (%) S
2a	H	SCH_3	95	90	157—158	43.96	4.06	5.13		44.07	4.10	5.31	
2b	H	SC_2H_5	93	91	125—126	46.00	4.56	4.88	33.43	46.00	4.32	4.87	33.11
2c	*p*-Cl	SCH_3	95	92	164—165	39.00	3.27	4.55	31.24	38.98	3.01	4.42	31.52
2d	*p*-CH_3	SCH_3	98	93	194—196	46.00	4.56	4.88	33.43	45.94	4.33	4.64	33.37
4a	H	Cl	94		158—160	41.30	3.08	5.35		41.16	3.10	5.41	
4b	*p*-Cl	Cl	87		112—113	36.49	2.38	4.76	21.65	36.36	2.13	4.54	21.89
4c	*p*-CH_3	Cl	60		142—143	43.55	3.66	5.08		43.25	3.41	4.83	
5a	H	NH_2	99		207—208	44.63	4.16	11.57	26.43	44.41	4.28	11.51	26.35
5b	H	$N(CH_3)_2$	98	89	185—186	48.89	5.22	10.37	23.68	48.61	5.17	10.33	23.54
5c	*p*-Cl	$N(CH_3)_2$	99	95	174—176	43.34	4.30	9.19	21.04	43.14	4.00	9.07	21.23
5d	*p*-CH_3	$N(CH_3)_2$	96	80	192—193	50.70	5.67	9.86	22.51	50.51	5.64	9.73	22.47
7a	H	OCH_3	96	90	176—178	46.70	4.31	5.45	24.88	46.86	4.49	5.67	24.93
7b	H	OC_2H_5	94	90	155—157	48.71	4.83	5.16	23.58	48.55	4.87	5.27	24.38
7c	*p*-Cl	OCH_3	92	83	174—175	41.16	3.45	4.80	21.98	41.40	3.64	4.87	22.04
7d	*p*-CH_3	OCH_3	57	57	188—190	48.71	4.83	5.16	23.58	48.45	4.63	4.91	23.50

TABLE 2. $R^1C_6H_4CH_B{=}CH_ASO_2NHCS{-}Y$

Compd	R^1	Y	Yield (%)	Mp (°C)	Calcd (%) C	Calcd (%) H	Calcd (%) N	Calcd (%) S	Found (%) C	Found (%) H	Found (%) N	Found (%) S
3a	H	SCH_3	98	106—108	43.96	4.06	5.13		44.09	4.01	4.84	
3b	*p*-Cl	SCH_3	94	114—117	39.00	3.27	4.55	31.24	39.11	3.30	4.38	30.63
6a	H	$N(CH_3)_2$	85	176—178	48.89	5.22	10.37	23.68	48.84	5.09	10.04	23.97
6b	*p*-Cl	$N(CH_3)_2$	95	119—120	43.34	4.30	9.19	21.04	43.31	4.36	9.23	20.77
6c	*p*-CH_3	$N(CH_3)_2$	99	121—123	50.70	5.67	9.86	22.51	50.85	5.72	9.98	22.16
8a	H	OCH_3	85	91— 92	46.70	4.31	5.45	24.88	46.51	4.27	5.21	24.44
8b	*p*-Cl	OCH_3	98	128—129	41.16	3.45	4.80	21.98	41.39	3.55	4.96	21.81
8c	*p*-CH_3	OCH_3	100	117—119	48.71	4.83	5.16	23.59	49.01	4.56	5.04	23.52

removed *in vacuo*, and the residual solution was acidified with concd. HCl to give 6.80 g (98%) of **3a**. Recrystallization from benzene–petroleum ether gave yellow crystals. IR (KBr): 3170 (ν_{NH}), 1620 ($\nu_{C=C}$), 1360 and 1150 cm^{-1} (ν_{SO_2}). NMR ($CDCl_3$): δ 2.59 (s, 3H, CH_3), 7.14 (d, 1H, H_A), 7.84 (d, 1H, H_B), J_{AB}=15.0 Hz, 7.48±0.03 (5H, phenyl).

3-Chloro-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine (4a). Excess chlorine was bubbled through a solution of **2a** (16.4 g, 0.060 mol) in chloroform (120 m*l*) cooled to 0—5°C over a 1-hr period. The colorless solution turned orange and yielded methanesulfenyl chloride. The chloroform was removed *in vacuo*, CCl_4 (20 m*l*) was added to the crystals, and the mixture was filtered to give 14.8 g (94%) of **4a**. Recrystallization from CCl_4 gave colorless crystals.

3-Dimethylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine (5b). *Step (D)*: To **4a** (1.60 g, 0.006 mol) in chloroform (20 m*l*), we added 40% aqueous dimethylamine (1.37 g, 0.012 mol), after which the reaction mixture was stirred for 1 hr at room temperature. The chloroform was then removed *in vacuo*, and water (20 m*l*) was added to the residue. The cooled precipitate was filtered to give 1.62 g (98%) of **5b**. Recrystallization from methanol gave colorless crystals.

3-Methoxy-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine (7a). *Step (F)*: A solution of **4a** (2.62 g, 0.010 mol) in methanol (30 m*l*) was refluxed for 2 hr, diluted with water (10 m*l*), and then cooled overnight. The crystals which formed were filtered to give 2.47 g (96%) of **7a**. Recrystallization from methanol gave colorless crystals.