BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 525—528 (1972)

The Synthesis of the New 1,4,2-Dithiazine Ring[1]

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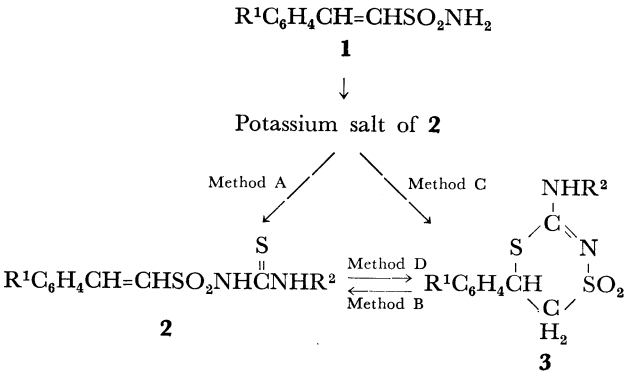
(Received May 21, 1971)

Some derivatives of *N*-(2-phenylethene-1-sulfonyl)-*N'*-alkylthioureas of the $R^1C_6H_4CH{=}CHSO_2NHCSNHR^2$ **2** type were synthesized by a reaction between 2-phenylethene-1-sulfonamides **1** and isothiocyanates in acetone in the presence of K_2CO_3. A new heterocyclic system, 3-alkylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine **3**, was obtained by the intramolecular Michael cycloaddition of **2** in weakly basic media, and also by the thermal cyclization of **2**. The carbon-sulfur bond in **3** could be cleaved to give **2** again in strongly basic media.

A previous study[2] in this laboratory has dealt with *N*-benzenesulfonyl-*N'*-alkylthioureas obtained from benzenesulfonamides and alkyl isothiocyanates. When 2-phenylethene-1-sulfonamide[3] **1**, in which the α, β double bond is activated by a neighboring sulfonyl group,[4] was used, either the corresponding sulfonylthioureas **2** or the intramolecular cycloadducts, 3-alkylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazines **3**, were formed, depending upon the work-up procedure. Recently, the synthesis of **2** (R^1=H, R^2=allyl and phenyl) was briefly reported,[5] but **3** has never yet been prepared. This paper will describe the synthesis, cleavage, and structural elucidation of a new heterocycle **3**. The process is outlined below.



Results

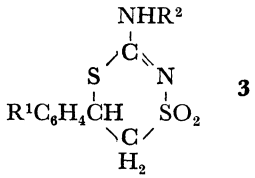
N-(2-Phenylethene-1-sulfonyl)-N'-alkylthioureas **2**.
A mixture of **1**, potassium carbonate, and alkyl isothiocyanate in acetone was refluxed for 15—25 hr with stirring to yield the potassium salt of **2** as a normal product. This was filtered, dissolved in water, and acidified to give **2** (Table 1, Method A). The structure of **2** was confirmed by a study of its IR, NMR,

1) Presented in part at the 24th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1971.
2) S. Hirooka, *Nippon Kagaku Zasshi*, **83**, 156 (1962).
3) B. M. Culbertson and S. Dietz, *J. Chem. Soc., C*, **1968**, 90, 992.
4) E. D. Bergmann, D. Ginsburg, and R. Pappo, "Organic Reactions," Vol. 10, New York (1959), p. 241.
5) S. Hartig, *J. Prak. Chem.*, **33**, 216 (1966).

Table 1. $R^1C_6H_4CH_B{=}CH_ASO_2NHCSNHR^2$ **2**

Compd.	R^1	R^2	Yield (%) A[a]	Yield (%) B[b]	Mp (°C)	UV $\lambda_{max}^{C_2H_5OH}$ (ε_{max})	Calcd (%) C	Calcd (%) H	Calcd (%) N	Calcd (%) S	Found (%) C	Found (%) H	Found (%) N	Found (%) S
2a	H	CH_3	95	94	137—138	267 (23700)	46.88	4.72	10.93		46.85	4.89	10.95	
2b	H	C_2H_5	67	87	96— 98	267 (22700)	48.89	5.22	10.37		48.84	5.29	10.26	
2c	H	*n*-C_4H_9	72	76	110—111	267 (22200)	52.34	6.08	9.39		52.51	6.06	9.30	
2d	H		57	79	130—131		55.55	6.22	8.64		55.80	6.34	8.78	
2e	*p*-Cl	CH_3	85	90	240—242	274 (11300)	41.30	3.81	9.63	22.05	41.54	4.05	9.75	22.13
2f	*p*-Cl	C_2H_5	44	87	110—111		43.34	4.29	9.19	21.03	43.41	4.16	9.30	20.99
2g	*m*-Cl	CH_3	94	92	233—235		41.30	3.81	9.63	22.05	41.37	3.85	9.72	22.05
2h	*o*-Cl	CH_3	90	93	216—218		41.30	3.81	9.63	22.05	41.05	3.92	9.72	22.16
2i	*p*-Br	CH_3	80	96	245—247	276 (27500)	35.82	3.31	8.36	19.13	35.90	3.19	8.21	19.28
2j	*p*-CH_3	CH_3	94	100	149—151	277 (25600)	48.89	5.22	10.37		48.71	5.22	10.30	
2k	*p*-CH_3	C_2H_5	23	76	108—110	273 (23200)	50.70	5.67	9.86	22.51	50.72	5.57	9.66	21.92

a) Method A, b) Method B.

Table 2.  **3**

Compd.	R^1	R^2	Yield (%) C[a]	Yield (%) D[b]	Mp (°C)	UV $\lambda_{max}^{C_2H_5OH}$ (ε_{max})	Calcd (%) C	Calcd (%) H	Calcd (%) N	Calcd (%) S	Found (%) C	Found (%) H	Found (%) N	Found (%) S
3a	H	CH_3	87	82	210—211	218 (23500)	46.88	4.72	10.93	24.98	46.75	4.67	10.80	24.70
3b	H	C_2H_5	61	94	174—175	218 (21600)	48.89	5.22	10.37		48.97	5.14	10.29	
3c	H	*n*-C_4H_9	77	96	150—151	218 (19900)	52.34	6.08	9.39		52.36	5.95	9.26	
3d	H		63	86	201—202	218 (19800)	55.55	6.22	8.64		56.29	6.03	8.35	
3e	*p*-Cl	CH_3	81	92	250—252	225 (21200)	41.30	3.81	9.63	22.05	41.35	4.05	9.75	22.13
3f	*p*-Cl	C_2H_5	67	92	201—202		43.34	4.29	9.19	21.03	43.43	4.09	9.19	21.10
3g	*m*-Cl	CH_3	94	89	234—236	220 (25100)	41.30	3.81	9.63	22.05	41.34	3.96	9.68	22.18
3h	*o*-Cl	CH_3	84	93	222—224	219 (21800)	41.30	3.81	9.63	22.05	41.48	3.84	9.65	22.12
3i	*o*-Cl	C_2H_5	71	90	150—151	219 (24800)	43.34	4.29	9.19	21.03	43.53	4.32	9.27	21.17
3j	*p*-Br	CH_3	68	88	249—251	228 (20400)	35.82	3.31	8.36	19.13	36.01	3.32	8.35	19.20
3k	*p*-Br	C_2H_5	55	90	230—232	228 (19700)	37.82	3.75	8.02	18.36	37.89	3.61	8.35	18.36
3l	*p*-CH_3	CH_3	94	86	215—217	223 (27700)	48.89	5.22	10.37	23.68	47.60	5.06	10.00	23.68
3m	*p*-CH_3	C_2H_5	49	85	204—206	223 (28200)	50.70	5.67	9.86		50.85	5.75	9.82	

a) Method C, b) Method D.

and mass spectra and by the results of elemental analyses. The IR spectrum of **2a** displayed bands at 3320 (ν_{NH}) and 1610 ($\nu_{C=C}$) cm^{-1}. The NMR spectrum of **2a** exhibited an AB pattern centered at δ 7.28 and δ7.77 (J_{AB}=15.2 Hz) due to the vicinal olefinic protons, H_A and H_B. The large magnitude of this coupling proves that **2** has the *trans* rather than the *cis* configuration.

3-Alkylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazines **3**. *The Base-Catalyzed Intramolecular Cyclization of* **2**. When the potassium salt of **2** described above was dissolved in warm water (Table 2, Method C), or when **2** was dissolved in a dilute alkali (Table 2, Method D), a new heterocycle, **3**, began to separate out after a few minutes. This Michael-type reaction carried out at pH values below 12.55 gave **3** in a good yield, and the rate of cycloaddition increased with an increase in the base concentration. Only a one-fourth equivalent of the base was sufficient to effect the cycloaddition of the sulfonylthiourea. In the pH range from 12.55 to 13.40, a mixture of **2** and **3** was obtained. Under strongly basic conditions (pH>13.40), no cycloaddition occurred. The IR spectrum of **3a** displayed a strong band at 1560—1535 cm^{-1} due to the N=C bond, but no absorption due to the C=C group was observed in the region of 1610 cm.$^{-1}$ In NMR pattern of **3a**, ring protons, $H_AH_CH_B$ appeared as an ABX pattern consisting of three quartets of H_A centered at δ3.53, H_C δ 3.67 and H_B δ 5.00 (J_{AC}=14.0 Hz, J_{AB}=11.7 Hz, and J_{BC}=4.4 Hz) respectively (Fig. 1). The observed coupling constants, J_{AB} and J_{BC}, may be compared with those for the axial-axial and axial-equatorial protons respectively. The peak at *m/e* 121.011 in the mass spectrum was in entire agreement with the fragment ion $C_6H_5CS^+$, derived from only the six-membered heterocycle, **3**. The structures of **3b—3m** were inferred because they were analogous with **3a** in their preparations and spectral data. The Michael mechanism is assumed to be like Scheme 1.

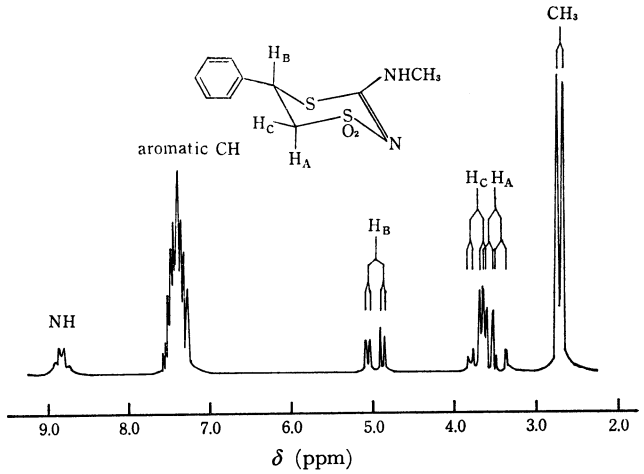
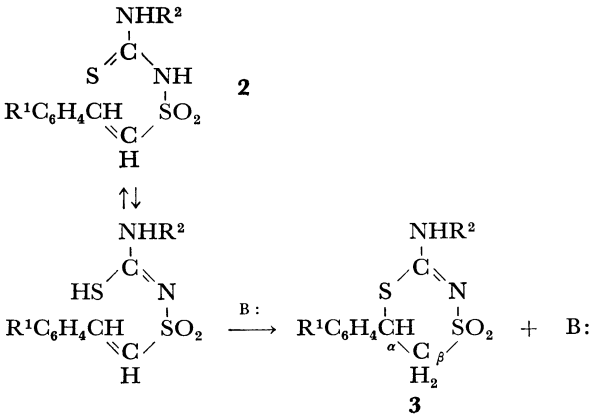


Fig. 1. NMR spectrum of **3a** in DMSO-d_6.

Thermal Cyclization of **2**. Thioureas, **2**, were cyclized to **3** by heating; they were then divided into two groups. The changes in their IR spectra showed that the first group, **2a—2d, 2f, 2j**, and **2k**, underwent a cyclization upon melting, while the second group, **2e** and **2g—2i**, underwent such a cyclization before melting. The cyclization temperatures of the latter, observed in their DTA curves, were as follows: **2e**, 141—146°C; **2g**, 131—135°C; **2h**, 140—145°C; **2i**, 157—160°C. These cycloadducts, when recrystallized, gave melting points identical with those of the products obtained by Methods C and D.



Scheme 1.

Base-Catalyzed Ring-Cleavage of **3**. The **3** cycloadduct could be split into **2** when the reaction media were more basic than those used in effecting the cycloaddition (Table 1, Method B). Cleavage proceeded very fast in a solvent such as alkaline aqueous acetone, even at 0°C. Only cleaved **2** was obtained when the pH of the solution was above 13.30. A mixture of **2** and **3** was obtained in the pH range from 12.70 to 13.30. This ring-cleavage is the reverse of the Michael cycloaddition, and a mechanism in the direction the reverse of that in Scheme 1 is assumed.

Discussion

We have been interested in **2** because the SO_2 group can conjugate with and activate a neighboring ethylenic double bond and stabilize the thiolate anion in basic media. As **2** has both donor and acceptor in one molecule, it should be possible to effect intramolecular Michael cycloaddition. It has indeed been found that **2** gives the intramolecular cycloadduct **3** in weakly basic media. Compounds with the general formulation $-CH=CHSO_2NHC(=S)-$ would give intramolecular Michael cycloadducts.

A Michael reversible system can be influenced by the basicity of the solution. Cleavage seems to require a base B:, strong enough to remove active β-hydrogen. A β sulfonyl group is known to accelerate the rate of the base-catalyzed elimination.[6] Cleavage proceeded too rapidly to determine certain details of this reaction, but the higher rate of cleavage was clearly associated with the higher concentration of the base.

Experimental

The melting points were determined on a Yanagimoto micro-melting-point measuring apparatus MP-S2 and are

6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York (1959), p. 499.

uncorrected. The IR and UV spectra were recorded on JASCO IRA-1 and Hitachi EPS-3T spectrometers respectively. The NMR spectra were determined with a Varian HA-100 spectrometer, with TMS as the internal standard and the mass spectra, with a JMS-01SG spectrometer.

N-*(2-Phenylethene-1-sulfonyl)*-N'-*methylthiourea* ***2a***.

Method A: To 2-phenylethene-1-sulfonamide (3.00 g, 0.0164 mol) in acetone (30 m*l*), we added methyl isothiocyanate (1.32 g, 0.0180 mol) and anhydrous potassium carbonate (1.32 g, 0.0220 mol), after which the reaction mixture was refluxed for 20 hr with stirring. The resulting potassium salt of **2a** was collected on a filter and washed with acetone to remove the unchanged sulfonamide. This salt was dissolved in water (200 m*l*), and the solution was acidified with concentrated hydrochloric acid to give 4.0 g (95%) of **2a**. Recrystallization from methanol then gave colorless crystals. IR (KBr): 3320 (ν_{NH}), 1610 ($\nu_{C=C}$), 1570 (δ_{NH}), 1495, 1435, 1380 (ν_{SO_2}), 1150, and 1130 (ν_{SO_2}), 1050, 960, 885, 740, and 690 cm^{-1}. NMR (acetone-d_6): δ 3.08 (d, J_{NHCH_3}=5.0 Hz, 3H, CH_3), 7.28 (d, J_{AB}=15.2 Hz, 1H, H_A), 7.77 (d, J_{AB}=15.2 Hz, 1H, H_B), 7.47±0.05 (m, 5H, phenyl), 8.40 (broad, 1H, SO_2NH), 8.90 (broad, 1H, NH). Mass spectrum (75 eV) *m/e* (rel. intensity): 77 (56), 91 (24), 103 (41), 135 (41), 136 (100), 192 (29), 256 (M^+, 1.8).

Method B: To 3-methylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine (0.51 g, 0.0020 mol) in acetone (30 m*l*), we added a 1.0 N NaOH solution (4.0 m*l*, 0.0040 mol) and then stirred the mixture for 1 hr at room temperature. The acetone was then evaporated under reduced pressure, and the residual solution was acidified with concentrated hydrochloric acid to give 0.48 g (94%) of ***2a***.

3-Methylamino-5-phenyl-1,1-dioxo-5,6-dihydro-1,4,2-dithiazine ***3a***. *Method C*: When potassium salt of **2a** obtained from 2-phenylethene-1-sulfonamide (2.20 g, 0.0120 mol) by Method A was dissolved in warm water (150 m*l*), **3a** began to separate out after a few minutes. After the mixture had stood overnight, it was filtered to give 1.91 g (87%) of **3a**. Recrystallization from methanol gave colorless crystals. IR (KBr): 3280 (ν_{NH}), 1560—1535 ($\nu_{N=C}$), 1405, 1300 (ν_{SO_2}), 1125 (ν_{SO_2}), 960, 750, and 690 cm^{-1}. NMR (DMSO-d_6): δ 2.74 (d, J_{NHCH_3}=4.5 Hz, 3H, CH_3), 3.53 (q, J_{AC}=14.0 Hz, J_{AB}=11.7 Hz, 1H, H_A), 3.67 (q, J_{AC}=14.0 Hz, J_{BC}=4.4 Hz, 1H, H_C), 5.00 (q, J_{AB}=11.7 Hz, J_{BC}=4.4 Hz, 1H, H_B), 7.41±0.1 (m, 5H, phenyl), 8.70 (broad, 1H, NH). Mass spectrum (75 eV) *m/e* (rel. intensity): 77 (26), 78 (25), 91 (38), 104 (100), 119 (34), 121.011 (13), 135 (38), 136 (25), 177 (6), 191 (20), 256.032 (calculated molecular weight, 256.034, 21).

Method D: When **2a** (0.77 g, 0.0030 mol) was dissolved in a warm 0.1 M K_2CO_3 solution (30 m*l*, 0.0030 mol), **3a** began to separate out in a few minutes. After the mixture had stood overnight, it was filtered to give 0.63 g (82%) of **3a**.

The authors wish to thank Dr. M. Kondo, Mr. H. Kuwano, and Mr. T. Kinoshita of Sankyo Co., Limited, Tokyo, for their help in NMR and mass spectrum study. We are indebted to Mr. Y. Okabe, Mr. H. Yamada, and Mr. K. Hori for assistance in preparing some of the compounds.