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Reactions of β-Carbonylethylthiosulfates and β-Carbamoylethyl Disulfides with Amines

MITSURU FURUKAWA, TAKESHI YUKI, RANKO KIYOFUJI, YOKO KOJIMA and SEIGORO HAYASHI

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

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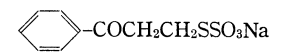
The reactions of sodium 2-phenylcarbamoylethylthiosulfate, sodium 2-cyclohexylcarbamoylethylthiosulfate and sodium 2-benzoylethylthiosulfate with aqueous alkylamines were attempted and found to give the corresponding N-β-carbonylethyl-N-alkylamines and sometimes bis(β-carbonylethyl)sulfides, though the same reactions in anhydrous state is known to give the corresponding disulfides as the only product isolated. The reaction between bis(2-phenylcarbamoylethyl) disulfide or bis(2-cyclohexylcarbamoylethyl) disulfide and aqueous cyclohexylamine was also attempted under similar conditions and found to give the corresponding sulfides. The mechanisms of these reactions were also discussed.

Alkylthiosulfates generally react with amines to form disulfides.[2] These have been extensively studied, particularly by Milligan and Swan.[3,4] The interesting reaction of α-carbamoylmethylthiosulfate with amines has been first reported by them[3,4] to give thiooxamide and later extensions and developments of the reaction were made by the authors.[5,6] However, regarding the reaction of β-carbonylethylthiosulfates, in which a second methylene group is introduced between the carbonyl and the thiosulfate radical, with amines, only one instance[3] has hitherto been known in the literature, no details being described. Namely, sodium 2-phenylcarbamoylethylthiosulfate reacts with cyclohexylamine or morpholine at 135° to give a 20% yield of bis(2-phenylcarbamoylethyl)disulfide and to recover a 70% yield of the unchanged thiosulfate. Some further examples and various extensions and developments of this reaction are now reported.

The particular substances of β-carbonylethylthiosulfates used in this work were sodium 2-phenylcarbamoylethylthiosulfate (I), sodium 2-cyclohexylcarbamoylethylthiosulfate (II) and sodium 2-benzoylethylthiosulfate (III). In the reactions of these thiosulfates with amines,

I

II

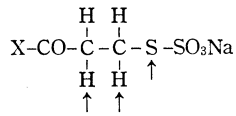


III

the following three mechanistic pathways are possible by considering the disulfide cleavage[7–16] with alkaline reagents; 1) Direct displacement by the nucleophilic attack of amines on the

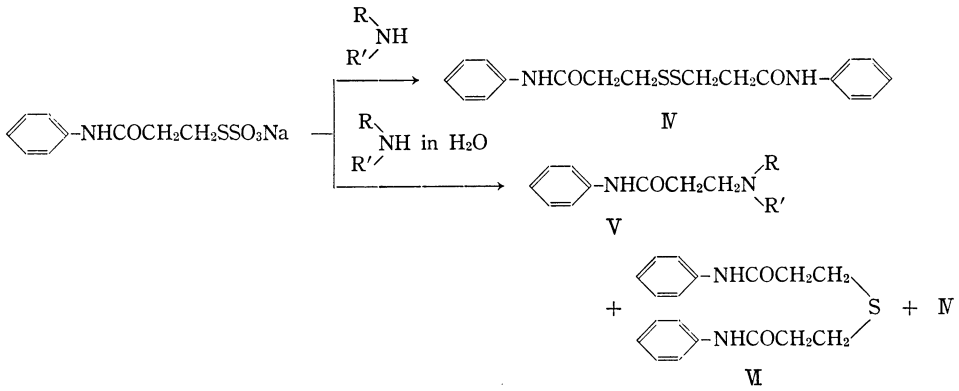
1) Location: *Oe-hon-machi, Kumamoto.*

2) B. Milligan and J.M. Swan, *Rev. Pure Appl. Chem.*, **12**, 72 (1962).
3) B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1959**, 2969.
4) B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1961**, 1194.
5) S. Hayashi, M. Furukawa, Y. Fujino, and K. Shiraishi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2247 (1971).
6) M. Furukawa, K. Shiraishi, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1921 (1972).
7) A. Schöberl, *Ann.*, **507**, 111 (1933).
8) A. Schöberl, E. Berninger, and F. Harren, *Chem. Ber.*, **72B**, 1545 (1934).
9) D.S. Tarbell and D.P. Harnish, *Chem. Rev.*, **49**, 11 (1951).
10) J.M. Swan, *Angew. Chem.*, **68**, 215 (1956).
11) A.J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).
12) F. Asinger, M. Thiel, and W. Schäfer, *Ann.*, **637**, 146 (1960).
13) J.P. Danehy and J.A. Kreuz, *J. Am. Chem. Soc.*, **83**, 1109 (1961).
14) E.G. Howard, *J. Org. Chem.*, **27**, 2212 (1962).
15) R.G. Hiskey, B.D. Thomas, and J.A. Kepler, *J. Org. Chem.*, **29**, 3671 (1964).
16) R.G. Hiskey, J.A. Kepler, and B.D. Thomas, *J. Org. Chem.*, **29**, 3684 (1964).



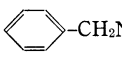
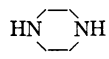
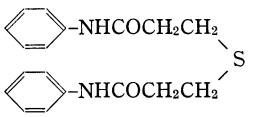
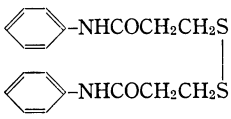
sulfen sulfur atom of the thiosulfates. 2) Olefin-forming E 2 reaction by β-elimination. 3) Initial formation of thioaldehyde by removal of an α-hydrogen atom. Therefore, a variety of compounds in addition to disulfides may form in this reaction.

First, sodium 2-phenylcarbamoylethylthiosulfate (I) was allowed to react with various alkylamines, such as cyclohexylamine, benzylamine, piperidine, pyrrolidine and piperazine. When I was heated in these anhydrous alkylamines under reflux for one hour, bis(2-phenylcarbamoylethyl)disulfide (IV) was produced in about 20% yield as the only product isolated. However, the same reaction in an aqueous solution exhibited quite different behaviors. Heating of I with two equivalent amounts of the alkylamines in an aqueous solution under reflux for 5—12 hours gave N-2-phenylcarbamoylethyl-N-alkylamines (V) in 15—75% yields, sometimes accompanying small amounts of bis(2-phenylcarbamoylethyl)disulfide (IV) and (or) bis(2-phenylcarbamoylethyl)sulfide (VI), which were identified with authentic samples

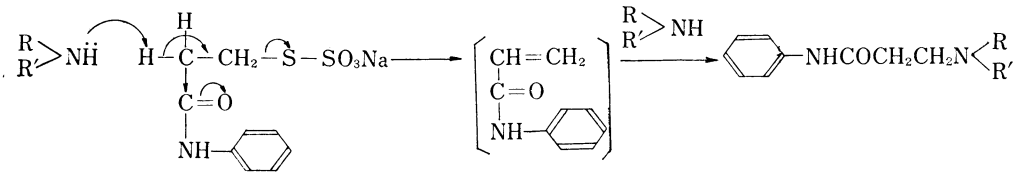


by thin-layer chromatography (TLC), mixed melting point determination and comparison of the infrared (IR) spectra. The whole results obtained were summarized in Table I. Furthermore, the reaction of I with alkylamines at room temperature gave V as the only product isolated, no traces of any IV and VI being isolated.

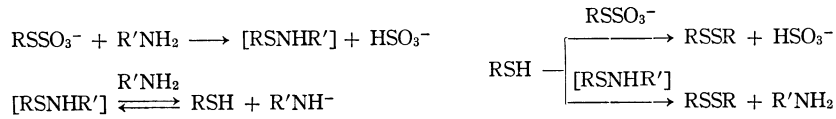
Table I. The Yield of the Product obtained by the Reaction of Sodium 2-Phenylcarbamoylethylthiosulfate with Amines

Product (%)					
	74	40	18	none	20
	none	trace	3	6	none
	1	trace	trace	none	none

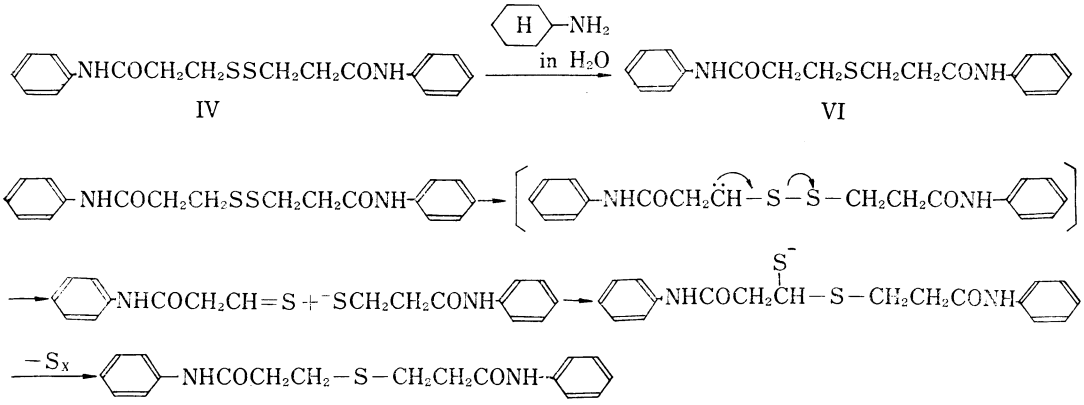
It is presumed that V was formed by further addition of alkylamines to the vinyl intermediates formed through the passible pathway 2, though no trace of any vinyl intermediates were isolated. In fact, however, the olefin formation is observed in the decomposition of



thiosulfates by treatment with aqueous alkali.[17] In the formations of the disulfide (IV) and monosulfide (VI), the nucleophilic attack of amines on the sulfen sulfur atom, pathway 1, might participate. Oae[18] has presumed that thiosulfates react with amines to give the corresponding sulfenamides, followed by decomposition to give disulfides. The intermediate



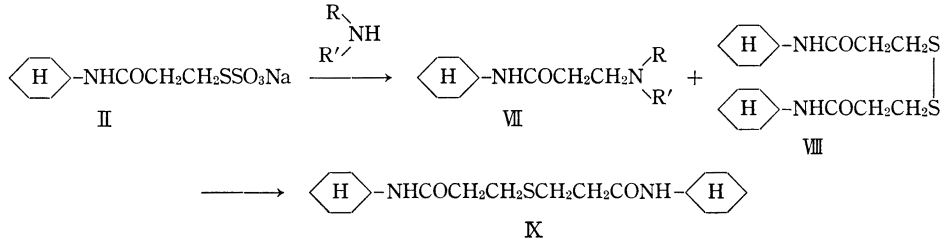
of sulfenamide was practically apprehended by us[19] in the reaction of sodium benzylthiosulfate with morpholine, which was confirmed to be converted into dibenzyl disulfide. In connection with the formation of the monosulfides (VI), Hiskey[16] has assumed that the treatment with alkoxide is due to the initial cleavage by α-elimination to phenylglyoxthial and phenacyl mercaptide, recombination of them and elimination of a sulfur atom to give diphenacyl sulfide. In order to confirm whether the analogous decomposition of disulfide to monosulfide occurrs with amine or not, IV was treated with aqueous cyclohexylamine under reflux for 5 hours. As expected, VI was obtained in 30% yield. Therefore, it is assumed that VI would be formed through IV which followed by α-elimination as follow. If IV undergoes β-elimination, V should be also formed. However, no trace of V was observed to form.



The fact that α-elimination rather than β-elimination occurrs preferably in IV is noted, in spite of the stronger acidity of β-hydrogen atom. It is presumed that the following resonance due to the participation of 3 *d* orbit of sulfur atom is much effective for the formation of carbanion intermediate.

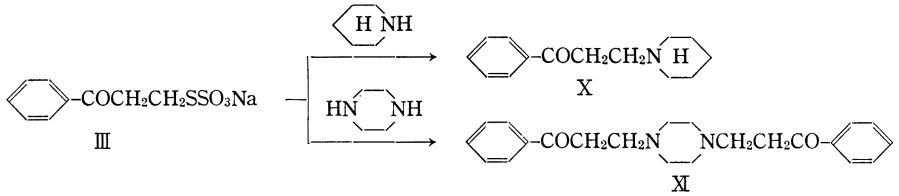
17) H. Distler, *Angew. Chem.*, **79**, 520 (1967).
18) S. Oae, G. Tsukamoto, and T. Kurusu, *Kagaku* (Kyoto), **26**, 1066 (1971).
19) M. Furukawa, K. Shiraishi, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2315 (1972).

Sodium 2-cyclohexylcarbamoylethylthiosulfate (II) was analogously allowed to react with aqueous alkylamines, such as cyclohexylamine, benzylamine, pyrrolidine and piperazine under reflux for 5—19 hours. In all cases except the reaction with pyrrolidine, N-2-cyclohexyl carbamoylethyl-N-alkylamines (VII) were obtained in 15—70% yields, accompanying a extremely small amount of bis(2-cyclohexylcarbamoylethyl)disulfide (VIII). However, no formation of bis(2-cyclohexylcarbamoylethyl)sulfide (IX) expected was observed in all



cases even by TLC, though conversion of VIII into IX by treatment with cyclohexylamine was readily carried out in 19% yield. It is probably presumed that, in comparison with I, II would undergo preferable β-elimination more than nucleophilic attack on the sulfur atom.

Sodium 2-benzoylethylthiosulfate (III) was also allowed to react with aqueous piperidine and piperazine. The reactions readily proceeded at room temperature and by heating under reflux for one hour, respectively, to give N-2-benzoylethylpiperidine (X) and N,N-bis(2-benzoylethyl)piperazine (XI) in 90% and 29% yields, respectively. In both cases, no formation of the corresponding disulfide and monosulfide anticipated was observed by TLC.



If these β-carbonylethylthiosulfates undergo α-elimination, in which the methylene hydrogen adjacent to the sulfur atom is attacked with amines, the corresponding β-carbonylthioamides would be expected to form. However, in all cases, no formation of any β-carbonylthioamide was observed by TLC. Therefore, it is presumed that the attack to the α methylene hydrogen, pathway 3, is of no importance.

Experimental

Reaction of Sodium 2-Phenylcarbamoylethylthiosulfate (I) with Amines——a) With Anhydrous Cyclohexylamine: A suspension of 3.0 g of sodium 2-phenylcarbamoylethylthiosulfate in 10 ml of cyclohexylamine was heated under reflux for 1 hr. After cooling, the solution was extracted with EtOAc. The extract was neutralized with dil. HCl, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give colorless plates of bis(2-phenylcarbamoylethyl)disulfide melting at 161° and 172° (double melting point), which was identified with an authentic sample.[20] *Anal.* Calcd. for $C_{18}H_{20}O_2N_2S_2$: C, 59.97; H, 5.59; N, 7.77. Found: C, 60.06; H, 5.43; N, 7.58. IR ν_{max}^{KBr} cm^{-1}: 3285, 1658 (CONH).

b) With Aqueous Cyclohexylamine: A solution of 2.8 g (0.01 mole) of sodium 2-phenylcarbamoylethylthiosulfate and 2.0 g (0.02 mole) of cyclohexylamine in 30 ml of H_2O was refluxed for 5 hr. After cooling, the solution was extracted with EtOAc and the extract was stirred with a small amount of dil. HCl.

20) G.G. Stoner and G. Dougherty, *J. Am. Chem. Soc.*, **63**, 987 (1941).

The precipitates deposited were collected by filtration and recrystallized from EtOH to give colorless plates of N-2-phenylcarbamoylethyl-N-cyclohexylamine HCl, whose detailed data were summarized in Table II. IR ν_{max}^{KBr} cm^{-1}: 3280, 3200, 3128, (NH), 1641 (CO). The filtrate was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue gave 0.08 g (1.2%) of bis(2-phenylcarbamoylethyl)disulfide melting at 161° and 172° (double mp), which was identified with an authentic sample.[20]

c) With Aqueous Benzylamine: A solution of 2.8 g (0.01 mole) of sodium 2-phenylcarbamoylethylthiosulfate and 2.1 g (0.02 mole) of benzylamine in 20 ml of H_2O was refluxed for 8 hr. The solution was treated by the same procedure as described above to give colorless plates of N-2-phenylcarbamoylethyl-N-benzylamine HCl, whose detailed data were illustrated in Table II. IR ν_{max}^{KBr} cm^{-1}: 3245, 3195, 3125 (NH); 1668 (CO). A small amount of a mixture of bis(2-phenylcarbamoylethyl) disulfide and monosulfide was also obtained, which was identified by TLC and IR spectra.

d) With Aqueous Piperidine: A solution of 2.8 g (0.01 mole) of sodium 2-phenylcarbamoylethylthiosulfate and 1.8 g (0.02 mole) of piperidine in 20 ml of H_2O was refluxed for 8.5 hr. After cooling, the precipitates deposited were collected by filtration and washed with H_2O. The precipitates were extracted with cold MeOH and the extract was evaporated to dryness. Recrystallization from MeOH gave 0.1 g (3%) of colorless plates of bis(2-phenylcarbamoylethyl) sulfide melting at 163.5°, which was identified with an authentic sample. *Anal.* Calcd. for $C_{18}H_{20}O_2N_2S$: C, 65.87; H, 6.15; N, 8.53. Found: C, 66.21; H, 6.32; N, 8.29. IR ν_{max}^{KBr} cm^{-1}: 3310, 1653 (CONH). Insoluble part in cold MeOH was recrystallized from H_2O–MeOH to give colorless plates of N-2-phenylcarbamoylethylpiperidine. IR ν_{max}^{KBr} cm^{-1}: 3310; 1612 (CONH). Mass Spectrum *m/e*: 232 (M^+).

e) With Aqueous Pyrrolidine: A solution of 2.8 g (0.01 mole) of sodium 2-phenylcarbamoylethylthiosulfate and 1.4 g (0.02 mole) of pyrrolidine in 20 ml of H_2O was heated for 11.5 hr under reflux. After cooling, benzene was added to the stirred solution and the precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.2 g (6%) of colorless plates of bis(2-phenylcarbamoylethyl) sulfide melting at 163.5°, which was identified with an authentic sample.

f) With Aqueous Piperazine: A solution of 2.8 g (0.01 mole) of 2-phenylcarbamoylethylthiosulfate and 2.0 g of piperazine hexahydrate in 20 ml of H_2O was refluxed for 5 hr. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give colorless needles of N,N-bis(2-phenylcarbamoyl)piperazine, whose detailed data were summarized in Table II. IR ν_{max}^{KBr} cm^{-1}: 3119, 1662 (CONH).

Table II. N-2-Phenylcarbamoylethyl-N-alkylamine Hydrochloride

R	R′	Yield (%)	mp (°C)	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	74	199—202	$C_{15}H_{23}ON_2Cl$	63.73	8.23	9.91	63.77	8.02	9.56
	H	40	238—241	$C_{16}H_{19}ON_2Cl$	66.07	6.58	9.64	66.36	6.54	9.51
		20	207—208 (free)	$C_{22}H_{28}O_2N_4$	69.44	7.42	14.73	69.09	7.20	14.78

Reaction of Sodium 2-Cyclohexylcarbamoylethylthiosulfate (II) with Amines——a) With Anhydrous Cyclohexylamine: A suspension of 3.1 g (0.01 mole) of sodium 2-cyclohexylcarbamoylethylthiosulfate in 10 ml of cyclohexylamine was refluxed for 1 hr. After cooling, the mixture was extracted with EtOAc and the extract was neutralized with dil. HCl, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from EtOH to give colorless plates of bis(2-cyclohexylcarbamoylethyl) disulfide melting at 171°, which was identified with an authentic sample. *Anal.* Calcd. for $C_{18}H_{32}O_2N_2S_2$: C, 58.02: H, 8.66; N, 7.52. Found: C, 58.51; H, 8.81; N, 7.37. IR ν_{max}^{KBr} cm^{-1}: 3297, 1640 (CONH).

b) With Aqueous Cyclohexylamine: A solution of 3.1 g (0.01 mole) of sodium 2-cyclohexylcarbamoylethylthiosulfate and 2.0 g (0.02 mole) of cyclohexylamine in 30 ml of H_2O was refluxed for 5 hr. After cooling, the solution was extracted with EtOAc and the extract was stirred with a small amount of dil. HCl. The precipitates deposited were collected by filtration and recrystallized from EtOH to give colorless plates of N-2-cyclohexylcarbamoylethyl-N-cyclohexylamine HCl, whose detailed data were summarized in Table III. IR ν_{max}^{KBr} cm^{-1}: 3280, 3195 (NH): 1641 (CO). The filtrate was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue gave a samll amount of bis(2-cyclohexyl-

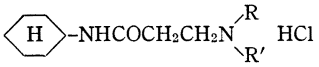
carbamoylethyl)disulfide melting at 171°, which was identified with an authentic sample by mixed melting point determination and comparison of the IR spectrum.

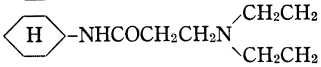
c) With Aqueous Benzylamine: A solution of 3.1 g (0.01 mole) of sodium 2-cyclohexylcarbamoylethylthiosulfate and 2.1 g (0.02 mole) of benzylamine in 30 ml of H_2O was heated for 13 hr under reflux. The solution was treated by the same procedure as described above to give N-2-cyclohexylcarbamoylethyl-N-benzylamine, whose detailed data were illustrated in Table III. IR ν_{max}^{KBr} cm^{-1}: 3295, 3192 (NH); 1646 (CO). A small amount of bis(2-cyclohexylcarbamoylethyl)disulfide melting at 171° was also isolated.

d) With Aqueous Pyrrolidine: A solution of 3.1 g (0.01 mole) of sodium 2-cyclohexylcarbamoylethylthiosulfide and 1.4 g (0.02 mole) of pyrrolidine in 20 ml of H_2O was heated for 14.5 hr under reflux. After cooling, benzene was added with stirring to the solution and the precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.1 g (3%) of colorless plates of bis(2-cyclohexylcarbamoylethyl)-disulfide melting at 171° which was identified with an authentic sample.

e) With Aqueous Piperazine: A solution of 3.1 g (0.01 mole) of sodium 2-cyclohexylcarbamoylethylthiosulfate and 2.0 g of piperazine hexahydrate was refluxed for 19.5 hr. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give N,N-bis(2-cyclohexylcarbamoylethyl)piperazine, whose details were summarized in Table III. IR ν_{max}^{KBr} cm^{-1}: 3290, 1640 (CONH).

Table III. N-2-Cyclohexylcarbamoylethyl-N-alkylamine Hydrochloride



R	R′	Yield (%)	mp (°C)	Formula	Analysis % Calcd. C	H	N	Found C	H	N
	H	52	244	$C_{15}H_{29}ON_2Cl$	62.37	10.12	9.70	61.96	10.10	9.55
	H	66	250	$C_{16}H_{25}ON_2Cl$	64.71	8.49	9.44	64.63	8.42	9.94
		18	246 (free)	$C_{22}H_{40}O_2N_4$	67.31	10.27	14.27	66.95	10.00	14.21

N-(2-Benzoylethyl)piperidine Hydrochloride (X)——To a solution of 2.7 g (0.01 mole) of sodium 2-benzoylethylthiosulfate in 20 ml of H_2O was added with stirring 1.8 g (0.02 mole) of piperidine at room temperature. After stirring for additional 30 min, the solution was extracted with EtOAc. The extract was repeatedly washed with H_2O and stirred with a small amount of conc. HCl. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 3.3 g (90%) of colorless plates melting at 190—195°. *Anal.* Calcd. for $C_{14}H_{20}$ ONCl:C, 66.25; H, 7.95; N, 5.52. Found: C, 66.16; H, 8.03; N, 5.06. IR ν_{max}^{KBr} cm^{-1}: 1681 (CO).

N,N-Bis(2-benzoylethyl)piperazine——A solution of 2.7 g (0.01 mole) of sodium 2-benzoylethylthiosulfate and 2.0 g of piperazine hexahydrate was heated for 1 hr under reflux. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give 0.73 g (30%) of pale yellow needles melting at 140—145°. *Anal.* Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.39; H, 7.48; N, 7.99. Found: C, 75.12; H, 7.23; N, 7.84. IR ν_{max}^{KBr} cm^{-1}: 1674 (CO).

Reaction of Bis(2-phenylcarbamoylethyl) Disulfide (VI) with Cyclohexylamine——A mixture of 1.8 g of bis-2-phenylcarbamoylethyl disulfide, 1.0 g of cyclohexylamine and 10 ml of H_2O was heated for 5 hr under reflux. After cooling, the mixture was extracted with EtOAc and the extract was neutralized with dil. HCl, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Recrystallization of the residue from EtOH gave 0.5 g (30%) of colorless plates of bis(2-phenylcarbamoylethyl)sulfide melting at 163.5°, which was identified with an authentic sample by mixed melting point determination and comparison of the IR spectrum.

Reaction of Bis(2-cyclohexylcarbamoylethyl) Disulfide (VIII) with Cyclohexylamine——A mixture of 1.8 g of bis-2-cyclohexylcarbamoylethyl disulfide, 1.0 g of cyclohexylamine and 20 ml of H_2O was heated for 5 hr under reflux. The mixture was treated by the same procedure as described above to give 0.3 g (19%) of colorless plates of bis(2-cyclohexylcarbamoylethyl) sulfide melting at 185°, which was identified with an authentic sample by mixed melting point determination and comparison of the IR spectrum. *Anal.* Calcd. for $C_{18}H_{32}O_2N_2S$: C, 63.49; H, 9.48; N, 8.23. Found: C, 63.10; H, 9.65; N, 8.17. IR ν_{max}^{KBr} cm^{-1}: 3290, 1638 (CONH).

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