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# The Conversion of α-Carbonylmethylthiosulfates into Thiocarboxamides

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The reaction of sodium phenacylthiosulfate with amine was found to form acetophenone as by-product and elucidated to proceed through the intermediate formation of diphenacyl disulfide. The reaction between sodium ethoxycarbonylmethylthiosulfate with cyclohexylamine was also confirmed to proceed analogously through the formation of diethoxycarbonylmethyl disulfide, but not sodium cyclohexylcarbamoylmethylthiosulfate and dicyclohexylcarbamoylmethyl disulfide, to give N,N′-dicyclohexylthiooxamide and cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate. Furthermore, the salt was proved to be formed *via* the intermediate ethoxycarbonyl-N-cyclohexylthiocarboxamide, but not by hydrolysis of N,N′-dicyclohexylthiooxamide.

In an earlier paper,[2] it was shown that thiocarboxamides were formed when sodium ethoxycarbonylmethylthiosulfate and sodium phenacylthiosulfate were heated with amines under reflux. Some further examples, various developments and extensions of this reaction are now reported.

The more detailed examination for the reaction of sodium phenacylthiosulfate (I) with amines, such as cyclohexylamine and morpholine, was carried out. When heated to boiling in anhydrous and aqueous cyclohexylamine, benzoyl-N-cyclohexylthiocarboxamide (II) and 1,4-diphenyl-1,4-butanedione (III) were obtained, as described in the previous paper.[2] In both cases, acetophenone (IV) was found to form and confirmed by the conversion into the phenylhydrazone. Analogously heating in anhydrous and aqueous morpholine gave acetophenone (IV) together with benzoyl-N-(3-oxapentamethylene)thiocarboxamide (V), though any 1,4-diphenyl-1,4-butanedione (III) was not isolated.

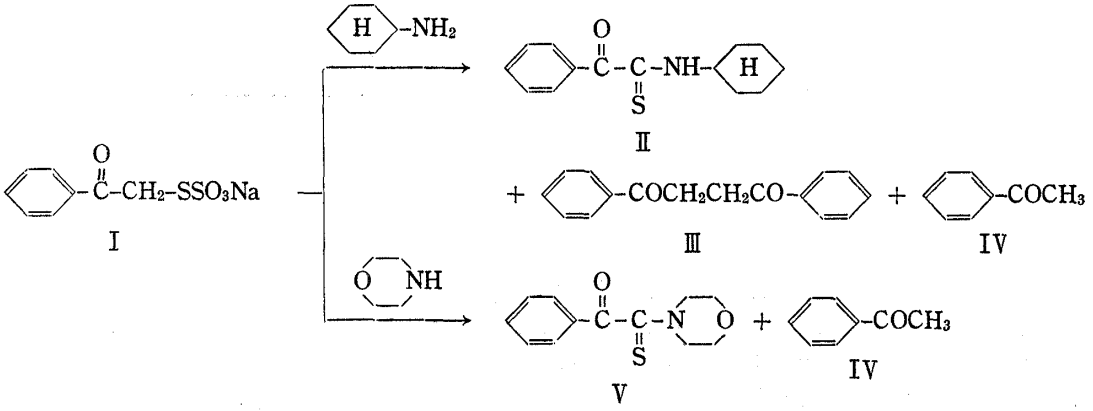

Chart 1

These reactions were also pursued by means of thin-layer chromatograph (TLC) and diphenacyl disulfide (VI) formed in the course of the reaction was observed to disappear gradually. This suggests that the reaction would proceed through the intermediate for-

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

2) S. Hayashi, M. Furukawa, Yoko Fujino, and Kenzo Shiraishi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2247 (1971).

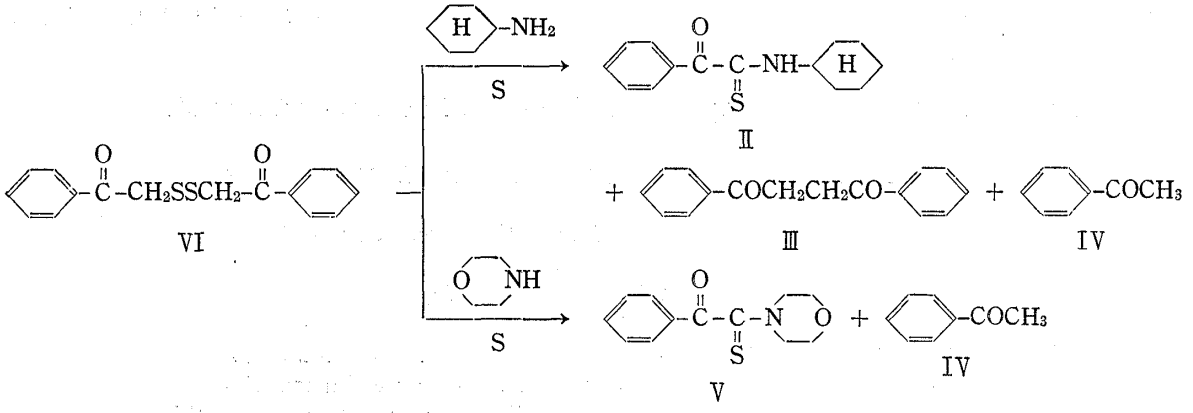

Chart 2

mation of diphenacyl disulfide (VI). In order to elucidate this assumption, diphenacyl disulfide (VI) which prepared by alkaline decomposition of sodium phenacylthiosulfate[3] was allowed to react with cyclohexylamine and morpholine in the presence of added sulfur under the refluxing condition. When heated to boiling in cyclohexylamine, benzoyl-N-cyclohexylthiocarboxamide (II) and 1,4-diphenyl-1,4-butanedione (III) were obtained in 43% and 17% yields, respectively, together with acetophenone (IV). Heating in morpholine under similar conditions also gave a 51.0% yield of benzoyl-N-(3-oxapentamethylene)thiocarboxamide (V) and acetophenone (IV), no trace of any 1,4-diphenyl-1,4-butanedione (III) being isolated. These results almost paralleled the reaction between sodium phenacylthiosulfate (I) and amines. It would be evident that the reaction of sodium phenacylthiosulfate (I) with amine proceeds through the formation of diphenacyl disulfide intermediate (VI).

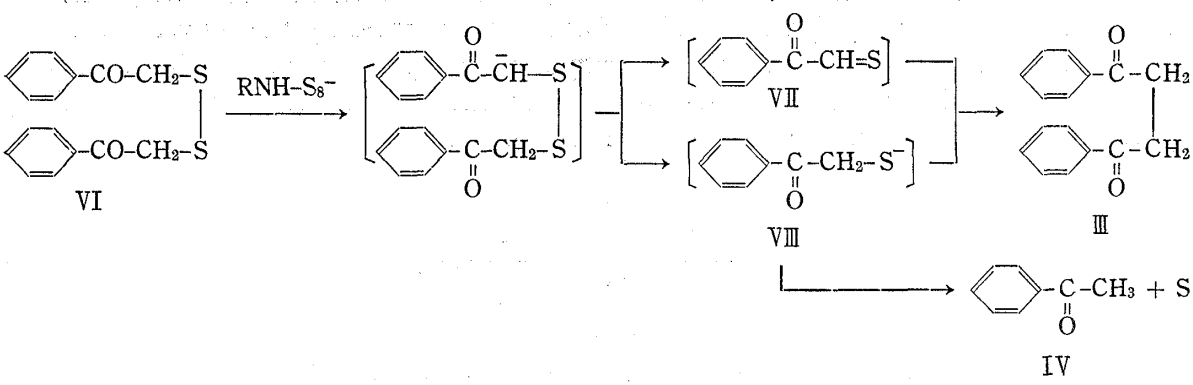

Chart 3

In connection of the formation of 1,4-diphenyl-1,4-butanedione (III) and acetophenone (IV), the analogous decomposition of diphenacyl disulfide (VI) with potassium ethoxide has been reported by Hiskey.[4] The alkaline decomposition is presumed to be initiated by α-elimination of the methylene hydrogen in diphenacyl disulfide (VI), followed by cleavage of the S-S bond to form benzoylthioaldehyde (VII) and phenacylthio anion (VIII), which by decomposition or recomposition give 1,4-diphenyl-1,4-butanedione (III) and acetophenone (IV). Such a mechanism would be also possible in the reaction between diphenacyl disulfide (VI) and amine. The effect of amine on the α-elimination might be enhanced by the formation of aminosulfen anion[5] from amine and sulfur.

3) T.S. Price and D.F. Twiss, *J. Chem. Soc.*, **1908**, 1648.
4) R.G. Hiskey, J.A. Kepler, and B.D. Thomas, *J. Org. Chem. Soc.*, **29**, 3686 (1964).
5) R.E. Davis and H.F. Nakshbendi, *J. Am. Chem. Soc.*, **84**, 2085 (1962).

We have already elucidated that the reaction of sodium benzylthiosulfate with amine proceeds through the intermediate formation of phenylmethanesulfenamide to give dibenzyl disulfide.[6] Asiger[7] has also reported that phenacylsulfenmorpholide which prepared by the reaction of diphenacyl disulfide (VI) with chlorine and then with morpholine is converted by standing overnight in morpholine into benzoyl-N-(3-oxapentamethylene)thiocarboxamide (II) and diphenacyl disulfide (VI). By these facts, it is presumed that the reaction of sodium phenacylthiosulfate (I) with amine would be initiated by the nucleophilic attack of the amine to the sulfenyl sulfur of S-$SO_3$ group at the first step to form phenacylsulfenamide, followed by the conversion into diphenacyl disulfide (VI) to give benzoyl-N-substituted thiocarboxamide (II, V), 1,4-diphenyl-1,4-butanedione (III) and acetophenone (IV) at the final step. Probably acetophenone would further undergo the Willgerodt reaction[8,9] to give the thiocarboxamide, though it could not be isolated.

It has been reported by Milligan[10] that sodium ethoxycarbonylmethylthiosulfate (IX) reacts with cyclohexylamine by heating for 5 min under reflux to yield N,N′-dicyclohexylthiooxamide (XI) in 26% yield and the reaction proceeds through the formation of sodium cyclohexylcarbamoylmethylthiosulfate (X), without any special reason.

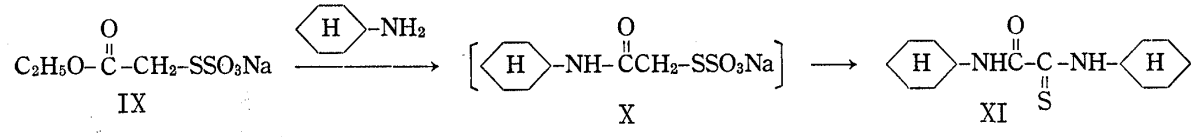


Chart 4

On the other hand, we have found that heating of sodium ethoxycarbonylmethylthiosulfate (IX) in aqueous cyclohexylamine for 15 min under reflux gives not only 67% of N,N′-dicyclohexylthiooxamide (XI) but also 17% of cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (XII).[6] If the reaction proceeds through the formation of sodium cyclohexylcarbamoylmethylthiosulfate (X), dicyclohexylcarbamoylmethyl disulfide (XIII) would be predictable as the intermediate. In fact, when sodium cyclohexylcarbamoylmethylthiosulfate (X) was heated in aqueous cyclohexylamine under similar conditions, dicyclohexylcarbamoylmethyl disulfide (XIII) was obtained in 29% yield, together with a 70% yield of N,N′-dicyclohexylthiooxamide (XI). However, the pursuation of the reaction of sodium ethoxycarbonylmethylthiosulfate (IX) with aqueous cyclohexylamine detected only diethoxycarbonylmethyl disulfide intermediate (XIV) in the course of the reaction, no trace of any sodium cyclohexylcarbamoylmethylthiosulfate (X) and dicyclohexylcarbamoylmethyl disulfide (XIII) being observed. Furthermore, heating of dicyclohexylcarbamoylmethyl disulfide (XIII) with cyclohexylamine under similar conditions gave only N,N′-dicyclohexylthiooxamide (XI), without formation of any cyclohexylaminothiocarbonylcarboxylate (XII). These results suggest that the intermediate would be ethoxycarbonyl-N-cyclohexylthiocarboxamide (XV), but not sodium cyclohexylcarbamoylmethylthiosulfate (X).

As expected, hydrolysis of N,N′-dicyclohexylthiooxamide to cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (XII) was not carried out with aqueous cyclohexylamine under similar conditions. On the contrary, when ethoxycarbonyl-N-(3-oxapentamethylene)-thiocarboxamide (XVI), which readily obtained by heating sodium ethoxycarbonylmethylthiosulfate (IX) with morpholine, was heated in aqueous cyclohexylamine for 15 min under reflux, cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (XII) was obtained in 25% yield, together with 8% of N,N′-dicyclohexylthiooxamide (XI).

6) M. Furukawa, K. Shiraishi, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), in Press.
7) F. Asinger, W. Schafer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem.*, **75**, 1050 (1963).
8) K. Kindler, *Ann.*, **431**, 187 (1923).
9) M. Carmack and M.A. Spielman, *Org. React.*, **3**, 83 (1946).
10) B. Milligan and J.M. Swan, *J. Chem. Soc.*, **1959**, 2969; **1961**, 1194.

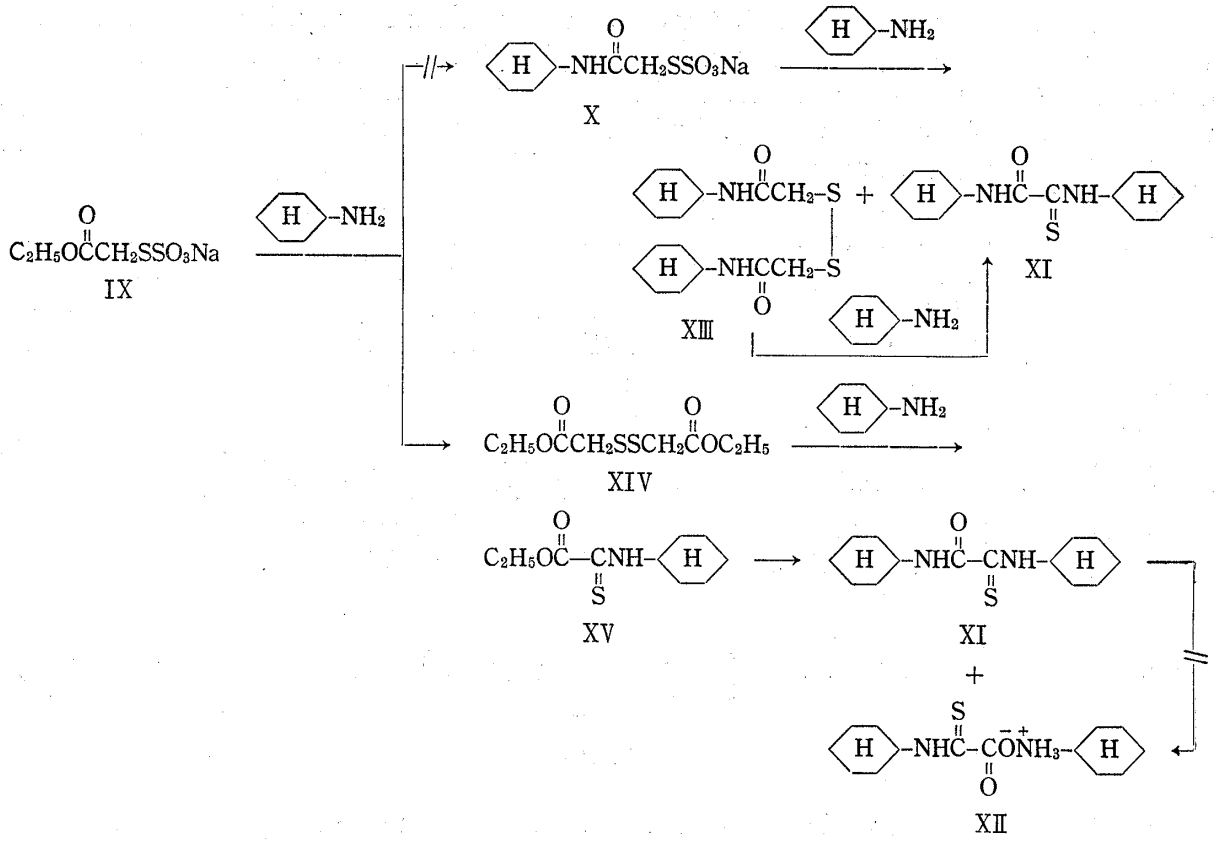

Chart 5

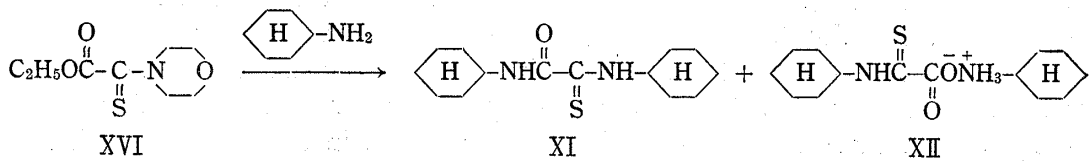

Chart 6

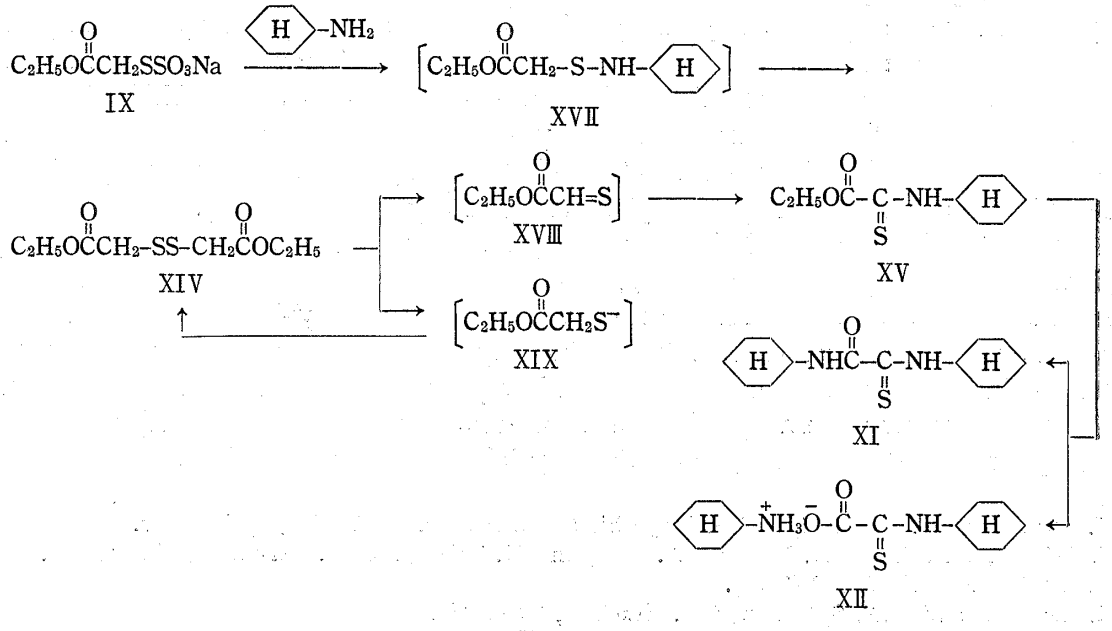

Chart 7

By all of the results described above, it is presumed that the reaction of sodium ethoxycarbonylmethylthiosulfate (IX) with cyclohexylamine would be initiated by nucleophilic attack of cyclohexylamine to the sulfen sulfur to form ethoxycarbonylmethanesulfenamide (XVII), followed by the conversion into the disulfide (XIV), which by α-elimination of the methylene hydrogen results in cleavage of S-S bond and forms ethoxycarbonylthioaldehyde (XVIII) and ethoxycarbonylmethylthio anion (XIX). The thioaldehyde (XVIII) would undergo Kindler reaction[8] with further cyclohexylamine to form ethoxycarbonyl-N-cyclohexylthiocarboxamide (XV), followed by the conversion into N,N'-dicyclohexylthiooxamide (XI) and by the hydrolysis to give cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate (XV).

## Experimental

**Reaction of Sodium Phenacylthiosulfate with Cyclohexylamine**——a) In Anhydrous Cyclohexylamine: A mixture of 5.4 g of sodium phenacylthiosulfate and 30 ml of cyclohexylamine was heated for 15 min under reflux. After cooling, the mixture was acidified with dil. HCl and yellow precipitates deposited were collected by filtration. To the solution of the precipitates in EtOH was added a small amount of dil. HCl and the solution was refluxed for 30 min. After removal of EtOH by evaporation, the residue was extracted with ether and extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated. The residue was recrystallized from EtOH to give 2.0 g (42.6%) of yellow plates of benzoyl-N-cyclohexylthiocarboxamide melting at 129.5—130°. To the filtrate was added a small amount of phenylhydrazine and the solution was stood overnight. Precipitates deposited were recrystallized from EtOH to give acetophenone phenylhydrazone melting at 105—106°, which was identified by mixed melting point determination and infrared (IR) comparison with an authentic sample.[11] *Anal.* Calcd. for $C_{14}H_{16}ONS$: C, 68.26; H, 6.55; N, 5.68. Found: C, 68.19; H, 6.93; N, 5.73. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1662 (C=O), 1066 (C=S).

The filtrate separated from the yellow precipitates was extracted with ether and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to dyness. The residue was extracted with EtOH and the precipitates deposited on cooling were recrystallized from benzene–pet. ether to give 0.8 g (16.7%) of colorless needles of 1,4-diphenyl-1,4-butanedione melting at 145—145.5°. *Anal.* Calcd. for $C_{16}H_{14}O_2$: C, 80.62; H, 5.92. Found: C, 80.72; H, 5.88. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1678 (C=O). NMR ($CDCl_3$) $\tau$: 5.60 (4H, singlet, $-\overset{O}{\overset{\|}{C}}-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-$), 2.05—2.97 (10 H, multiplet, aromatic hydrogen).

b) In Aqueous Cyclohexylamine: A solution of 5.4 g of sodium phenacylthiosulfate and 5.9 g of cyclohexylamine in 30 ml of $H_2O$ was refluxed for 15 min. By the same procedure as described above, 2.0 g (42.6%) of benzoyl-N-cyclohexylthiocarboxamide and 0.4 g (8.4%) of 1,4-diphenyl-1,4-butanedione were obtained. Acetophenone was also detected by conversion into the phenylhydrazone.

**Reaction of Sodium Phenacylthiosulfate with Morpholine**——a) In Anhydrous Morpholine: A mixture of 5.4 g of sodium phenacylthiosulfate and 30 ml of morpholine was heated for 15 min. under reflux. After cooling, the mixture was neutrallized with dil. HCl and extracted with AcOEt. The extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated under reduced pressure. The residue was recrystallized from EtOH to give 2.9 g (61.7%) of yellow plates of benzoyl-N-(3-oxapentamethylene)thiocarboxamide melting at 115.5—116.5°. *Anal.* Calcd. for $C_{12}H_{13}O_2NS$: C, 61.09; H, 5.55; N, 5.94. Found: C, 61.46; H, 5.58; N, 5.94. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1658 (C=O), 1029 (C=S). To the filtrate was added a small amount of phenylhydrazine and the solution was stood overnight. Precipitates deposited were recrystallized from EtOH to give acetophenone phenylhydrazone[11] melting at 105—106°.

b) In Aqueous Morpholine: A solution of 5.4 g of sodium phenacylthiosulfate and 5.2 g of morpholine in 30 ml of $H_2O$ was refluxed for 15 min. By the same procedure as described above, 2.4 g (51.1%) of benzoyl-N-(3-oxapentamethylene)thiocarboxamide melting at 115.5—116,5° was obtained. Acetophenone was also detected by conversion into the phenylhydrazone.

**Reaction of Diphenacyl Disulfide with Amines**——a) With Cyclohexylamine: A mixture of 3.0 g of diphenacyl disulfide, 0.32 g of sulfur and 20 ml of cyclohexylamine was heated for 15 min under reflux. After cooling, the mixture was acidified with dil. HCl and the precipitates deposited were collected by filtration. The precipitates were dissolved in EtOH and the solution added a small amount of dil. HCl was refluxed for 30 min. After removal of EtOH by evaporation, the residue was extracted with ether and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated. The residue was recrystallized from EtOH to give 2.0 g (42.6%) of yellow plates of benzoyl-N-cyclohexylthiocarboxamide melting at 129.5—130°, which was identified with an authentic sample. To the recrystallization filtrate was added a small

11) R.L. Shriner, W.C. Ashley, and E. Welch, *Org. Synth.*, **22**, 99 (1947).

amount of phenylhydrazine and the solution was stood overngiht. The precipitates deposited were collected by filtration and recrystallized from EtOH to give acetophenone phenylhydrazone melting at 105—106°, which was identified with an authentic sample.

The filtrate separated from the yellow precipitates was extracted with ether and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to dryness. The residue was extracted with EtOH on heating and the precipitates deposited on cooling were recrystallized from benzene–pet. ether to give 0.8 g (16.7%) of colorless needles of 1,4-diphenyl-1,4-butanedione melting at 145—145.5°, which was identified with an authentic sample.

b) With Morpholine: A mixture of 3.0 g of diphenacyl disulfide, 0.32 g of sulfur and 20 ml of morpholine was heated for 15 min. After cooling, the mixture was neutralized with dil. HCl and extracted with AcOEt. The extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated under reduced pressure. Recrystallization of the residue from EtOH gave 2.4 g (51.0%) of benzoyl-N-(3-oxapentamethylene)-thiocarboxamide melting at 115—116°, which was identified with an authentic sample. From the recrystallization filtrate, acetophenone was detected by conversion into the phenylhydrazone.

**Reaction of Sodium Cyclohexylcarbamoylmethylthiosulfate with Cyclohexylamine**——A solution of 2.9 g of sodium cyclohexylcarbamoylmethylthiosulfate and 3.0 g of cyclohexylamine in 30 ml of $H_2O$ was heated for 15 min under reflux. After cooling, the mixture was extracted with AcOEt and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and concentrated under reduced pressure. The concentrated solution was chromatographed on silica gel. Development with benzene and then with EtOH gave 1.9 g (70%) of N,N′-dicyclohexylthiooxamide melting at 167—168° after recrystallization from EtOH and 1.0 g (29%) of dicyclohexylcarbamoylmethyl disulfide melting at 165—166° after recrystallization from EtOH. These compounds were identified by mixed melting point determination and IR comparison with authentic samples.

**Reaction of Dicyclohexylcarbamoylmethyl Disulfide with Cyclohexylamine**——A mixture of 1.7 g of dicyclohexylcarbamoylmethyl disulfide, 1.5 g of cyclohexylamine and 0.16 g of sulfur in 20 ml of $H_2O$ was heated for 15 min under reflux. After cooling, the mixture was extracted with AcOEt and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and concentrated under reduced pressure. The concentrated solution was chromatographed on silica gel. Development with benzene gave N,N′-dicyclohexylthiooxamide which was identified with an authentic sample.

**Reaction of Diethoxycarbonylmethyl Disulfide with Cyclohexylamine**——A mixture of 2.4 g of diethoxycarbonylmethyl disulfide and 0.32 g of sulfur in 30 ml of cyclohexylamine was heated for 15 min under reflux. After cooling, the mixture was poured into a small amount of $H_2O$ and extracted with ether. The precipitates deposited on cooling from water layer were collected and recrystallized from EtOH to give 0.3 g (5%) of cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate melting at 184—185°, which was identified with an authentic sample. The extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to dryness. The residue was recrystallized from EtOH to give 1.6 g (30.0%) of N,N′-dicyclohexylthiooxamide melting at 167—168°, which was identified with an authentic sample.

**Reaction of Diethoxycarbonylmethyl Disulfide with Morpholine**——A mixture of 2.4 g of diethoxycarbonylmethyl disulfide and 0.32 g of sulfur in 20 ml of morpholine was heated for 15 min under reflux. After cooling, the precipitates deposited were collected by filtration and recrystallized from EtOH to give 1.3 g (25%) of morpholinium morpholinothiocarbonylcarboxylate melting at 181—181.5°. *Anal.* Calcd. for $C_{10}H_{18}O_4N_2S$: C, 45.79; H, 6.92; N, 10.68. Found: C, 46.15; H, 6.80; N, 10.78. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1630 (C=O), 1028 (C=S).

The filtrate was neutralized with dil. HCl and extracted with ether and the extracts were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated. The residue was distilled under reduced pressure to give yellow liquid of ethoxycarbonyl-N-(3-oxapentamethylene)thiocarboxamide boiling at 150—151°/3 mm, which was identified with an authentic sample. IR $\nu_{max}^{film}$ $cm^{-1}$: 1735 ($CO_2C_2H_5$), 1064 (C=S).

**Reaction of Ethoxycarbonyl-N-(3-oxapentamethylene)thiocarboxamide with Cyclohexylamine**——A solution of 1.0 g of ethoxycarbonyl-N-(3-oxapentamethylene)thiocarboxamide and 1.0 g of cyclohexylamine in 30 ml of $H_2O$ was heated for 15 min under reflux. After cooling, the precipitates deposited were collected by filtration and extracted with benzene. The unsoluble crystals were collected by filtration and recrystallized from EtOH to give 0.35 g (25%) of cyclohexylammonium cyclohexylaminothiocarbonylcarboxylate melting at 184—185°, which was identified with an authentic sample. The benzene extract was evaporated and the residue was recrystallized from EtOH to give 0.1 g (8%) of N,N′-dicyclohexylthiooxamide melting at 166—167°, which was identified with an authentic sample.