594. *The Conversion of Carbamoylmethyl Thiolsulphates into Thio-oxamides; a New Variant of the Willgerodt–Kindler Reaction.*

By BRIAN MILLIGAN and J. M. SWAN.

Substituted thio-oxamides (II) are obtained in 21—96% yield by heating carbamoylmethyl thiolsulphates (I) with a primary or secondary amine. A mechanism proposed for the reaction invokes formation of a thioaldehyde and then of either an anil or a substituted diaminomethane from which the product is derived by a Willgerodt–Kindler reaction.

Nomenclature.—Symmetrical and unsymmetrical disubstituted monothio-oxamides (II) are described here for the first time. The Editor has suggested that we name them as derivatives of thio-oxamide using prefixes N^{O}- and N^{S}- to indicate the nitrogen atoms next to CO and CS respectively (cf. the use of N^{1} and N^{4} for sulpha drugs). Hence (IIa) (R = Ph, R′ = C_6H_{11}) is N^{S}-cyclohexyl-N^{O}-phenyl(thio-oxamide), the parentheses being necessary since " phenylthio " would denote PhS. When one of the nitrogen atoms is involved in ring formation this method is abandoned and a rule made that Ph·NH·CO·CS– is named *N*-phenyl-α-thio-oxamoyl. Thus the product obtained by heating sodium phenylcarbamoylmethyl thiolsulphate (I; R = Ph) with morpholine, namely, (IIb; R = Ph, R_2'' = –CH_2·CH_2·O·CH_2·CH_2–), is named 4-(phenyl-α-thio-oxamoyl)-morpholine.

In a study of azo-dyes and other compounds containing thiolsulphate groups, we have found that various carbamoylmethyl thiolsulphates (I) react with primary or secondary amines when heated, to give substituted thio-oxamides (II):

$$\underset{\text{(I)}}{R\cdot NH\cdot CO\cdot CH_2\cdot S\cdot SO_3Na} \xrightarrow{R'NH_2 \text{ or } R_2''NH} \underset{\text{(IIa)}}{R\cdot NH\cdot CO\cdot CS\cdot NHR'} \text{ or } \underset{\text{(IIb)}}{R\cdot NH\cdot CO\cdot CS\cdot NR_2''}$$

In compounds (I) the group R was hydrogen, phenyl, cyclohexyl, 4-phenylazophenyl, or 1-phenylazo-2-naphthyl, and the amines used were cyclohexylamine, aniline, morpholine, and allylamine. The reaction was carried out most readily by boiling the sodium alkyl thiolsulphate (Bunte salt) with an excess of the anhydrous amine; reaction times varied between three and thirty minutes. N^{S}-Cyclohexyl-N^{O}-phenyl(thio-oxamide) (IIa; R = Ph, R′ = C_6H_{11}) was also obtained by fusion of cyclohexylammonium phenylcarbamoylmethyl thiolsulphate. It is noteworthy that with cyclohexylamine good yields of thio-oxamides were obtained in some cases when the reaction was carried out in aqueous solution at 100°. For example, the amides (IIa; R = Ph·N_2·C_6H_4 and Ph·N_2·$C_{10}H_6$, R′ = C_6H_{11}) were obtained in this manner from the salts (I) in 86% and 96% yield respectively. The salt (I; R = Ph·N_2·C_6H_4) failed to react with liquid ammonia, and with boiling aqueous ammonia gave di-(*p*-phenylazophenylcarbamoylmethyl) disulphide. Reaction of the analogous salt (I; R = Ph·N_2·$C_{10}H_6$) with boiling aqueous ammonia also gave a disulphide; and sodium cyclohexylcarbamoylmethyl thiolsulphate (I; R = C_6H_{11}) gave the corresponding disulphide and a small amount of *N*-cyclohexyloxamide. The last product is probably derived from an intermediate thio-oxamide by desulphurisation in the ammoniacal solution.[1]

Although sodium phenylcarbamoylmethyl thiolsulphate (I; R = Ph), when heated to boiling in aqueous cyclohexylamine, gave the thio-oxamide (IIa; R = Ph, R′ = C_6H_{11}) in 55% yield, it failed to react in aqueous aniline, and in aqueous morpholine gave a high yield of di(phenylcarbamoylmethyl) disulphide. Heating sodium benzyl thiolsulphate in aqueous or anhydrous amines gave dibenzyl disulphide, no trace of any thiobenzamide being isolated. The reaction also failed when a second methylene group was introduced between the carbamoyl and the thiolsulphate radical. Thus, after sodium 2-(phenylcarbamoyl)-

[1] Bernthsen, *Annalen*, 1877, **184**, 290.

ethyl thiolsulphate had been heated in cyclohexylamine or morpholine at 135° for 10 min., unchanged Bunte salt (70%) and di-(2-phenylcarbamoylethyl) disulphide (20%) were isolated.

By heating thiolsulphates with amines we hoped initially to synthesise sulphenamides according to the equation $R{\cdot}S{\cdot}SO_3Na + R'{\cdot}NH_2 \longrightarrow RS{\cdot}NHR' + NaHSO_3$. Such sulphenamides derived from (I) would be hardly distinguishable by analysis (two hydrogen atoms) from the thio-oxamide (II). However, oxidation of the new compounds with peracetic acid caused desulphurisation with formation of oxamides, whereas sulphenamides would have been converted into sulphonamides without loss of sulphur. The oxamides were identified by analysis and in some cases by comparison of melting points with recorded values. It was also necessary to establish that the thioamide group was derived from the $\cdot CH_2{\cdot}S{\cdot}SO_3^-$ unit, and not from the carbamoyl group, with simultaneous conversion of $\cdot CH_2{\cdot}S{\cdot}SO_3^-$ into $\cdot CO{\cdot}NRR'$. Heating sodium carbamoylmethyl thiolsulphate (I; R = H) with aniline gave the expected N^S-phenyl(thio-oxamide) (IIa; R = H, R′ = Ph) and not the isomeric N^O-phenyl (thiooxamide) (IIa; R = Ph, R′ = H). Identity was established by m. p. and by oxidation with ferricyanide to benzothiazole-2-carboxyamide.[2]

The formation of thio-oxamides by reaction of Bunte salts with amines has an obvious similarity to the Kindler reaction [3-5] which, developed as a variant of the Willgerodt reaction,[4,5] consists in the conversion of aromatic aldehydes and aryl ketones into aryl alkyl thioamides or ω-aryl-aliphatic thioamides by anhydrous amines and sulphur at high temperatures. The appropriate aldimine or ketimine (Schiff's bases) can be used in place of the mixture of carbonyl compound and amine,[3,6] and derivatives of acids are also formed by heating ketoximes, azines, hydrazones, etc., with sulphur.[7] Furthermore, the phenylmethylenediamine derived from benzaldehyde and morpholine yields benzothiomorpholide when heated with sulphur; [8] benzylamine and sulphur give *N*-benzylthiobenzamide; [9] diethylamine and sulphur give *N*-ethylthioacetamide; [10] and dibenzyl disulphide with morpholine and sulphur yields benzothiomorpholide.[8] We have shown that heating sodium benzyl thiolsulphate with morpholine and sulphur also gives benzothiomorpholide, whereas in the absence of added sulphur only dibenzyl disulphide is obtained. In our reaction of carbamoylmethyl thiolsulphate with amines, the sulphur required by the Kindler reaction must be made available from the thiolsulphate radical by some process peculiar to this class of Bunte salt.

The following mechanism is proposed. As the first step we envisage nucleophilic elimination of sulphite ion from the " inner " sulphur atom of the $\cdot S{\cdot}SO_3^-$ group, as in nucleophilic elimination of groups such as halogen, $\cdot NR_3^+$ and $\cdot SR_2^+$ from carbon. Thus if B: is a base, we write:

$$B: + -\overset{\beta}{C}H_2-\overset{\alpha}{S}-SO_3^- \longrightarrow BH^+ + -CH{=}S + SO_3^{2-}$$

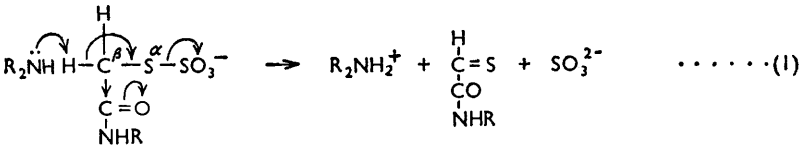
$$\text{Cf.}\quad B: + -\overset{\beta}{C}H_2-\overset{\alpha}{C}H_2-X \longrightarrow BH^+ + -CH{=}CH_2 + X^-$$

As with the olefin-forming *E*2 reaction,[11] this elimination of sulphite should be facilitated by electron-attracting groups on the β-carbon atom. This may explain the apparent necessity for the carbamoyl group at this position, so that the synchronous

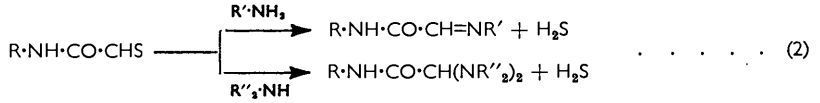
[2] Reissert, *Ber.*, 1904, **37**, 3708.
[3] Kindler, *Annalen*, 1923, **431**, 187; *Arch. Pharm.*, 1927, **265**, 389.
[4] Carmack and Spielman, *Organic Reactions*, 1946, **3**, 83.
[5] McOmie, *Ann. Reports*, 1948, **45**, 210.
[6] Böttcher and Bauer, *Annalen*, 1950, **568**, 218.
[7] Stanck, *Coll. Czech. Chem. Comm.*, 1947, **12**, 671.
[8] King and McMillan, *J. Amer. Chem. Soc.*, 1948, **70**, 4143.
[9] McMillan, *ibid.*, p. 868.
[10] Moore and Saville, *J.*, 1954, 2083.
[11] Ingold, " Structure and Mechanism in Organic Chemistry," Bell & Sons Ltd., London, 1953, Chap. VIII.

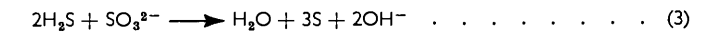
displacement can be pictured as in step 1. The thioaldehyde formed then reacts with further amine to give hydrogen sulphide and either an anil or a substituted diaminomethane (step 2); the hydrogen sulphide liberated reacts with sulphite to form sulphur (step 3).

Step 3 is justified by the observation that a solution of sulphur dioxide or sodium

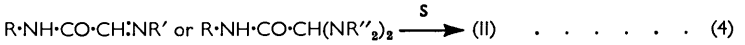


hydrogen sulphite in boiling cyclohexylamine reacted with hydrogen sulphide to give a dark mixture containing free sulphur. When this mixture was poured into water, large amounts of thiosulphate derived from sulphur and unchanged sulphite were detected.

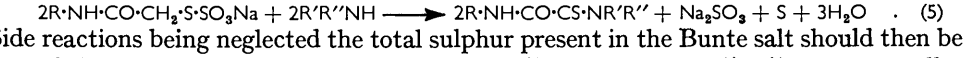




A mechanism has been suggested [8] for the reaction of sulphur with anils [3,6] and methylenediamines,[8] by analogy with which we write for the final step:

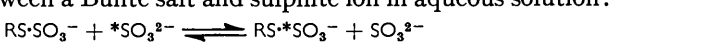


Summation of steps 1—4 gives:



Side reactions being neglected the total sulphur present in the Bunte salt should then be accounted for as thioamide (50%), sulphite (25%), and sulphur (25%), or as smaller amounts of sulphite and sulphur with corresponding amounts of thiosulphate. In fact, when sodium phenylcarbamoylmethyl thiolsulphate was supended in cyclohexylamine, heated under reflux for 5 minutes, and then poured into water, the total sulphur was accounted for as thio-oxamide (42·3%), sulphide (1·3%), sulphite (17·6%), and thiosulphate (31·6%).

It follows from the above mechanism that the sulphur in the thio-oxamide arises from *both* of the sulphur atoms initially present in the Bunte salt. A sample of sodium phenylcarbamoylmethyl thiolsulphate labelled with ^{35}S in the SO_3^- group was prepared by the exchange which occurs between a Bunte salt and sulphite ion in aqueous solution: [12]



When labelled material was heated in cyclohexylamine, radioactivity was found both in the inorganic salts and in the thio-oxamide. While not proving our mechanism, this appears to exclude * any process involving a continuous attachment of the " inner " sulphur atom of the thiolsulphate group to the methylene carbon atom, at least for the reaction carried out in anhydrous medium.

If step 1 is indeed the first step of the reaction it constitutes a novel kind of elimination, not only because the electron shells which remain complete throughout the co-operative displacement are shared by a carbon–sulphur bond rather than a carbon–carbon pair, but

* *Added, June 30th,* 1959.—It is possible that the radioactive label could be introduced into the thio-oxamide by an exchange process, so that postulation of carbon–sulphur fission (step 1) would no longer be necessary. However, when a mixture of N^S-cyclohexyl-N^O-phenyl[^{35}S](thio-oxamide) and sodium carbamoylmethyl thiolsulphate was heated in cyclohexylamine the original thio-oxamide was found to have retained all its activity, whereas the newly synthesised N^S-cyclohexyl(thio-oxamide) was non-radioactive. Similarly, when sodium phenylcarbamoylmethyl thiolsulphate was heated in cyclohexylamine containing potassium[^{35}S]sulphide and sulphur, the thio-oxamide formed was radioactive, whereas when this same (unlabelled) thio-oxamide was heated in the cyclohexylamine–sulphur mixture, virtually no exchange occurred.

[12] Fava and Pajaro, *J. Amer. Chem. Soc.*, 1956, **78**, 5203; Swan, *Nature*, 1957, **180**, 643; Fava and Iliceto, *J. Amer. Chem. Soc.*, 1958, **80**, 3478.

also because the ejected sulphite anion already holds a formal negative charge before reaction. In most examples of the olefin-forming elimination,[11] the group displaced is initially either formally positive or neutral. Nucleophilic displacement from sulphur has also been invoked by Rosenthal and Oster [13] to explain the alkaline decomposition of certain disulphides (step 6), although in other cases, particularly with cystine derivatives, the disulphide breakdown appears to be the consequence of a more conventional olefin-forming elimination [14] with fission of a carbon–sulphur bond and elimination of a disulphide anion, RS·S$^-$ (step 7).

$$B: + R\cdot\overset{\beta}{C}H_2-\overset{\alpha}{S}-S-CH_2R \longrightarrow BH^+ + R\cdot CH{=}S + R\cdot CH_2\cdot S^- \quad (6)$$

$$B: + R_2\overset{\beta}{C}H-\overset{\alpha}{C}H_2-S\cdot SR' \longrightarrow BH^+ + R_2C{=}CH_2 + R'S\cdot S^- \quad (7)$$

Nucleophilic displacement of sulphur (as S_2) from a *nitrogen* atom has been proposed by Saville [15] to explain the formation of dibenzylamine and *N*-benzyl(thiobenzamide) from *NN'*-dithiobisdibenzylamine at 140°. The displacement step is written as:

$$(Ph\cdot CH_2)_2N^- \cdots H-\underset{Ph}{CH}-\underset{CH_2Ph}{N}-S-S^+ \longrightarrow (Ph\cdot CH_2)_2NH + Ph\cdot CH{=}N\cdot CH_2Ph + S_2$$

and, as in our case, the sulphur liberated is then supposed to combine with the Schiff's base by a Kindler reaction to give *N*-benzyl(thiobenzamide).

An alternative to step 1 might be to assume that the first product is a sulphenamide (see above) which then undergoes the elimination:

$$B: + R\cdot NH\cdot CO\cdot CH_2\cdot S\cdot NR'R'' \longrightarrow BH^+ + R\cdot NH\cdot CO\cdot CH{=}S + R'R''N^-$$

Since aromatic Bunte salts are not capable of transformation into thioamides, they might possibly yield sulphenamides with amines. When sodium *o*-nitrophenyl thiolsulphate was heated with aniline or cyclohexylamine, di-(*o*-nitrophenyl) disulphide was obtained in high yield, but potassium phenyl thiolsulphate was recovered unchanged from similar experiments.

Alkyl thiolsulphates are known to react readily with aqueous cyanide to give thiocyanates and sulphite ion.[16] However, reaction of sodium phenylcarbamoylmethyl thiolsulphate with aqueous potassium cyanide gave 3-phenylpseudothiohydantoin, isomeric with the linear thiocyanate. This result could be expected on the basis of the known reaction of ω-chloroacetanilide with potassium thiocyanate, since the ω-thiocyanoacetanilide first formed cyclises to 3-phenylpseudothiohydantoin which in turn can isomerise to 2-phenyliminothiazolid-4-one.[17]

3-Phenylpseudothiohydantoin gave N^S-cyclohexyl-N^O-phenyl(thio-oxamide) in 23% yield when heated with cyclohexylamine, but no thio-oxamide was derived from the isomeric 2-phenyliminothiazolid-4-one. Phenylcarbamoylmethyl thiolcarbamate also gave the thio-oxamide in low yield on reaction with cyclohexylamine.

Experimental

Light petroleum refers to the fraction of b. p. 55—70° unless otherwise stated. Microanalyses were carried out by the C.S.I.R.O. Microanalytical Laboratory.

Sodium p-*Thiolsulphatoacetamido*(*azobenzene*).—*p*-Aminoazobenzene was converted into its *chloroacetyl* derivative in 77% yield by Ronwin's method.[18] This crystallised from ethanol as yellow needles, m. p. 153° (Found: C, 61·9; H, 4·6; N, 14·9. $C_{14}H_{12}ON_3Cl$ requires C, 61·5; H, 4·4; N, 15·4%).

A solution of sodium thiosulphate pentahydrate (8·5 g.) in water (170 ml.) was added to a

[13] Rosenthal and Oster, *J. Soc. Cosmetic Chemists*, 1954, **5**, 286.
[14] Tarbell and Harnish, *Chem. Rev.*, 1951, **49**, 1; Swan, *Nature*, 1957, **179**, 965.
[15] Saville, *J.*, 1958, 2880.
[16] Footner and Smiles, *J.*, 1925, **127**, 2887.
[17] Wheeler and Johnson, *Amer. Chem. J.*, 1902, **28**, 121.
[18] Ronwin, *J. Org. Chem.*, 1953, **18**, 127.

boiling solution of *p*-chloroacetamidoazobenzene (9·5 g.) in ethanol (170 ml.) and the mixture heated under reflux for 30 min. The resulting clear solution was allowed to cool, whereupon the Bunte *salt* separated as orange plates (11·5 g., 95%). For analysis it was recrystallised once from water and then twice from ethanol (Found: C, 45·1; H, 3·6; S, 17·3. $C_{14}H_{12}O_4N_3S_2Na$ requires C, 45·0; H, 3·2; S, 17·2%).

Di-(p-*phenylazophenylcarbamoylmethyl*) *Disulphide*.—(i) A solution of the preceding salt (1·5 g.) and sodium mercaptoacetate (2·0 g.) in water (60 ml.) was heated on a steam-bath for 1 hr., then cooled, and the *product* (1·35 g., 97%) was filtered off, washed, dried, and crystallised from aqueous *NN*-dimethylformamide as pale orange needles, m. p. 209° (Found: C, 62·6; H, 4·6; S, 11·6. $C_{28}H_{24}O_2N_6S_2$ requires C, 62·2; H, 4·4; S, 11·8%).

(ii) Concentrated hydrochloric acid (2·5 ml.) was heated with the same salt (2·4 g.) in ethanol (120 ml.) for 45 min. Water was added and the resulting flocculent precipitate (1·0 g.) was filtered off. After several crystallisations from ethanol the disulphide (0·3 g.), m. p. 208°, was obtained. A small amount of *p*-aminoazobenzene was isolated from the mother-liquors.

(iii) Excess of bromine water was added to a solution of the salt (1·0 g.) in water (40 ml.), and part of the flocculent precipitate was separated by centrifugation. Crystallisation from aqueous *NN*-dimethylformamide gave the disulphide, m. p. 208°.

(iv) Addition of 30% aqueous ammonia (5 ml.) to a boiling solution of the salt (0·5 g.) in water (30 ml.) gave the disulphide, m. p. 202° after one crystallisation from 2-methoxyethanol.

N^S-*Cyclohexyl*-N^O-p-*phenylazophenyl*(*thio-oxamide*).—Cyclohexylamine (2 ml.) was added to a hot solution of the Bunte salt (2·0 g.) in water (30 ml.), and the mixture was boiled for 5 min. The precipitated *thioamide* (1·6 g., 82%) crystallised from aqueous *NN*-dimethylformamide as orange leaflets, m. p. 180° (Found: C, 65·8; H, 6·1; N, 15·1; S, 8·7. $C_{20}H_{22}ON_4S$ requires C, 66·3; H, 6·1; N, 15·5; S, 8·8%).

Sodium 1-*Phenylazo*-2-*thiolsulphatoacetamidonaphthalene*.—2-*Chloroacetamido*-1-*phenylazonaphthalene*, obtained in 67% yield from 1-phenylazo-2-naphthylamine, crystallised from ethanol as red needles, m. p. 131° (Found: C, 66·6; H, 4·5; N, 12·5. $C_{18}H_{14}ON_3Cl$ requires C, 66·8; H, 4·3; N, 13·0%).

The chloroacetyl derivative (4·3 g.) was converted into the Bunte *salt* in the usual way. The mixture was evaporated under reduced pressure, and the residue extracted with boiling ethanol. Addition of ether precipitated the salt (3·4 g., 61%) as an orange powder. A sample was prepared for analysis by crystallisation from ethanol–ether (Found: C, 49·0; H, 3·6; S, 14·5. $C_{18}H_{14}O_4N_3S_2Na,H_2O$ requires C, 48·9; H, 3·6; S, 14·5%).

Di-(1-*phenylazo*-2-*naphthylcarbamoylmethyl*) *Disulphide*.—(i) Addition of bromine-water to an aqueous solution of the preceding salt gave an immediate flocculent orange precipitate, which was collected by centrifugation and crystallised from aqueous *NN*-dimethylformamide. The *disulphide* separated as red needles, m. p. 201° (Found: C, 67·9; H, 4·6; S, 9·8. $C_{36}H_{28}O_2N_6S_2$ requires C, 67·5; H, 4·4; S, 10·0%).

(ii) Addition of 15N-ammonia (3 ml.) to a solution of the salt (0·35 g.) in boiling water (15 ml.) gave an orange-red precipitate. One crystallisation from aqueous *NN*-dimethylformamide gave the disulphide (0·1 g.), m. p. 198°.

N^S-*Cyclohexyl*-N^O-1-*phenylazo*-2-*naphthyl*(*thio-oxamide*).—Reaction of the 2-naphthyl Bunte salt with cyclohexylamine as described above gave the *thio-oxamide* in 96% yield. It crystallised from aqueous *NN*-dimethylformamide as red needles, m. p. 184° (Found: C, 69·3; H, 5·8; N 13·0; S, 8·1. $C_{24}H_{24}ON_4S$ requires C, 69·2; H, 5·8; N, 13·5; S, 7·7%).

Sodium Phenylcarbamoylmethyl Thiolsulphate.—This Bunte salt, obtained in 90% yield by reaction of ω-chloroacetanilide with sodium thiosulphate in the usual way, crystallises from water as a monohydrate.[19]

Cyclohexylammonium Phenylcarbamoylmethyl Thiolsulphate.—Cyclohexylamine (0·6 ml.) was added to a solution of the preceding salt (1·0 g.) in hot water (15 ml.) containing acetic acid (0·6 ml.). On cooling, the *cyclohexylammonium salt* (1·1 g.) separated as plates, m. p. 135·5° (Found: N, 7·7; S, 18·6. $C_{14}H_{22}O_4N_2S$ requires N, 8·1; S, 18·5%).

Aniline Phenylcarbamoylmethyl Thiolsulphate.—This *salt*, similarly prepared, crystallised from water as plates, m. p. 180° (Found: S, 18·4. $C_{14}H_{16}O_4N_2S_2$ requires C, 18·5%).

N^S-*Cyclohexyl*-N^O-*phenyl*(*thio-oxamide*).—(i) Cyclohexylamine (0·6 ml.) was added to a solution of sodium phenylcarbamoylmethyl thiolsulphate (1·0 g.) in boiling water (20 ml.). The yellow oil (0·54 g., 55%) which separated gave the *thio-oxamide* as yellow needles, m. p. 130°

[19] Weiss and Sokol, *J. Amer. Chem. Soc.*, 1950, **72**, 1687.

(from ethanol) (Found: C, 64·4; H, 6·9; N, 10·4; S, 12·1. $C_{14}H_{18}ON_2S$ requires C, 64·1; H, 6·9; N, 10·6; S, 12·1%).

(ii) (*a*) The sodium salt (2·25 g.) was suspended in cyclohexylamine (5 ml.) and heated for 5 min. The mixture was partitioned between ethyl acetate and water, and the organic phase washed with dilute acid, dried and evaporated, giving N^S-cyclohexyl-N^O-phenyl(thio-oxamide) (2·0 g., 86%), needles (from ethanol), m. p. and mixed m. p. 130°. The aqueous extract was shown to contain considerable amounts of thiosulphate by qualitative tests with acids, silver nitrate, and barium chloride.

(*b*) The sodium salt (3·28 g., 11·4 mmoles) was heated with cyclohexylamine as in (*a*). The mixture was partitioned between ethyl acetate (50 ml.) and water (20 ml.), and the ethyl acetate was then washed twice with water (2 × 10 ml.). The combined aqueous extracts were extracted twice with ether; dissolved ether was removed under reduced pressure, and the aqueous solution made up to 50 ml. This solution was analysed for sulphide, sulphite, and thiosulphate, as outlined by Mitchell and Ward.[20] The amounts of these three anions, expressed as mg.-atoms of S, were 0·3, 4·0, and 7·2 respectively. N^S-Cyclohexyl-N^O-phenyl(thio-oxamide) (2·53 g., 84·5%) was isolated from the ethyl acetate extract. Under the conditions of estimation, unchanged Bunte salt in the aqueous solution did not interfere.

(iii) A sample of cyclohexylammonium phenylcarbamoylmethyl thiolsulphate was heated at 140° for 5 min. Crystallisation of the molten mass from ethanol gave N^S-cyclohexyl-N^O-phenyl-(thio-oxamide), m. p. 130°.

Conversion of Sodium Phenylcarbamoylmethyl [^{35}S]*Thiolsulphate into* N^S-*Cyclohexyl*-N^O-*phenyl-(thio-oxamide)*.—Aluminium discs (25 mm. diam., 4 mm. thick, 1 cm.^{2} well) were used for mounting radioactive samples, which were counted at infinite thickness by a thin-end Geiger-Müller tube (EHM 2^S) with a conventional scaler unit.

Sodium phenylcarbamoylmethyl thiolsulphate (0·25 g.) was dissolved in an ammoniacal solution of ammonium [^{35}S]sulphite (10 ml.; 2 μc/ml.) which had been adjusted to pH 8 by addition of acetic acid. After 2 days at room temperature, the solution was freeze-dried and ammonium acetate and sulphite were removed by vacuum-sublimation. The residue crystallised from ethanol–ether, and the labelled Bunte salt was heated at 70°/0·1 mm. until constant radioactivity was obtained. An average figure of 3450 c.p.m. was obtained.

The Bunte salt was then converted into N^S-cyclohexyl-N^O-phenyl(thio-oxamide) by cyclohexylamine as described in (ii*a*). The thio-oxamide was separated from inorganic material by the method outlined in (ii*b*). The aqueous solution was freeze-dried: the residue had an activity of 4960 c.p.m. After crystallisation from aqueous ethanol, the thio-oxamide gave 760 c.p.m., which fell to 740 c.p.m. after a second crystallisation.

Oxidation of N^O-*Cyclohexyl*-N^S-*phenyl(thio-oxamide)*.—40% Peracetic acid (2 ml.) was added to a solution of the thio-oxamide (0·4 g.) in acetic acid (4 ml.). The yellow colour was instantly discharged. Water was added, and the precipitate was filtered off and crystallised from 2-methoxyethanol. *N*-Cyclohexyl-*N'*-phenyloxamide separated as needles, m. p. 205° (lit.,[21] 209°)

N-*Phenyl-α-thio-oxamoylmorpholine*.—Sodium phenylcarbamoylmethyl thiolsulphate (0·5 g.) and morpholine (3 ml.) were heated under reflux for 3 min. The *thioamide* (0·30 g., 68%) crystallised from methanol as pale yellow prisms, m. p. 166° (Found: C, 57·6; H, 5·6; S, 12·8. $C_{12}H_{14}O_2N_2S$ requires C, 57·6; H, 5·6; S, 12·8%). The m. p. was considerably depressed on admixture with a sample of di(phenylcarbamoylmethyl) disulphide, m. p. 164°.

NN'-*Diphenyl(thio-oxamide)* (*Monothio-oxanilide*).—The last-named salt (5 g.) was heated with aniline (10 ml.) at 160° for 15 min. The mixture was poured into water and extracted with ethyl acetate. This extract was washed with dilute acid, dried, and evaporated. A solution of the residue (1·6 g.) in benzene (100 ml.) was passed through a column of alumina, an orange band of impurities being retained at the top of the column. The eluate was evaporated to small volume, and light petroleum added, whereupon the thioamide (0·90 g., 21%) separated as yellow needles, m. p. 142°. Recrystallisation from ethanol raised the m. p. to 143·5° (lit.,[22] m. p. 143—144°). Found: C, 66·0; H, 4·7; N, 10·5; S, 12·2. Calc. for $C_{14}H_{12}ON_2S$: C, 65·6; H, 4·7; N, 10·9; S, 11·9%).

Oxidation with peracetic acid gave oxanilide as plates, m. p. and mixed m. p. 245°.

[20] Mitchell and Ward, " Modern Methods in Quantitative Chemical Analysis," Longmans, Green & Co., London, 1932, p. 138.
[21] de Vries, *Rec. Trav. chim.*, 1942, **61**, 223.
[22] Frerichs and Wildt, *Annalen*, 1908, **360**, 105.

N^S-*Allyl*-N^O-*phenyl*(*thio-oxamide*).—The last-named salt (1·5 g.) and allylamine (5 ml.) were heated under reflux on a steam-bath for 30 min. The product (0·48 g.) was chromatographed in benzene on alumina. The eluate contained the *thioamide*, m. p. 83° (from light petroleum) (Found: C, 60·1; H, 5·3; S, 14·4. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·5; S, 14·5%).

Oxidation of the thioamide with peracetic acid in the usual way gave N-*allyl*-N′-*phenyloxamide* as needles, m. p. 142° (from aqueous methanol) (Found: C, 64·9; H, 5·7. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9%).

Reaction of Sodium Phenylcarbamoylmethyl Thiolsulphate with Aqueous Amine Solutions.—(i) Aniline (0·6 ml.) was heated with the salt (1·0 g.) in water (20 ml.) on a steam-bath for 30 min. The precipitate (0·05 g.) was collected, and crystallised from aqueous methanol as needles, m. p. 161° undepressed on admixture with a sample of di(phenylcarbamoylmethyl) disulphide.

Addition of acetic acid (0·5 ml.) to the aqueous filtrate gave a precipitate (0·7 g.) of aniline (phenylcarbamoylmethyl) thiolsulphate, m. p. 177°.

(ii) Morpholine (1 ml.) was added to a solution of the Bunte salt (1·0 g.) in water (15 ml.). An immediate white precipitate separated. The mixture was heated on a steam-bath for a few minutes, then cooled and filtered. Crystallisation of the residue (0·52 g.) from methanol gave di(phenylcarbamoylmethyl) disulphide, m. p. 161°.

Reaction of Sodium Phenylcarbamoylmethyl Thiolsulphate with Potassium Cyanide.—Potassium cyanide (3 g.) was added to a solution of the salt (5·0 g.) in boiling water (50 ml.), and the solution allowed to cool spontaneously. Extraction with ethyl acetate gave 3-phenylpseudothiohydantoin (0·9 g.), m. p. 148° (from aqueous ethanol). The m. p. was considerably depressed on admixture with (phenylcarbamoylmethyl) thiolcarbamate, m. p. 147—148° (lit.,[23] m. p. 147°). Heating the product at 160° for 5 min. gave 2-phenyliminothiazolid-4-one, m. p. 177° (lit.,[17] m. p. 178°) (from ethyl acetate–light petroleum).

Reaction of 3-Phenylpseudothiohydantoin with Cyclohexylamine.—3-Phenylpseudothiohydantoin (0·5 g.) and cyclohexylamine (3 ml.) were heated under reflux for 10 min., then acidified and extracted with ethyl acetate. Evaporation of the extract gave a residue (0·15 g., 23%) which after two crystallisations from aqueous ethanol had m. p. 131°, undepressed on admixture with N^S-cyclohexyl-N^O-phenyl(thio-oxamide).

Reaction of phenylcarbamoylmethyl thiolcarbamate (2·0 g.) with cyclohexylamine (6 ml.) in the same way also gave N^S-cyclohexyl-N^O-phenyl(thio-oxamide) (0·15 g., 5%).

Sodium Cyclohexylcarbamoylmethyl Thiolsulphate.—This compound was obtained in 80% yield by reaction of chloroacetylcyclohexylamine with sodium thiosulphate in the usual way. The mixture was evaporated to dryness under reduced pressure and the residue was extracted with boiling ethanol from which the *product* was precipitated with ether (Found: C, 33·3; H, 5·6; N, 4·5; S, 21·4. $C_8H_{14}O_4NS_2Na,H_2O$ requires C, 32·8; H, 5·5; N, 4·8; S, 21·8%).

Di(*cyclohexylcarbamoylmethyl*) *Disulphide.*—Excess of aqueous iodine–potassium iodide was added to a concentrated aqueous solution of the last-mentioned thiolsulphate at 100°. After 5 min. the excess of iodine was discharged with sodium thiosulphate, and the *disulphide* filtered off and crystallised from aqueous ethanol. Colourless needles, m. p. 165°, were obtained (Found: N, 8·1; S, 18·4. $C_{16}H_{28}O_2N_2S_2$ requires N, 8·1; S, 18·6%).

NN′-*Dicyclohexyl*(*thio-oxamide*).—The last-mentioned thiolsulphate (1·0 g.) was heated under reflux with cyclohexylamine (3 ml.) for 5 min., and the product precipitated by acid. The *thioamide* (0·95 g., 95%) crystallised from ethanol as yellow plates, m. p. 165° (Found: N, 10·0; S, 11·7. $C_{14}H_{24}ON_2S$ requires N, 10·4; S, 11·9%). The m. p. was considerably depressed on admixture with a sample of di(cyclohexylcarbamoylmethyl) disulphide.

With peracetic acid the thioamide gave *NN*′-dicyclohexyloxamide, m. p. 273° (lit.,[21] m. p. 273°).

Reaction of Sodium Cyclohexylcarbamoylmethyl Thiolsulphate with Aqueous Ammonia.—A solution of the thiolsulphate (1 g.) in 5% aqueous ammonia (15 ml.) was boiled for several minutes, then cooled and the precipitate was collected. Crystallisation from ethanol gave a small crop of colourless plates, m. p. 225°, raised to 228° by a second crystallisation. The m. p. was undepressed on admixture with *N*-cyclohexyloxamide (lit.,[21] m. p. 234°; see below).

Addition of water to the mother-liquor gave a substantial precipitate from which di(cyclohexylcarbamoylmethyl) disulphide, m. p. 154°, was obtained by crystallisation from aqueous ethanol.

Sodium Carbamoylmethyl Thiolsulphate.—This compound was prepared from chloroacetamide and sodium thiosulphate in the usual way. It could not be extracted from the residue

[23] Beckurts and Frerichs, *J. prakt. Chem.*, 1902, **66**, 181.

with hot ethanol, nor would it crystallise from water, and the crude mixture of Bunte salt and sodium chloride was used as such. On addition of a solution of *S*-benzylthiuronium chloride to an aqueous solution, a precipitate of S-*benzylthiuronium carbamoylmethyl thiolsulphate* separated. It crystallised from water as needles, m. p. 138° (Found: S, 28·5. $C_{10}H_{15}O_4N_3S_3$ requires S, 28·5%).

N^S-*Cyclohexyl*(*thio-oxamide*).—A suspension of the crude Bunte salt in cyclohexylamine was heated under reflux for 10 min. The product was chromatographed in benzene on alumina. The *thioamide* was eluted with ether–benzene (1 : 4); it crystallised from light petroleum as yellow laths, m. p. 108° (Found: C, 52·1; H, 7·7; N, 14·6; S, 17·3. $C_8H_{14}ON_2S$ requires C, 51·6; H, 7·5; N, 15·1; S, 17·2%).

Oxidation with peracetic acid gave *N*-cyclohexyloxamide as needles, m. p. 230° (from 2-methoxyethanol).

N^S-*Phenyl*(*thio-oxamide*).—Reaction of the crude Bunte salt with aniline at 160° for 10 min. gave a product from which N^S-phenyl(thio-oxamide), m. p. 167° (lit.,[2] 169°), was obtained by chromatography on alumina followed by crystallisation from ethanol.

Oxidation with potassium ferricyanide in alkaline solution gave benzothiazole-2-carboxyamide as plates, m. p. 238° (lit.,[2] 238—240°).

Cyclohexylammonium Benzyl Thiolsulphate.—Cyclohexylamine (2 ml.) was added to a warm solution of sodium benzyl thiolsulphate (5 g.) in water (50 ml.) containing acetic acid (2 ml.). A small quantity (0·5 g.) of oil separated, and the aqueous phase was decanted. The oil crystallised from ethanol as needles, m. p. 68°, undepressed on admixture with dibenzyl disulphide. Cooling the aqueous phase deposited crystals. These were filtered off, and recrystallised (3·6 g.) from water. The *cyclohexylammonium salt* was obtained as needles, m. p. 137° (Found: C, 51·6; H, 7·0. $C_{13}H_{21}O_3NS_2$ requires C, 51·5; H, 7·0%).

A sample of the salt was heated at 140° for 10 min. Crystallisation of the melt from methanol gave dibenzyl disulphide, m. p. 70°.

Reaction of Sodium Benzyl Thiolsulphate with Amines.—(i) A solution of the thiolsulphate (1·0 g.) and cyclohexylamine (2 ml.) in water (25 ml.) was heated on a steam-bath for 10 min., then extracted with ethyl acetate, and the extracts were washed with dilute hydrochloric acid and dried. Evaporation gave dibenzyl disulphide (0·24 g., 44%). The aqueous phase was acidified, and extracted with ethyl acetate. This extract gave an oil (0·11 g.).

(ii) A suspension of the thiolsulphate (2·0 g.) in morpholine (3 ml.) was heated under reflux for 5 min. Dilute hydrochloric acid was added to the cold mixture, and the precipitate (0·8 g.) filtered off. Crystallisation from methanol gave dibenzyl disulphide, m. p. 68°.

(iii) A similar experiment with cyclohexylamine instead of morpholine also gave dibenzyl disulphide.

(iv) The thiolsulphate (5·6 g.), sulphur (3·2 g.), and morpholine (10 ml.) were heated under reflux for 15 min. The neutral product (4·67 g.) gave thiobenzomorpholide (3·45 g., 67%) as pale yellow prisms, m. p. 137° (from methanol).

Reaction of Sodium o-*Nitrophenyl Thiolsulphate with Amines.*—Sodium *o*-nitrophenyl thiolsulphate was prepared by reaction of *o*-nitrobenzenesulphenyl chloride with sodium sulphite as described by Lecher and Hardy.[24]

(i) The Bunte salt (1·0 g.) was heated with aniline (2 ml.) at 140° for 10 min. On addition of dilute hydrochloric acid to the cold mixture, di-*o*-nitrophenyl disulphide (0·49 g., 85%) was precipitated.

(ii) Reaction of the Bunte salt with cyclohexylamine under similar conditions also gave the disulphide.

Attempted Reaction of Potassium Phenyl Thiolsulphate with Amines.—Potassium phenyl thiolsulphate was prepared by reaction of diphenyl disulphide with potassium sulphite.[24]

Heating it with cyclohexylamine or aniline at 140°, or with aqueous cyclohexylamine at 100°, did not result in reaction, the Bunte salt being recovered unchanged in each case.

Reaction of Sodium 2-(*Phenylcarbamoyl*)*ethyl Thiolsulphate with Amines.*—This Bunte salt was prepared from the corresponding chloro-compound as described by Weiss and Sokol.[19] Reaction with cyclohexylamine or morpholine at 135° for 10 min. gave a product from which unchanged Bunte salt (70%) and di-(2-phenylcarbamoylethyl) disulphide (20%) were isolated.

Division of Protein Chemistry (formerly Biochemistry Unit),
Commonwealth Scientific and Industrial Research Organization,
Melbourne, Australia. [*Received, February 16th*, 1959.]

[24] Lecher and Hardy, *J. Org. Chem.*, 1955, **20**, 475.