Reactions of Co-ordinated Ligands Part VII.[1] Reactions of Co-ordinated Thiol Esters and Thiolate Anions

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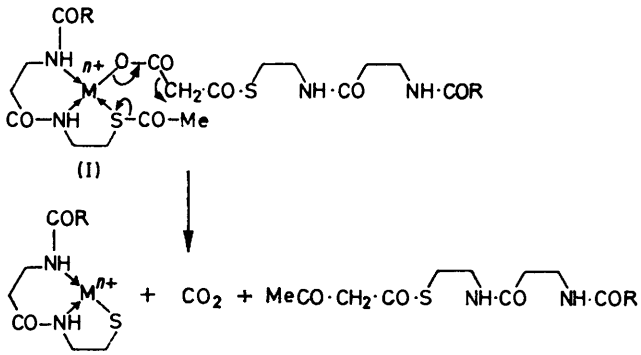
The methanolysis of several thiol esters has been found to be promoted by transition metal ions, notably Cu^{2+}. The interaction in solution between the thiol esters and metal ions has been studied by observation of contact shifts in the ^1H n.m.r. spectrum. and by the method of continuous variations. The interaction. which is thought to involve the sulphur atom of the thiol ester group rather than the carbonyl oxygen atom, was found to be greater for copper(II) than for nickel(II) ions. A number of solid copper(II) complexes of β-amino-thiol esters with a metal : thiol ester ratio of 1 : 1 have been prepared and characterised.

The reaction between acid chlorides and the nickel(II) chelates of β-amino-thiols has been found to be a convenient method for the preparation of β-amino-thiol esters.

ONE of the ways in which metal ions can promote nucleophilic substitutions of a carboxylic acid derivative (RCO·L) is by co-ordinating with the leaving group (L). This co-ordination not only inhibits the resonance stabilisation of the derivative and thus renders it more susceptible to nucleophilic attack, but also increases the rate at which the leaving group departs from the tetrahedral reaction intermediate. With carboxylic esters this type of promotion occurs only when the alkoxy-oxygen atom forms part of a chelating system, as in esters of 8-hydroxyquinoline [2] and 2-(2-hydroxyethyl)-pyridine,[3] for with esters of simple alcohols and phenols the co-ordination preferentially involves the carbonyl oxygen atom. Although substitutions of esters of simple thiols are strongly promoted by certain heavy metal ions,[4] *e.g.* Hg^{2+} and Ag^{+}, because of the high affinity of these ions for sulphur, transition metal ions such as Cu^{2+}, Ni^{2+}, and Co^{2+} are less effective. By analogy



SCHEME 1

with the oxygen systems, however, it can be predicted that the latter type of ion should be much more effective in the case of thiol esters in which the sulphur atom forms part of a chelating group [*cf.* structure (VIIIc)]. This prediction could possibly be of importance in connection with some of the biochemical roles of co-enzyme-A, for although the ability of this coenzyme to act as an acyl carrier, for example, is usually explained in terms of the normal high reactivity of the thiol ester group,[5] it is apparent that co-ordination [as shown in the partial structure (I), for example] would activate the thiol ester group towards nucleophilic substitution and also towards carbanion formation at the α-position of the acyl residue. Scheme 1 indicates a hypothetical way in which the former effect could be involved in the formation of acetoacetyl-coenzyme-A from a complex of acetyl-coenzyme-A and a metal salt of malonyl-co-enzyme-A.

In this paper we report evidence that the methanolysis of esters of β-amino-thiols is promoted by copper(II) and other transition metal ions, and which suggests that this promotion involves co-ordination of the thiol ester group with a metal ion.

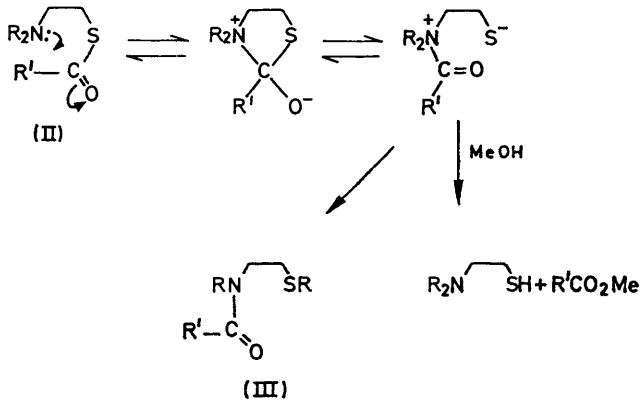
In the absence of metal ions the methanolysis of a number of thiol esters [equation (1)] was conveniently

$$RCO{\cdot}SR' + MeOH \longrightarrow RCO_2Me + R'SH \quad (1)$$

followed by measuring the decrease in absorbance of the reaction mixtures in the 270 nm region. This decrease arises from the fact that at this wavelength alkyl carboxylates have extinction coefficients about one tenth of those of the corresponding *S*-alkyl thio-carboxylates. The results are presented in Table 1, which shows that the esters examined were of two distinct types. The first type, *e.g.* *SS'*-ethylene bisthio-benzoate, was almost unaffected when refluxed in methanol for 1 h, whereas the second type underwent substantial methanolysis under the same conditions. The difference between the two types can be related to the presence in the reactive esters of a basic nitrogen atom which allows the methanolysis to proceed by the intramolecular mechanism shown in Scheme 2. A similar mechanism has been suggested by Bruice [6] to explain the extremely high rate (*ca.* 10^6 times faster) with which *S*-n-propyl 4-(imidazol-4-yl)thiobutyrate undergoes hydrolysis in comparison with *S*-ethyl thio-acetate and the coenzyme-A model, *S*-(2-acetamido-ethyl) thioacetate. The same type of process (see Scheme 2) has also been proposed for the acyl migration (II) ⟶ (III) which thiol esters of type (II; R = H) rapidly undergo.[7]

[1] Part VI, R. P. Houghton and G. W. Cooper, *Tetrahedron Letters*, 1970, 3915.
[2] R. H. Barca and H. Freiser, *J. Amer. Chem. Soc.*, 1966, **88**, 3744.
[3] E. Uhlig, H. Raimann, and K. Staiger, *Z. anorg. Chem.*, 1967, **351**, 296.
[4] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, p. 277.
[5] P. J. Hawkins and D. S. Tarbell, *J. Amer. Chem. Soc.*, 1953, **75**, 2982.
[6] T. C. Bruice, *J. Amer. Chem. Soc.*, 1959, **81**, 5444.
[7] T. Wieland, H. U. Lang, and D. Liebsch, *Annalen*, 1955, **597**, 227.

Having examined the behaviour of metal-free systems, we then studied the effect of metal ions on the methanolyses. With transition metals present it was not possible to follow the reactions spectrophotometrically because



SCHEME 2

of the high absorption by the metal ions in the 270 nm region. The methanolysis of benzoate and *p*-nitrobenzoate esters was therefore followed by isolating the resultant methyl ester and then determining this product spectrophotometrically. With pyridine-2-carboxylates this technique was not possible, and the concentration of methyl pyridine-2-carboxylate was determined after the metal had been removed with the disodium salt of ethylenediaminetetra-acetic acid. Experiments with mixtures of the metal salt, thiol ester, thiol, and methyl ester of known composition showed the accuracy of the determinations to be greater than 95% with benzoate and *p*-nitrobenzoate esters, and greater than 90% with pyridine-2-carboxylate esters. Although the results are presented in Table 1, it is informative to consider in detail the effect of copper(II) ions on the methanolysis of the various thiol esters. With esters of type (II; R = Me or Et) the methanolysis rates were enhanced by the metal. Although the increases in rate were not very large they must be interpreted with care, for in metal-free solutions the methanolyses undoubtedly proceed largely by the intramolecular route shown in Scheme 2. This route will be inhibited by copper(II) because tertiary amino-groups have a strong affinity for this metal, and hence a significant proportion of the ester will be complexed with the metal through this group, whose nucleophilic properties will consequently be reduced substantially. Furthermore, as the results described in this paper indicate, thioester groups have comparatively weak co-ordinating properties and hence it is likely that only a small proportion of the thiol ester is chelated with the metal [*cf.* structure (VIIIc)], *i.e.* rather than merely complexed through the tertiary amino-group. If this is the case, and the activation is caused by co-ordination of the thioester group the resultant increase in reactivity must be much greater than is suggested by the observed increase in the rate of reaction. Unfortunately, without knowledge of the various stability constants associated with complex formation a quantitative measure of the increase in reactivity cannot be obtained.

As expected on the basis of the low co-ordinating ability of an un-ionised amide group, copper(II) ions had a very small effect on the methanolysis of *S*-(2-benzamidoethyl) thiobenzoate. In contrast, although the methanolysis of *S*-[2-(2-pyridylcarbonylaminoethyl)] thiobenzoate occurred at a negligible rate in the absence of metal, the reaction was 60% complete within 1 h in the presence of 1 equiv. of copper(II) ions, presumably because the pyridine nitrogen atom facilitates the co-ordination of the thiol ester as shown in structure (IV). With *S*-[2-(2-pyridylcarbonylaminoethyl)] pyridine-2-thiocarboxylate the rate of methanolysis was increased by copper(II) ions but not to as great an extent as with *S*-[2-(2-pyridylcarbonylaminoethyl)] thiobenzoate. This difference may be ascribed to tetradentate chelation [see (V)], for this type of chelation would stabilise the co-ordinated thioester group towards methanolysis because of the difficulty associated with the breakage of bonds within chelate systems.

TABLE 1

Degree (%) of methanolysis of various thiol esters in the presence of metal ions *

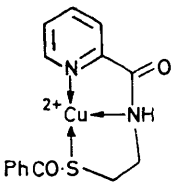
Ester	Metal ion: None	Cu^{2+}	Ni^{2+}	Hg^{2+}	Pb^{2+}	Ag^{+}	Na^{+}
(II; R = R′ = Me)	70	100					70
(II; R = Me, R′ = Ph)	40	90	40	70	70	60	40
(II; R = Me, R′ = *p*-NO_2·C_6H_4)	80	90 †	80				80
(II; R = Et, R′ = Ph)	40	80	40				
PhCO·NH·$[CH_2]_2$·S·COPh	5	10 ‡					
$(PhCO·S·CH_2)_2$	5	20					
PyCO·NH·$[CH_2]_2$·S·COPh §	5	60		60			
PyCO·NH·$[CH_2]_2$·S·COPy §	5	25					

* Ester and metal ion (as acetate) both 0·01M; solution heated under reflux for 1 h; degree of methanolysis given to the nearest 5%. † Result after 30 min. ‡ Result after 2 h. § Py = 2-pyridyl.

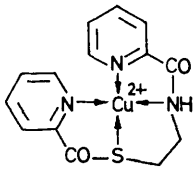
During the copper-promoted methanolyses of *S*-[2-(2-pyridylcarbonylamino)ethyl] pyridine-2-thiocarboxylate and thiobenzoate a highly insoluble black solid was deposited from the solutions. Degradation of this solid with hydrochloric acid and precipitation of the copper(II) as the sulphide showed that the solid was a 1 : 1 copper complex of *N*-(2-mercaptoethyl)pyridine-2-carboxamide.

The metal : ligand ratio associated with complex formation in methanol was determined by the method of continuous variation (Job's method) for the thiol ester *S*-(2-dimethylaminoethyl) thiobenzoate (II; R = Me, R′ = Ph) and the thioether 2-(2-dimethylaminoethyl-

thio)acetophenone (VI). The latter ligand produced quite large changes in the visible spectra when added to solutions of metal salts, and was found to form 2 : 1 and



(IV)



(V)

$Me_2N{\cdot}[CH_2]_2S{\cdot}CH_2COPh$

(VI)

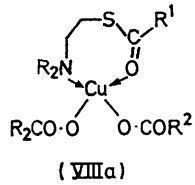
1 : 1 complexes with nickel(II) and copper(II), respectively. In contrast the thiol ester produced comparatively little change in the spectra of solutions of most metal salts, and with nickel(II), for example, the observed spectra represented no more than the addition of the spectra of metal salt and thiol ester. With copper(II), however, distinct changes in the visible spectrum were observed—principally a shift of the lowest energy *d–d* band from 610 to 690 nm—and from the combined results of several experiments an estimate of ligand : metal ratio of 1 : 1 ∓ 0·2 was made.

In contact shift (n.m.r.) experiments with [$^2H_6$]-dimethyl sulphoxide as solvent the thioether showed the simplest behaviour, and the signals due to the *N*-methyl, *N*-methylene, and *S*-methylene groups disappeared at almost equal rates and at relatively low concentrations of either copper(II) or nickel(II) ions; the signals due to the aromatic protons were affected only at much higher concentration of these metal ions. These observations imply that the thioether co-ordinates in a bidentate manner through nitrogen and sulphur, and because low concentrations of metal produce quite large effects the stability constant of the resultant complex must be high. In contrast the thiol ester showed a more complex behaviour, of one type in the case of copper(II) and of another type in that of nickel(II). With nickel the signals due to the *N*-methyl and *N*-methylene groups were affected at moderate levels of the metal, but the remainder of the spectrum remained unaffected until the concentration of the paramagnetic ion was so high that even the reference signal (of sodium trimethylsilylpropanesulphonate) was broadened by the bulk susceptibility effect. This indicates that the ligand is weakly co-ordinated to the metal but only through the tertiary amino-group. With copper(II) ions, however, although the *N*-methyl and *N*-methylene signals disappeared first as with nickel(II), the signal due to the *S*-methylene group disappeared before that of the aromatic protons. This implies that some, albeit weak, interaction also exists between the metal and the thioester group.

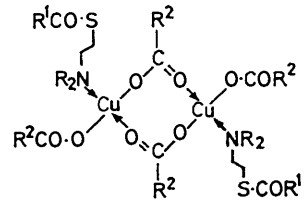
In an attempt to isolate the complex formed from copper(II) acetate and *S*-(2-dimethylaminoethyl) thiobenzoate, equimolar amounts of the two reactants were mixed in dry dioxan, but only an impure product which appeared to contain unchanged copper acetate was obtained. However, use of a 1 : 2 ratio of metal acetate to thiol ester readily afforded the desired complex as emerald green crystals whose analytical figures were consistent with the composition, $Me_2N{\cdot}[CH_2]_2{\cdot}S{\cdot}COPh,{-}Cu(OAc)_2$. Treatment of this complex with aqueous ethylenediaminetetra-acetic acid regenerated the thiol ester, but this product was contaminated with benzoic acid formed by hydrolysis of the ester either in the free or co-ordinated state (see later). Several analogous complexes (VIIb—f) were prepared similarly (see Table 2), and all of them had a 1 : 1 metal : thiol ester ratio even though a two-fold excess of the thiol ester was found to be necessary for the preparations to give pure samples of the complexes. Possibly the excess of ligand was necessary for the equilibrium between the metal salt and the complex to reach a position which ensured that only the complex crystallised out when the reaction mixture was processed.

$Me_2N{\cdot}[CH_2]_2{\cdot}S{\cdot}COR,CuX_2$

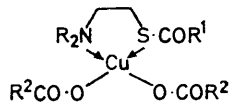
(VII)



(VIIIa)



(VIIIb)



(VIIIc)

The presence of the paramagnetic copper(II) ion in the complexes (VII) made it impossible to use n.m.r. directly to determine the exact manner in which the thiol esters were co-ordinated with the metal, but from the i.r. spectra co-ordination of the carbonyl oxygen atom [as in (VIIIa)] was excluded. In the case of the complex (VIIa), for example, the C=O stretching band occurred at 1670 cm^{-1}, as opposed to 1680 cm^{-1} in the free ligand. If the carbonyl oxygen atom were co-ordinated a much larger shift would probably have been observed, as in the case of chelated α-amino-esters.[8] The comparatively small shifts in the C=O stretching frequencies which were observed on complex formation are insufficient in themselves to distinguish between the most likely structures (VIIIb) and (VIIIc). Although co-ordination through sulphur [as in (VIIIc)] would be expected to shift the absorption band to higher frequency in keeping with the increased ketonic nature of the carbonyl group, there are no data in the literature to support or refute this idea. Indeed, co-ordination of an amide nitrogen atom to copper(II) has been observed to increase[9] and to decrease[10] the carbonyl stretching

[8] Y. Wu and D. H. Busch, *J. Amer. Chem. Soc.*, 1970, **92**, 3326.
[9] M. K. Kim and A. E. Martell, *J. Amer. Chem. Soc.*, 1966, **88**, 914.
[10] R. P. Houghton and R. R. Puttner, *Chem. Comm.*, 1970, 1270.

frequency. However, even if the complexes have the dimeric structure (VIIIb) in the solid state, this does not rule out the formation in solution of complexes of the type (VIIIc) in which the thioester group is co-ordinated and hence activated towards nucleophilic substitution.

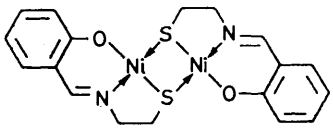
During the preparations of the copper(II)–thiol ester complexes it was found essential to use carefully dried solvents, for in the presence of moisture several different types of hydrolysis products were obtained. For example, when an attempt was made to prepare the complex (VIIg) from hydrated copper(II) nitrate and the appropriate thiol ester in dioxan which had not been dried the hydrogen nitrate salt of the thiol ester was obtained instead, together with another product which was tentatively identified as hydrated copper(II) oxide. The corresponding trichloroacetate salt was similarly isolated when the copper nitrate was replaced by copper(II) trichloroacetate. Presumably in both these cases the starting copper(II) salt reacted with the water present and the resultant nitric (or trichloroacetic) acid prevented complex formation by protonating the amino-group of the thiol ester.

Dissolution of the complex (VIIa) in water or exposure to air for a long period afforded a brown solid. This solid was also obtained in addition to methyl benzoate when the complex was heated in methanol. Although this solid was never obtained pure, the presence of a 2-dimethylaminoethanethiolate entity was indicated by the isolation of the amino-thiol hydrochloride when the solid was treated with hydrochloric acid. Treatment of a mixture of 2-dimethylaminoethanethiol and copper(II) sulphate with aqueous ammonia in the manner [11] used to prepare the yellow complex of formula $H_2N{\cdot}[CH_2]_2{\cdot}SCuCl$ afforded a bright yellow solid which rapidly turned brown when dried, and which then had an i.r. spectrum identical with that of the brown solid described above.

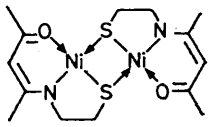
Another type of reaction which involved hydrolysis was encountered during attempts to prepare the trichloroacetate complex (VIIh). After being exposed to the atmosphere for a long period, a solution of copper(II) trichloroacetate and the *p*-nitrobenzoate ester (II; R = Me, R′ = p-$C_6H_4{\cdot}NO_2$) in acetonitrile deposited bright green crystals of the *p*-nitrobenzoate salt (VIIf). This salt was also formed in the exothermic reaction which occurred when 'anhydrous' copper(II) trichloroacetate was treated directly with a six-fold excess of the *p*-nitrobenzoate ester, and was identical with an authentic sample prepared from the ester and copper(II) *p*-nitrobenzoate in dry chloroform. Although it seems likely that the trichloroacetate complex (VIIh) was an intermediate in both these reactions, and this on hydrolysis produced *p*-nitrobenzoic acid, it is puzzling why 2-dimethylaminoethanethiol, which would be expected to be the other hydrolysis product, did not displace the *p*-nitrobenzoate ester from the copper to form the *p*-nitrobenzoate salt (IXa). Possibly the 2-dimethylaminoethanethiol was oxidised to the corresponding disulphide, which in small-scale experiments was found not to react with copper(II) salts in chloroform or acetonitrile. An authentic sample of the complex (IXa) was prepared from 2-dimethylaminoethanethiol and copper(II) *p*-nitrobenzoate, and was also obtained when the *p*-nitrobenzoate ester (II; R = Me, R′ = p-$C_6H_4{\cdot}NO_2$) and copper(II) *p*-nitrobenzoate were heated together in chloroform for a longer period than was required for complex formation and without protection from atmospheric moisture. In the second procedure the *p*-nitrobenzoate anion in the complex was almost certainly derived from the original copper salt rather than from the thiol ester, for the benzoate complex (IXb) was formed when either of the esters (II; R = Me, R′ = Ph or Me) was heated with copper(II) benzoate. In these preparations of the complexes of type (IX), the solution obtained when the two components were heated under reflux in chloroform for 20 min was deep purple, and in some cases almost black. Concentration of this solution

$Me_2N{\cdot}[CH_2]_2\ S{\cdot}Cu{\cdot}O{\cdot}COR$

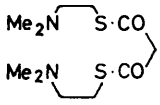
(IX) a; R=p-$C_6H_4{\cdot}NO_2$
b; R=Ph



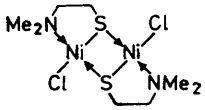
(X)



(XI)



(XII)



(XIII)

gave a purple solid which sometimes contained various amounts of a green solid. The purple solid was converted into the green solid when heated at 100° for a few minutes, and the colour change was accompanied by loss of up to 0·5 mol. equiv. of chloroform which was identified spectroscopically. The purple colour reappeared when the green solid was dissolved in chloroform and the solution was heated under reflux. From these observations it was deduced that the purple solid was a chloroform solvate of the copper(II) complex, other examples of which have already been described.[12]

The reaction between a thiol and an acid chloride is a well established method for the synthesis of thiol esters.[13] In an early report it was noted that this reaction could be modified by using the lead salt of the thiol,[14] but little was reported on the nucleophilic properties of co-ordinated thiolate anions until Busch

[11] W. O. Foye and J. Mickles, *J. Pharm. Sci.*, 1964, **53**, 1030.
[12] A. W. Addison and R. D. Gillard, *J.C.S. Dalton*, 1973, 2002.
[13] V. Meyer and W. Michler, *Ber.*, 1874, **7**, 1394.
[14] R. H. Levin, A. V. McIntosh, G. B. Spero, D. E. Rayman, and E. M. Meinzer, *J. Amer. Chem. Soc.*, 1948, **70**, 511.

and his co-workers showed that the nickel(II) complexes of β-amino-thiols reacted readily with alkyl halides to give β-amino-thioether complexes.[15] During the work described in this paper it was found that, with the exception of dimeric complexes in which the sulphide group forms a bridge between the two metal centres, *e.g.* the complexes (X) and (XI), nickel(II) complexes of thiols reacted very readily with acid chlorides. The reactions occurred almost instantaneously, even in non-basic solvents such as chloroform, and the resultant thiol esters were obtained in high yield after the nickel(II) had been removed as its dimethylglyoxime complex. Despite numerous attempts, no nickel(II)–thiol ester complexes were ever isolated from the reaction mixtures, but this is not surprising in view of the n.m.r. studies (described earlier) which failed to detect significant nickel(II)–thiol ester interaction in solution.

Attempts were made to extend the acylation process to the preparation of the tetradentate ligand (XII) from the complex $(Me_2N\cdot[CH_2]_2\cdot S)_2Ni$ and malonyl chloride, but instead of the expected product a brown complex which contained ionic chlorine ($AgNO_3$ test) and no carbonyl groups (i.r.) was obtained. On the basis of analytical data this complex was assigned the dimeric structure (XIII). The formation of this complex may be rationalised by assuming that the thiol ester produced in the initial reaction between the complex and one of the acid chloride groups of malonyl chloride is displaced by chloride anion from the metal because of the weak co-ordinating ability of the thioester group. Dimerisation of the resultant nickel(II) species would then give the complex (XIII). An almost identical process has been suggested by Busch to account for the fact that in some cases the alkylation by alkyl halides (RX) of nickel complexes $[(R'S)_2Ni]$ of thiols such as 2-(2-mercaptoethyl)pyridine produces dimers of the composition $(R'SNiX)_2$ rather than the expected thioether complexes $(R'SR)_2NiX_2$.

EXPERIMENTAL

Preparation of Thiol Esters.—*S*-(2-Dimethylaminoethyl) thioacetate,[16] thiobenzoate,[17] and *p*-nitrothiobenzoate [18] and *S*-(2-diethylaminoethyl) thiobenzoate [18] were prepared as the hydrochlorides by heating a mixture of the appropriate amino-thiol hydrochloride and acid chloride at 160° until no more hydrogen chloride was evolved (1—3 h), and then crystallising the resultant solid from methanol. The hydrochlorides, whose m.p.s agreed with the literature values in all cases, were converted into the corresponding free bases by treatment with a saturated solution of ammonia in chloroform. *S*-(2-Benzamidoethyl) thiobenzoate and *SS'*-ethylene bisthiobenzoate were prepared directly from the thiols and benzoyl chloride in a similar manner.

N-(2-*Mercaptoethyl*)*pyridine*-2-*carboxamide*.—A mixture of pyridine-2-carboxylic acid (10 g) and freshly distilled thionyl chloride (80 ml) was heated under reflux for 2 h, and then the unchanged thionyl chloride was removed under reduced pressure. The residue of crude pyridine-2-carbonyl chloride was dissolved in chloroform (250 ml), the solution was saturated with dry hydrogen chloride, and then 2-aminoethanethiol hydrochloride (7·2 g) was added at 0°. The mixture was stirred at 0° under nitrogen for 4 h and then filtered to give the *dihydrochloride* of S-(2-*aminoethyl*) *pyridine*-2-*thiocarboxylate* (6·8 g, 42%), m.p. 186—188° (from methanol–ether), $\nu_{max.}$ 1680 cm^{-1} (C=O) (Found: C, 37·6; H, 4·7; N, 11·1. $C_8H_{12}Cl_2N_2OS$ requires C, 37·7; H, 4·7; N, 11·0%). An S ⟶ N migration of the 2-pyridylcarbonyl group in the corresponding free base was carried out as follows: a mixture of the dihydrochloride (2·9 g) and chloroform (80 ml) saturated with ammonia was stirred under nitrogen for 30 min. Ammonium chloride was filtered off and the filtrate was passed through a short column of silica. Removal of the solvent gave the *mercapto-amide* (1·6 g, 77%) as an oil, $\nu_{max.}$ 2550 (SH) and 1666 cm^{-1} (CO), τ ($CDCl_3$) 8·5 (1H, t, SH), 7·45 (2H, m, $CH_2\cdot NH$), and 6·6 (2H, t, $CH_2\cdot S$) (Found: C, 52·1; H, 5·9; N, 15·25. $C_8H_{10}N_2OS$ requires C, 52·7; H, 5·5; N, 15·4%). The *hydrochloride* had m.p. 134—136° (from methanol–ether) (Found: C, 43·2; H, 5·3; N, 12·45. $C_8H_{11}ClN_2OS$ requires C, 43·9; H, 5·0; N, 12·8%).

S-[2-(2-*Pyridylcarbonylamino*)*ethyl*] *Thiobenzoate*.—A solution of the preceding thiol (1·50 g) and benzoyl chloride (2·0 g) in dichloromethane (40 ml) was kept under nitrogen for 16 h, and then the solvent and unchanged benzoyl chloride were removed under reduced pressure to leave the crude *thioester hydrochloride*, m.p. 154—156° (from benzene) (Found: C, 55·0; H, 4·8; N, 7·8. $C_{15}H_{15}ClN_2O_2S$ requires C, 55·8; H, 4·65; N, 8·7%). Treatment of this hydrochloride with a saturated solution of ammonia in chloroform (40 ml) followed by chromatography of the product on silica gel with chloroform–benzene (1 : 3 v/v) afforded the free *base* (1·26 g, 50% based on starting thiol), m.p. 57—61° (Found: C, 63·1; H, 5·0; N, 9·8. $C_{15}H_{14}N_2O_2S$ requires C, 62·9; H, 4·9; N, 9·8%).

S-[2-(2-*Pyridylcarbonylamino*)*ethyl*] *Pyridine*-2-*thiocarboxylate*.—A mixture of crude pyridine-2-carbonyl chloride [prepared from pyridine-2-carboxylic acid (50 g) as described above], 2-aminoethanethiol hydrochloride (35 g), and chloroform (500 ml) was heated under reflux (N_2) for 2½ h and then kept at room temperature for 24 h. The mixture was filtered and the solvent was removed under reduced pressure. Crystallisation of the residue from methanol–ether gave the thioester dihydrochloride (15 g, 35%) as rosettes, m.p. 160—162°, $\nu_{max.}$ 1695, 1670, and 1605 cm^{-1}. Treatment of this dihydrochloride with ammonia in chloroform according to the usual method afforded the *thioester*, m.p. 74—75° (from methanol), τ ($CDCl_3$) 6·6 (2H, m, $CH_2\cdot S$) and 6·2 (2H, m, $CH_2\cdot NH$) (Found: C, 58·2; H, 4·8; N, 14·6. $C_{14}H_{13}N_3O_2S$ requires C, 58·5; H, 4·5; N, 14·6%).

Copper-promoted Methanolysis of S-[2-(2-*Pyridylcarbonylamino*)*ethyl*] *Thiobenzoate*.—A mixture of the thioester (200 mg), copper(II) acetate (140 mg), and dry methanol (70 ml) was heated under reflux for 1 h and the black precipitate (110 mg) was filtered off. The amount of methyl benzoate present in the filtrate was determined as described in the Discussion section (57 mg, 60%). The black solid (67 mg) was treated with 5N-hydrochloric acid (10 ml) and the resultant yellow solution was diluted with water (10 ml). Hydrogen sulphide was bubbled through

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the solution, the precipitated copper(II) sulphide (19 mg) was filtered off, and the filtrate was basified (NaOH) and extracted with chloroform (3 × 5 ml). The extracts afforded an oil (24 mg) whose i.r. spectrum was indistinguishable from that of *N*-(2-mercaptoethyl)pyridine-2-carboxamide.

Kinetic Studies of the Methanolysis of Thiol Esters.—The appropriate thiol ester and metal acetate were heated together under reflux in dry methanol (25 ml; B.D.H., Karl Fischer grade; methanol dried in the usual manner with magnesium was found to be unsuitable owing to the presence of traces of magnesium methoxide which catalysed the methanolyses). In the case of benzoate and *p*-nitrobenzoate esters the methanol was removed under reduced pressure and the residue was extracted with ether (3 × 15 ml). The extracts were combined and washed successively with 2N-hydrochloric acid (2 × 25 ml) and water (2 × 25 ml), and then dried (Na_2SO_4). Dry ether was added to give a total volume of 50 ml and the methyl benzoate or *p*-nitrobenzoate present was determined by u.v. absorption spectroscopy. In the case of acetate and pyridine-2-carboxylate esters the residue left after removal of the methanol was dissolved in chloroform and the solution was extracted with aqueous disodium dihydrogen ethylenediaminetetra-acetate in order to remove the metal ions. The solution was dried (Na_2SO_4) and the amount of unchanged thiol ester present was determined from the u.v. absorption spectrum.

Preparation of the Thiol Ester Complexes (VII).—*General procedure.* The thiol ester (0·02 mol) and the anhydrous copper salt (0·01 mol) in dry, ethanol-free chloroform (50 ml) were stirred for 2 h and then any insoluble material was filtered off. The filtrate was concentrated to *ca.* 10 ml and then carefully diluted with n-hexane and filtered to give the complex as a green solid (30—40%). In the case of the complexes (VIIa—c) dioxan was used in place of chloroform.

to leave a solid (38 mg), which was identified (i.r. spectrum) as the hydrochloride of 2-dimethylaminoethanethiol.

Reaction between Hydrated Copper(II) *Nitrate and* S-(2-*Dimethylaminoethyl*) *Thiobenzoate in Dioxan.*—The salt (2·45 g) and the thiol ester (4·2 g) were heated together at 70° in a commercial sample of dioxan (50 ml) which had not been dried. After 10 min the large semi-transparent crystals (5·0 g, 91%) of the *hydrogen nitrate salt* of the thiol ester were collected by decantation and filtration; $\nu_{max.}$ 1380 (NO_3^-) and 1665 cm^{-1} (S·COPh); τ (D_2O) 6·8br (6H, s, $^+NMe_2$), 6·35 (4H, m, $S{\cdot}CH_2{\cdot}CH_2{\cdot}^+NMe_2$), and 2·0—2·5 (5H, Ph) (Found: C, 48·5; H, 6·3; N, 9·9. $C_{11}H_{16}N_2O_4S$ requires C, 48·5; H, 5·9; N, 10·3%). When hydrated copper(II) trichloroacetate was used in place of the copper(II) nitrate a 52% yield of the *hydrogen trichloroacetate salt* of the thiol ester was obtained as a deliquescent solid (Found: C, 41·8; H, 5·0; N, 3·9. $C_{13}H_{16}Cl_3NO_3S$ requires C, 41·5; H, 4·3; N, 3·8%).

Reaction between Copper(II) *Trichloroacetate and* S-(2-*Dimethylaminoethyl*) p-*Nitrothiobenzoate.*—The viscous dark brown tar which was formed from the exothermic reaction which occurred when the thiol ester (7·5 g) was added to 'anhydrous' copper(II) trichloroacetate [19] (1·6 g) was extracted with chloroform (3 × 25 ml). The extracts were combined and concentrated under reduced pressure to *ca.* 10 ml, and then diluted with n-hexane (10 ml). The supernatant liquid was decanted from the brown oil which was deposited, and kept for 2 days. Filtration gave bright green crystals (1·11 g, 42%) of the *p*-nitrobenzoate salt (VIIf), whose i.r. spectrum was indistinguishable from that of a sample prepared from copper(II) *p*-nitrobenzoate.

Preparation of the Benzoate Complex (IXb).—(*a*) 2-Dimethylaminoethanethiol was prepared from the hydrochloride (2·8 g) by treatment with ammonia in chloroform in the usual manner. The free base was redissolved in dry chloroform (100 ml) and the solution was stirred and heated under reflux for 30 min with anhydrous copper(II) benzoate

TABLE 2

Complexes (VII)

Complex	R	X	Found (%) C	H	Cl	Cu	N	S	Formula	Required (%) C	H	Cl	Cu	N	S
(VIIa)	Ph	$MeCO_2$	45·8	5·4		15·6	3·8	8·7	$C_{15}H_{21}CuNO_5S$	46·2	5·4		16·2	3·6	8·2
(VIIb)	p-$C_6H_4{\cdot}NO_2$	$MeCO_2$	41·6	4·6		14·9	6·7	7·4	$C_{15}H_{20}CuN_2O_7S$	42·6	4·7		14·2	6·7	7·5
(VIIc)	Ph	$CH_2Cl{\cdot}CO_2$	39·7	4·6	15·0		2·8		$C_{15}H_{19}Cl_2CuNO_5S$	39·2	4·3	15·4		3·0	
(VIId)	Ph	$PhCO_2$	57·3	5·3			3·2		$C_{25}H_{25}CuNO_5S$	57·3	4·6			2·6	
(VIIe)	p-$C_6H_4{\cdot}NO_2$	$PhCO_2$	51·6	4·3			4·7		$C_{25}H_{24}CuN_2O_7S$	51·7	4·2			4·8	
(VIIf)	p-$C_6H_4{\cdot}NO_2$	p-$C_6H_4{\cdot}NO_2$	45·8	3·4			6·1		$C_{25}H_{22}CuN_4O_{11}S$	46·1	3·4			8·6	
(VIIg)	Ph	NO_3													
(VIIh)	p-$C_6H_4{\cdot}NO_2$	$Cl_3C{\cdot}CO_2$													

Methanolysis of the Complex (VIIa).—The complex (1·30 g) and dry methanol (15 ml) were heated under reflux for 2 h, the methanol was removed under reduced pressure, and the residue was extracted with carbon tetrachloride (5 × 5 ml). A u.v. spectrophotometric determination (in MeOH) of the extract showed the presence of methyl benzoate (450 mg, 100%), and this ester (261 mg, 58%), b.p. 78—80° at 20 mmHg, was obtained when the extract was fractionated. The i.r. spectrum of this material was indistinguishable from that of an authentic sample.

The residue left after the extraction with carbon tetrachloride was crystallised from methanol to give a brown solid (190 mg). A portion (70 mg) of this was treated with 5N-hydrochloric acid (4 ml), and hydrogen sulphide was passed through the resultant solution. The precipitate was filtered off and solvent was removed from the filtrate (6·2 g). Insoluble material was filtered off, and the filtrate was concentrated under reduced pressure to *ca.* 15 ml and diluted with an equal volume of n-hexane. The mixture of green and purple solids (2·1 g) was heated (100°) to constant weight under reduced pressure to give the bright green 2-*dimethylaminoethylthiocopper*(II) *benzoate* (1·9 g, 33%) (Found: C, 46·1; H, 5·3; N, 4·3. $C_{11}H_{15}CuNO_2S$ requires C, 45·7; H, 5·2; N, 4·7%) and a colourless liquid which was collected in a cold-trap and identified (n.m.r. and mass spectra) as chloroform.

(*b*) The same complex (i.r. spectrum) was obtained (30—40%) when copper(II) benzoate (3·1 g) and either *S*-(2-dimethylaminoethyl) thiobenzoate (4·2 g) or thioacetate (2·9 g) were heated (60°) together in undried chloroform

[19] W. G. Bateman and D. B. Conrad, *J. Amer. Chem. Soc.*, 1915, **37**, 2553.

(50 ml) exposed to the atmosphere, and the resultant mixture was processed as described in (*a*).

Preparation of the p-*Nitrobenzoate Complex* (IXa).—2-*Dimethylaminoethylthiocopper*(II) p-*nitrobenzoate* was obtained as a grey solid (60—70%) when copper(II) *p*-nitrobenzoate was treated with either 2-dimethylaminoethanethiol or *S*-(2-dimethylaminoethyl) *p*-nitrothiobenzoate as described above in methods (*a*) and (*b*), respectively (Found: C, 35·7; H, 3·7; N, 7·3. $C_{11}H_{14}CuN_2O_4S,\frac{1}{3}CHCl_3$ requires C, 36·1; H, 3·8; N, 7·5%). Satisfactory analytical data were not obtained for the green solid which was formed when this complex was heated *in vacuo* to remove the chloroform.

Reaction of Benzoyl Chloride with the Nickel Complex of 2-*Dimethylaminoethanethiol*.—Benzoyl chloride (2·8 g) was slowly added with stirring to a solution of the complex (2·4 g) in dry chloroform (50 ml); the colour of the solution rapidly changed from red to green. The mixture was shaken with aqueous ammoniacal 1% dimethylglyoxime (2 × 50 ml), and after the precipitate of nickel dimethylglyoxime complex had been filtered off the chloroform was removed under reduced pressure. Distillation of the residue gave *S*-(2-dimethylaminoethyl) thiobenzoate (2·6 g, 62%), b.p. 120—125° at 25 mmHg (lit.,[17] 104° at 0·01 mmHg). In one experiment the reaction mixture was kept for 18 h and then filtered to give the thiobenzoate hydrochloride (4·5 g, 91%), m.p. 161—163° (from methanol) (lit.,[17] 164—165°) (Found: C, 54·2; H, 6·3; N, 5·8. Calc. for $C_{11}H_{16}ClNOS$: C, 53·9; H, 6·5; N, 5·7%).

Reaction of Phenacyl Chloride with the Nickel Complex of 2-*Dimethylaminoethanethiol*.—A solution of phenacyl chloride (3·1 g) and the nickel complex (2·4 g) in dry chloroform (50 ml) was heated under reflux for 1 h and then treated with aqueous dimethylglyoxime as described above. The precipitate was filtered off and the filtrate was fractioned to give 2-(2-dimethylaminoethylthio)acetophenone (1·35 g, 30%) as a yellow liquid, b.p. 65° at 1 mmHg, $\nu_{max.}$ 1680 cm^{-1}, τ ($CDCl_3$) 7·85 (6H, s, NMe_2), 7·35—7·60 (4H, m, $S{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2$), 6·0 (2H, s, $S{\cdot}CH_2{\cdot}CO$), and 2·9—2·6 (5H, m, Ph).

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