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CHROMATOGRAPHIC STUDY OF THE REACTION OF MERCURY(II) AND SILVER(I) IONS WITH NICKEL DITHIOCARBAMATE COMPLEXES DERIVED FROM SOME AROMATIC AMINE DRUGS

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SUMMARY

When nickel dithiocarbamate complexes derived from aromatic amines were reacted with mercury(II) or silver(I) ions, they did not undergo the expected simple exchange reaction wherein the corresponding mercury or silver complexes are formed. Instead, these ions caused the precipitation of sulphur, which facilitated the formation of non-chelating compounds. When a β-hydroxyl group was present in the aromatic amine ligand, a cyclic oxazolidine compound was formed; absence of the β-hydroxyl group led to the formation of isothiocyanate compounds. For example, reaction of mercury or silver with the nickel dithiocarbamate complexes derived from ($\pm$)-ephedrine and ($\pm$)-pseudoephedrine gave isomers of 5-phenyl-3,4-dimethyloxazolidine-2-thione, whereas the complex derived from ($\pm$)-amphetamine produced amphetamine isothiocyanate. The retention behaviour of these compounds was studied using high-performance liquid chromatography and gas chromatography and their structures were elucidated using chemical ionization mass spectrometry and proton nuclear magnetic resonance spectroscopy.

INTRODUCTION

Dithiocarbamates are valuable reagents for the spectrophotometric determination of heavy metals[1,2] and these reagents have been used extensively as ligands for the determination of inorganic species by high-performance liquid chromatography (HPLC). Both normal-phase[3,4] and reversed-phase[5,6] systems have been reported and the high UV absorbances of these chelates have allowed the analysis of metal ions at low levels.

An alternative application of dithiocarbamates to HPLC has been the analysis of organic primary and secondary amines after their reaction with carbon disulphide to produce a dithiocarbamate ligand and ultimately, a metal complex[7]. This procedure is complicated by the occurrence of ligand-exchange reactions leading to the formation of ternary, or mixed-ligand complexes. Ternary complex formation is illustrated below

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$$M(L_1)_2 + M(L_2)_2 \rightleftarrows 2ML_1L_2$$

where L_1 and L_2 are two different bidentate dithiocarbamate ligands. Liška and co-workers[8,9] have reported that three chromatographic peaks often appeared when a solution containing one metal ion and two different dithiocarbamate ligands was injected onto a silica column. They attributed two of these peaks to the binary complexes $M(L_1)_2$ and $M(L_2)_2$, and the remaining peak to the ternary complex ML_1L_2. When the number of metal ions or ligands in the mixture was increased, interpretation of the chromatograms was more difficult.

Appearance of a ternary complex peak in the chromatogram of a mixture of two binary complexes depends largely on the relative rates of the forward and reverse reactions in the above equilibrium. These rates, and the initial stability of the binary complexes, are governed by the nature of the ligand and the central metal ion[3,10]. Nickel chelates of dithiocarbamates have received particular attention because of their ready formation of ternary complexes.

Moriyasu *et al.*[11] have recently reported the HPLC analysis of a mixture of aliphatic amines after their conversion to mercury(II) dithiocarbamate chelates. In this work, no ternary complex peaks were observed and the chromatogram of the mixture contained only peaks attributed to the mercury complex of the dithiocarbamate ligand derived from each amine. This lack of a ternary complex peak was attributed to the high lability of the mercury complexes. The mercury complexes used were formed by reaction of the corresponding nickel complexes with mercuric ions; this procedure was based on the high formation constants of the mercury dithiocarbamate complexes.

The purpose of this communication is to report that whilst secondary aliphatic amines can be analysed in this manner by HPLC, the action of mercury on the dithiocarbamate chelates of aromatic amines, in particular the β-hydroxy aromatic amines, does not give the predicted mercury exchanged dithiocarbamate complexes. Our study shows that under such conditions, Hg^{2+} acts as a desulphurizing agent and with β-hydroxy aromatic amines, it facilitates the formation of substituted 5-phenyloxazolidine-2-thione compounds. Ag^+ was found to give a similar result.

EXPERIMENTAL

Preparation of nickel dithiocarbamate complexes

Reagents

(i) Carbon disulphide–chloroform solution. Carbon disulphide (analytical-reagent Grade, Ajax) was freshly distilled in an all glass apparatus and a 1% (v/v) solution was made up with redistilled chloroform.

(ii) Nickel–ammonia solution. 50 ml of 1% (w/v) $NiCl_2 \cdot 6H_2O$ in water was diluted to 100 ml with 35% ammonia solution (Aristar; BDH).

(iii) Aromatic amine solutions. (−)-Ephedrine, (−)-pseudoephedrine, (+)-pseudoephedrine, (±)-ephedrine, . (±)-β-hydroxyphenethylamine and (±)-amphetamine were obtained from Sigma (St. Louis, MO, U.S.A.). These materials were shown to be free from contaminants by gas chromatographic–mass spectrometric (GC–MS) analysis and by compositional data from microanalysis. Test solutions of approximately 1.0 mg/ml were accurately made up in methanol.

(iv) Solutions of Hg^{2+} and Ag^{+}. 1% (w/v) Solutions of analytical grade $HgCl_2$ and $AgNO_3$ were prepared using distilled water.

Procedure

To 1.0 ml of aromatic amine solution, 2 ml of nickel–ammonia solution were added and the mixture was then extracted with 5 ml of carbon disulphide–chloroform solution. The chloroform layer was washed with three 2-ml portions of distilled water and then dried over anhydrous sodium sulphate. The filtered chloroform layer was evaporated to dryness under a steady stream of nitrogen to remove excess carbon disulphide which may produce extraneous chromatographic peaks[12]. The residue was then redissolved in chloroform. The nickel complexes prepared in this way were shown to give only one chromatographic peak by HPLC and the structure of each complex was confirmed by desorption chemical ionization (DCI) mass spectrometry.

Reaction of mercury (silver) with nickel dithiocarbamate complexes

Two methods were used for the reaction of mercuric or silver ions with the dithiocarbamate ligands. The first method was similar to that described by Moriyasu *et al.*[11] (Method A) and the second method involved the direct reaction of mercury (or silver) with the dithiocarbamate ligand, without prior formation of a nickel complex.

Method A. To the chloroform solution of the corresponding nickel dithiocarbamate complex, aqueous mercuric chloride solution (or silver nitrate) was added and the mixture was shaken vigorously for a few seconds until the chloroform layer became clear. The precipitate which formed at this stage was filtered off and analysed by inductively coupled plasma atomic emission spectroscopy (ICPAES), using a Labtest Model V25 instrument (Labtest, Melbourne, Australia). The chloroform layer was washed twice with a small volume of distilled water and was finally dried over anhydrous sodium sulphate.

Method B. To 1 ml of aromatic amine solution, 1 ml of concentrated ammonia solution and 2 ml of carbon disulphide–chloroform solution were added and the mixture was lyophilized to dryness. The residue was then dissolved in 2 ml of 0.1 *M* acetate buffer, pH 5, containing 0.2 ml of mercuric chloride solution. The mixture was shaken vigorously for several seconds and then extracted with chloroform (5 ml). The chloroform layer was dried and diluted to an appropriate volume.

HPLC

Instrumentation and chromatographic procedure. The liquid chromatograph system consisted of a Waters Assoc. Model M6000 pump, Model U6K injector, Model M440 UV detector and a QD 15 Hitachi recorder. A 5 mm I.D. Radial-Pak silica cartridge was used in conjunction with a Waters RCM-100 radial compression module. The detector was operated at either 313 or 254 nm, with a sensitivity setting of 0.5 a.u.f.s. and all separations were carried out at 20°C with a recorder chart speed of 0.5 cm min^{-1} and a mobile phase flow-rate of 2 ml min^{-1}. The column was equilibrated with each mobile phase before use. A constant retention time was usually obtained after pumping 20–30 column volumes. When changing from one mobile phase to another, the column was washed with hexane–chloroform (50:50, v/v) before equilibrating with the new solvent.

Preparation of mobile phases. Organic solvents used for mobile phases were of

Analytical Grade and were distilled in all-glass apparatus. Solvents were dried by passing through a column of anhydrous sodium sulphate (2.5 × 30 cm) and were stored over a molecular sieve (Union Carbide, Type 3A) for at least 24 h before use. The exact ingredients of the mobile phases used are given in the captions to the figures. Mobile phases were aspirated through 0.7-μm glass microfibre paper filters (GF/F, Whatman), degassed in an ultrasonic bath and allowed to equilibrate to ambient temperature before use.

GC–MS

The instrumentation used in this section of the study was a Finnigan Model 3200 gas chromatograph, chemical ionization mass spectrometer interfaced to a 2300 Incos data system supplied by the same manufacturer. Methane served as the GC carrier and CI reagent gas (ion-source pressure 0.8 Torr). The ion-source temperature was maintained at a nominal 110°C by filament emission (0.8 mA).

A platinum wire loop desorption probe was used for identification of nickel dithiocarbamate complexes. The construction of this probe and the programmable current controller were essentially that given by Bruins[13]. Desorption of samples from the probe occurred typically at 1.0–1.5 A with the linearly programmed current adjusted at 2.0 A min^{-1}. The rapidity of the desorption process necessitated the setting of a fast mass scan rate on the Incos data system and this was typically less than 1.0 sec per scan.

Gas chromatography of pentafluoropropionate (PFP) derivatives of ephedrine and pseudoephedrine, and the products resulting from the action of Hg^{2+} (Ag^{+}) on nickel complexes, was performed using a 1.8 m × 2 mm I.D. U-shaped glass column packed with 3% OV-1 on Gas-Chrom Q (100–120 mesh) (Applied Science Labs.). The GC–MS interface oven and transfer line were maintained between 240 and 250°C and 1 min after sample injection the oven was temperature-programmed at 8°C min^{-1} to 250°C.

Ephedrine and pseudoephedrine were derivatized by heating 1.0 mg of sample for 30 min at 60°C with a mixture of pentafluoropropionic anhydride–ethyl acetate (1:1; 100 μl). After cooling, excess reagent was removed at room temperature in a stream of dry nitrogen, the residue reconstituted in anhydrous ethyl acetate (1 ml) and aliquots (2–4 μl) were then injected for GC–MS analysis.

Proton nuclear magnetic resonance spectroscopy

Proton nuclear magnetic resonance spectra were obtained using a Jeol FX pulsed Fourier Transform NMR spectrometer operating at 100 MHz and 35°C. All spectra were obtained using 8K data points, 1000 Hz band width, a pulse width of 7 μsec and acquisition time of 4 sec.

Samples of 4–6 mg were dissolved in about 2.0 ml of deuterochloroform in a 5.0-mm NMR sample tube. $^{2}H_2O$ was used for proton-exchange runs.

RESULTS AND DISCUSSION

The chromatogram obtained from the reaction of nickel with a mixture of the dithiocarbamate ligands derived from (−)-ephedrine, (+)-pseudoephedrine and (−)-pseudoephedrine is shown in Fig. 1a. Hereafter, these ligands will be referred to

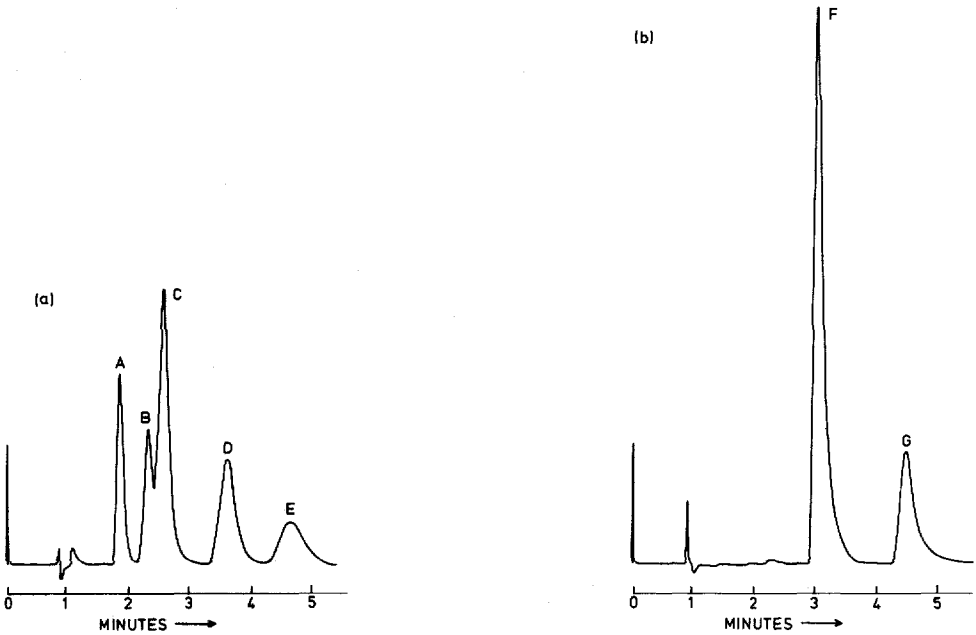

Fig. 1. (a) Chromatogram of the products of reaction of Ni^{2+} with dithiocarbamate ligands derived from (+)-ephedrine and (±)-pseudoephedrine. Mobile phase: 1.5% (v/v) isopropanol in chloroform–hexane (60:40, v/v). Peak identities (see text for key to abbreviations): A, $Ni[(CS_2:(-)eph)_2]$; B, $Ni[(CS_2:(-)eph)(CS_2:(+)pse)]$; C, $Ni[(CS_2:(-)eph)(CS_2:(-)pse)]$; D, unresolved $Ni[(CS_2:(-)pse)_2]$ and $Ni[(CS_2:(+)pse)_2]$; E, $Ni[(CS_2:(-)pse)(CS_2:(+)pse)]$. (b) Chromatogram obtained after reaction of the above mixture with mercury(II) or silver(I) ions. Mobile phase: hexane–chloroform (70:30, v/v). Peak identities: F, product derived from (±)-pseudoephedrine complexes; G, product derived from (−)-ephedrine complex.

by the respective abbreviations $(CS_2:(-)eph)$, $(CS_2:(+)pse)$ and $(CS_2:(-)pse)$. The chromatogram shows peaks due to binary and ternary complexes. Two types of ternary complex may be identified: the first contains both enantiomers of pseudoephedrine, namely $Ni[(CS_2:(-)pse)(CS_2:(+)pse)]$ and the second type contains structurally related, but not enantiomeric, ligands, namely $Ni[(CS_2:(-)eph)(CS_2:(+)pse)]$ and $Ni[(CS_2:(-)eph)(CS_2:(-)pse)]$.

In order to elute these complexes, it was necessary to include a polar modifier in the mobile phase; this was typically 0.2–1.0% (v/v) of isopropanol, triethylamine or dimethyl sulphoxide in a mobile phase of chloroform–hexane (60:40, v/v). The selectivity of different polar organic modifiers on the separation of these compounds is discussed elsewhere[14]. Such modifiers were required for the elution of complexes derived from any aromatic amine containing a β-hydroxyl group, indicating that this group caused a strong interaction of the molecule with the silica surface of the column.

When mercury(II) or silver(I) was substituted for nickel in an identical reaction mixture to that used in Fig. 1a, the chromatogram shown in Fig. 1b resulted. The same result was obtained when either of the alternative procedures described in the Experimental section was followed. The chromatogram contains only two peaks, the first of which resulted from pseudoephedrine and the second from ephedrine. The

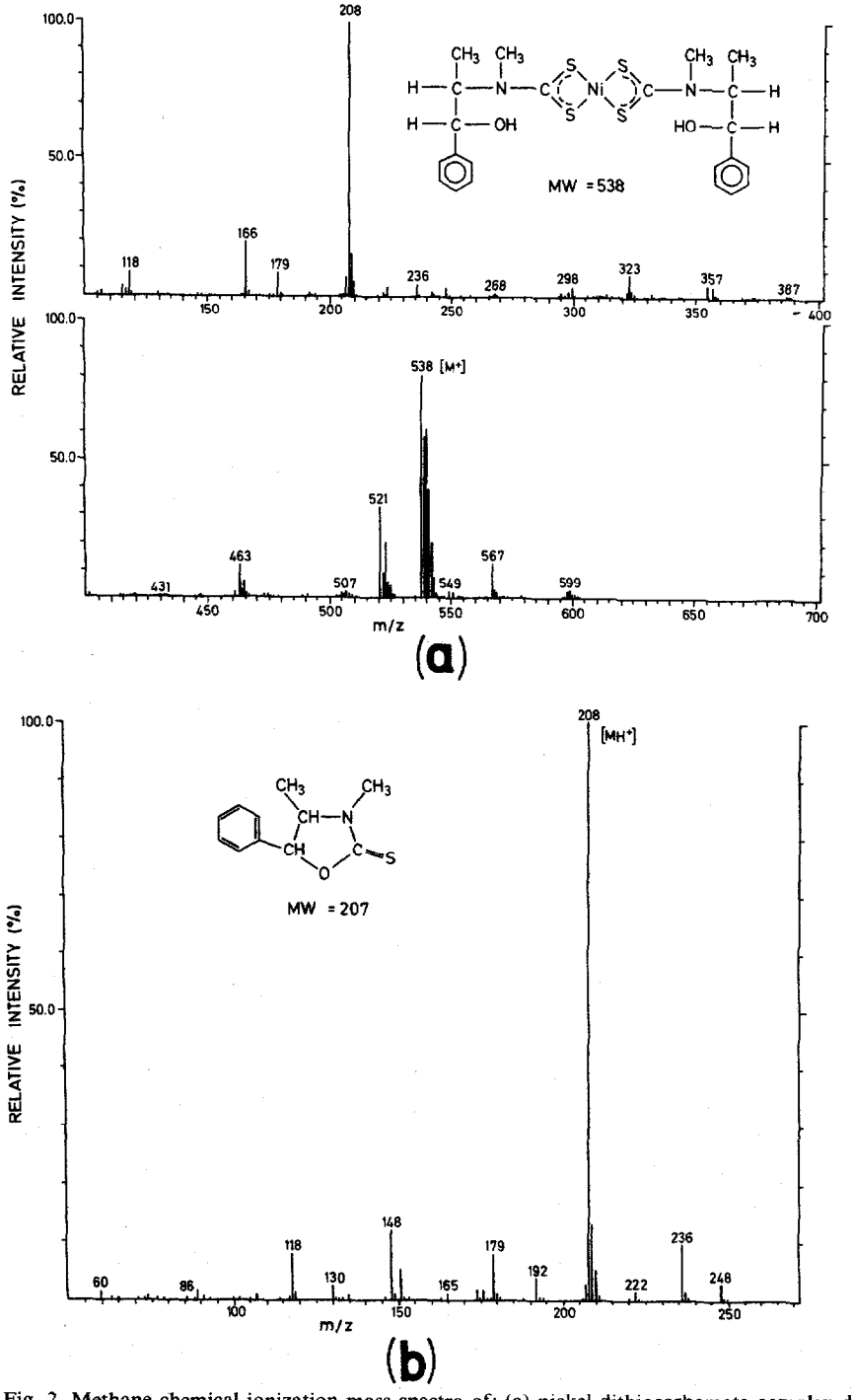

Fig. 2. Methane chemical ionization mass spectra of: (a) nickel dithiocarbamate complex derived from pseudoephedrine; (b) product of reaction of mercury(II) or silver(I) ions with the nickel dithiocarbamate complex derived from pseudoephedrine. The proposed structure of the product is illustrated.

simple explanation for the absence of ternary complex peaks is that such complexes were very labile, however some aspects of the chromatography suggest that the two peaks in the chromatogram were not due to mercury complexes of dithiocarbamate ligands. First, the mobile phase used for elution did not contain a polar modifier of the type previously found to be necessary for elution of complexes of ligands derived from amines containing a β-hydroxyl group[14]. Secondly, the elution order of the species was the reverse of that obtained with nickel complexes of the same ligands (see Fig. 1a). This reversal of elution order was also obtained for GC of the same mixtures as used for HPLC. In view of these anomalies, we have further investigated the identities of the two peaks appearing in Fig. 1b.

GC–MS of the reaction products of Hg^{2+} and the nickel dithiocarbamate complexes derived from ephedrine and pseudoephedrine gave two chromatographic peaks, both of which gave identical mass spectra (Fig. 2b). These spectra contained no molecular ion corresponding to the mercuric complexes of ephedrine or pseudoephedrine; the equivalent molecular ion was clearly identifiable in the mass spectrum of the nickel dithiocarbamate complex of pseudoephedrine (Fig. 2a). Fig. 2a also shows no evidence of Hg^{2+} present in the compound, suggesting that Hg^{2+} may have precipitated during the course of the reaction. This was confirmed when analysis of the precipitate (see Experimental) by ICPAES showed it to be HgS. Similar results were obtained when Ag^{+} was used.

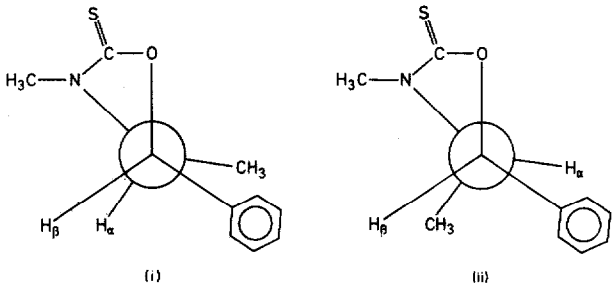

Fig. 3. Newman projections of isomers of 5-phenyl-3,4-dimethyloxazolidine-2-thione: (i) *erythro* isomer (derived from ephedrine); (ii) *threo* isomer (derived from pseudoephedrine).

TABLE I

FORMAL RATIONALIZATION OF PRINCIPAL FRAGMENTS APPEARING IN THE METHANE CI MASS SPECTRUM OF 5-PHENYL-3,4-DIMETHYLOXAZOLIDINE-2-THIONE (SEE FIG. 2)

m/z	*Fragment*
208	$[MH]^+$
236	$[M + C_2H_5]^+$
248	$[M + C_3H_5]^+$
179	$[MH - NCH_3]^+$
151	$[MH - CH_3CHNCH_3]^+$
148	$[MH - COS]^+$
130	$[MH - (C_6H_5 + H)]^+$
118	$[MH - (NCH_3COS + H)]^+$

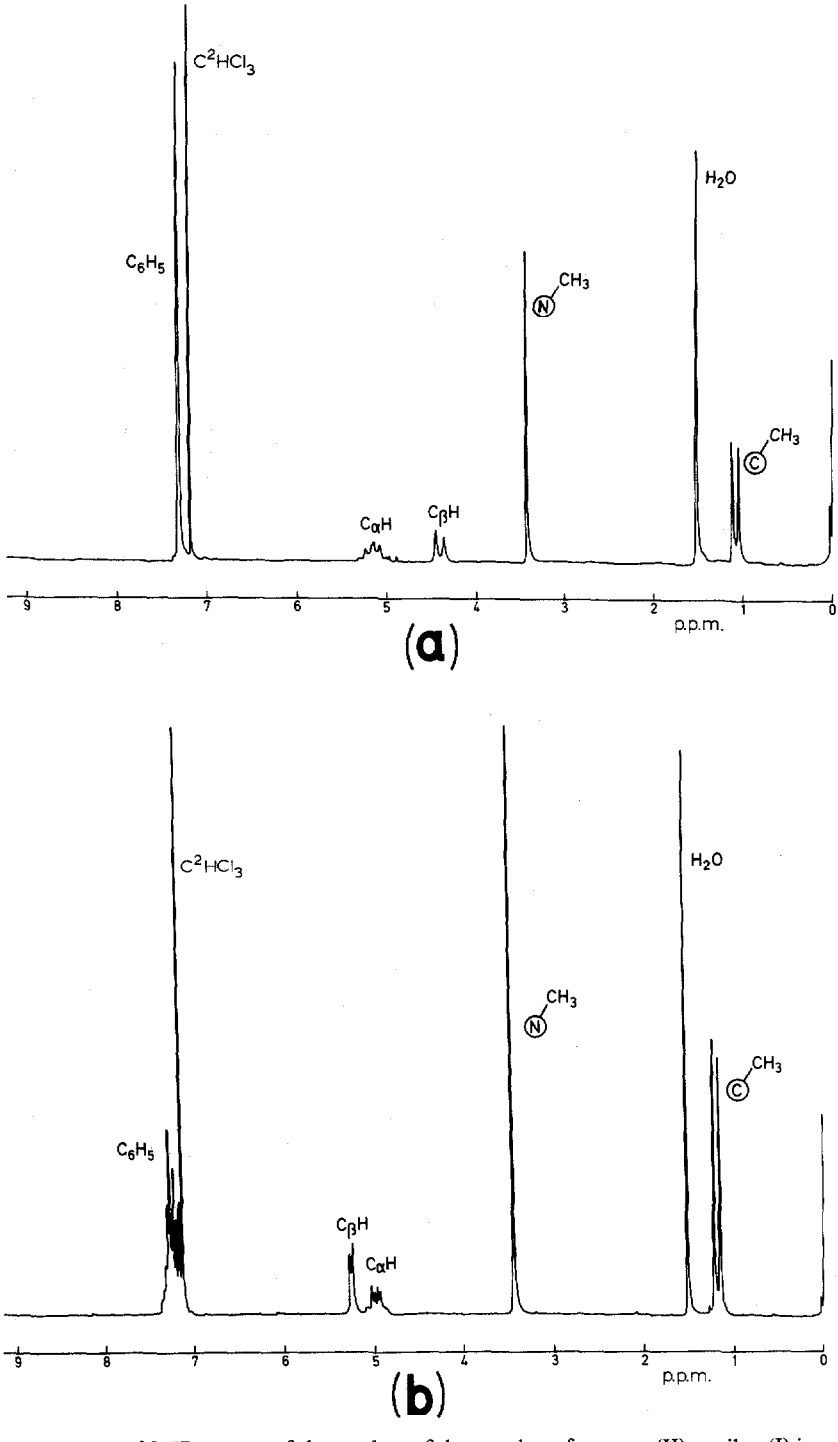

Fig. 4. Proton NMR spectra of the product of the reaction of mercury(II) or silver(I) ions with the nickel dithiocarbamate complexes derived from pseudoephedrine (a) and ephedrine (b).

Clearly the two compounds giving rise to the peaks in Fig. 1b were isomeric, and their molecular weights (207) and compositional data (63.7% C, 6.36% H, 6.79% N) suggested that they were isomers of 5-phenyl-3,4-dimethyloxazolidine-2-thione, the structure of which is given in Fig. 2b. Newman projections of the *erythro* and *threo* isomers of this compound are shown in Fig. 3. Rationalization of the major fragments appearing in the mass spectrum shown in Fig. 2b is given in Table I. Proton NMR spectra of the species produced by reaction of Hg^{2+} with nickel dithiocarbamate complexes derived from ephedrine and pseudoephedrine are shown in Fig. 4. These spectra are consistent with the proposal that the *erythro* isomer of 5-phenyl-3,4-dimethyloxazolidine-2-thione is produced from ephedrine and the *threo* isomer is produced from pseudoephedrine.

The cyclization of straight-chain compounds containing sulphur and β- or γ-hydroxyl groups using Hg^{2+} or Ag^{+} has been reported previously[15]. The role of the metal ion was to facilitate removal of a sulphur atom from the original molecule. Spencer and Daxenbichler[16] have recently published electron impact mass spectra of six oxazolidinethione compounds and they have observed that fragments due to fission of the oxazolidinethione ring system were more pronounced in compounds containing an aromatic substituent in the 5 position of the ring system.

When (±)-β-hydroxyphenethylamine was substituted for pseudoephedrine in the reactions described above, a similar cyclic product was produced. However when the nickel dithiocarbamate complex derived from (±)-amphetamine was similarly treated, a different mass spectral fragmentation pattern resulted (Fig. 5). In this case, formation of a cyclic compound was not possible since amphetamine does not con-

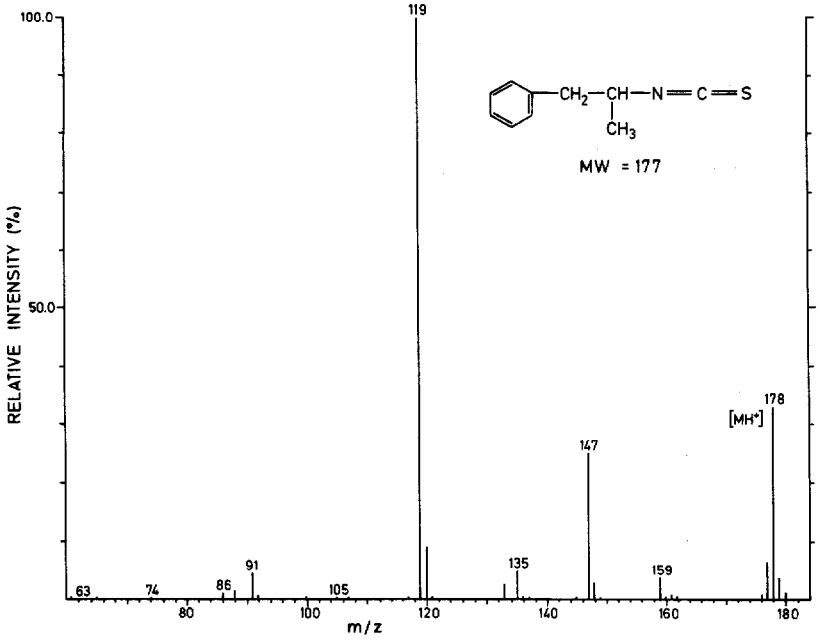

Fig. 5. Methane chemical ionization mass spectrum of the product of the reaction of mercury(II) or silver(I) ions with the nickel dithiocarbamate complex derived from (±)-amphetamine. The proposed structure of the product is illustrated.

tain a β-hydroxyl group, and amphetamine isothiocyanate was produced (see Fig. 5). The observed fragmentation pattern can be fully rationalized in terms of the structure of amphetamine isothiocyanate.

CONCLUSIONS

The method described by Moriyasu *et al.*[11] for the analysis of aliphatic amines by formation of their mercuric dithiocarbamate complexes is not applicable to the aromatic amines studied in this paper. When a mixture of the nickel complexes derived from ephedrine and pseudoephedrine was reacted with mercuric (or silver) ions, the resulting two products were not the expected corresponding mercuric (or silver) dithiocarbamate complexes, but were identified as isomers of 5-phenyl-3,4-dimethyloxazolidine-2-thione. This reaction occurred with other aromatic amines containing a β-hydroxyl group, however when this β-hydroxyl group was absent, reaction with Hg^{2+} or Ag^{+} produced isothiocyanate compounds.

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