INTERACTIONS OF HALOGENS WITH AMINES

by

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ABSTRACT

The individual stages of the interaction of amines with halogens - in particular, iodine - have been studied.

In the course of this investigation, it has been shown that amines and iodine interact initially via the nitrogen lone pair to form molecular complexes (CHARGE-TRANSFER COMPLEXES). Several of these have been isolated and some of their properties studied in detail. It was thus determined that these complexes can undergo further chemical change during which the hydrogen iodide which is generated converts any unreacted amine to the corresponding hydroiodide salt. The latter is inert to oxidation by iodine under the conditions employed. It has been shown that this mode of reaction is dependent upon the availability of α-aliphatic hydrogen in the amine molecule.

The initial oxidation product derived from the amine is the corresponding IMMONIUM SALT. This intermediate may, according to reaction conditions, undergo hydrolysis to secondary amine and carbonyl compound or conversion to ENAMINE; the latter may then undergo further transformation by inter- or intramolecular reaction.

The nature of the products isolated from the oxidation of several amines by iodine in isopropanol solution has been rationalised in terms of this generalised reaction pathway, which is analogous to those proposed by other workers for the oxidation of amines by other two-electron oxidants.

This reaction pathway also applies to the formation of an industrial disinfectant by the action of solid iodine on a commercially available tertiary amine mixture. It was thus demonstrated that most of the amine used is recovered from the reaction mixture as the base hydroiodide and that the hydrogen iodide needed for this conversion is

formed during the degradative oxidation of a minor proportion of the starting material.

Furthermore, it has been established that the biocidal principle of the commercial disinfectant formulation is the N-alkyldiethanolamine hydriodide. A concurrent study of the effect of structure on biological activity has confirmed the dependence of disinfectant activity on detergent properties in this class of disinfectants.

ACKNOWLEDGEMENTS

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CONTENTS

ABBREVIATIONS

CnDEA	$C_nH_{2n+1}N(CH_2CH_2OH)_2$
TED	Triethylenediamine
Hex	Hexamine
Q	Quinuclidine
A	Acceptor
D	Donor
C-T	Charge-Transfer
C.M.C.	Critical Micelle Concentration
M.I.C.	Minimum Inhibitory Concentration
p.m.r.	proton magnetic resonance
I.R.	Infrared
U.V.	Ultraviolet
e.s.r.	electron spin resonance
g.l.c.	gas-liquid chromatography
t.l.c.	thin layer chromatography
DNP	2,4-dinitrophenylhydrazine
s, vs	strong, very strong
m	medium
w, vw	weak, very weak

CHAPTER ONE

ISOLATION AND IDENTIFICATION OF THE ACTIVE PRINCIPLE IN A COMMERCIAL DISINFECTANT FORMULATION BASED ON THE *N*-ALKYLDIETHANOLAMINE - IODINE SYSTEM.

CHAPTER ONE: A. INTRODUCTION

THE HALOGENS AND HALOGEN DERIVATIVES AS DISINFECTANTS

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The halogens have been known since the early days of chemistry[1,2]; thus chlorine was recognised as an element by Sir Humphrey Davy in 1809 and iodine by Courtois in 1811, whilst bromine was discovered by Balard in 1826. In contrast, mainly because of its exceptionally high reactivity, fluorine was not isolated until 1886. Fluorine is often considered separately from the other halogens and as it has not been used as a disinfectant[3] it will not be discussed further here.

The utility of halogens and their simple compounds as disinfectants was recognised at an early stage. According to Mellor[1], chlorine must have been known to the alchemists for many centuries prior to Davy's work, and, in fact, one of the earliest records[3] of the use of chlorine as a disinfectant dates back to 1791 when the gas was employed as a fumigant in hospitals. Chlorine was known to destroy and prevent foul odours and, prior to the establishment of the germ theory of human disease, the belief that foul odours and diseases are interrelated, was probably the principal reason for its use in this connection.

In 1825, Labarraque used chlorinated soda solution for the treatment of infected wounds and recommended it for general disinfection[4]. This was followed by Semmelweiss' work on the use of calcium hypochlorite as a skin disinfectant to combat puerperal fever which is described in his famous book entitled 'Aetiologie' which was published in 1861[4].

The biocidal properties of hypochlorites under controlled laboratory conditions were demonstrated by Koch in 1881[5] and, following the work of Traube in 1894[5], hypochlorites rapidly became the standard reagent used in water purification. But the widespread use of hypochlorites did not begin until World War I when Dakin[6], in 1915, introduced the use of a 0.5% hypochlorite solution for the disinfection of open and infected wounds. The usefulness of this contribution to disinfection is evidenced by the fact that 'Dakin's Solution' was one of the standard products described in the British Pharmacopoeia until 1963. However, the war was also indirectly responsible for the use of chlorine gas itself, instead of hypochlorites, in water and sewage treatment, because the need for vast quantities of chlorine for use as a poison gas provided the impetus for the technical advances which led to the large scale production of liquid chlorine.

Andrewes and Orton, in 1904[7], were the first to suggest that undissociated hypochlorous acid, formed by the action of water on elemental chlorine or hypochlorites, respectively, according to the following equations, is the true biocidal agent, because the biological activity of the resulting solution decreases with a rise in pH.

$$Cl_2 + H_2O \longrightarrow HOCl + H^{\oplus} + Cl^{\ominus}$$

$$Ca(OCl)_2 + 2H_2O \longrightarrow Ca(OH)_2 + 2HOCl$$

In water treatment by chlorination, some of the chlorine combines with ammonia, amino acids and proteins present in natural waters, to form chloramines and other N-chloro compounds. The course of the reaction between chlorine and ammonia is somewhat complex and varies according to (a) the initial proportions of the two reactants, and (b) the pH of the solution, and according to Alan and Brookes[8] it proceeds as follows:-

$$NH_4^{\oplus} + HOCl \longrightarrow NH_2Cl + H_2O + H^{\oplus}$$

$$2NH_2Cl + HOCl \longrightarrow N_2 + 3HCl + H_2O$$

$$NH_2Cl + HOCl \longrightarrow NHCl_2 + H_2O$$

$$NHCl_2 + HOCl \longrightarrow NCl_3 + H_2O$$

These reactions have been utilised in drinking water treatment by the deliberate addition of ammonia to chlorinated water, as the resultant compounds produced are biocidal. The use of N-chloro compounds as biocidal agents dates back to Dakin's work on Chloramine T and related compounds[3]. Thus, it can be seen that chlorine itself, as well as simple inorganic derivatives and organic N-chloro compounds have been used widely in water purification and disinfection. They still play an important part in the field of public health because later work has shown them to be active against a wide range of bacteria, fungi, viruses and other micro-organisms[3,5].

In contrast, bromine has been but little employed in this field and does not seem to possess any advantages over chlorine, although mixtures of these halogens are claimed[9] to be more effective than the individual elements.

Iodine has a long history of use as a disinfectant. The first specific reference to its use on wounds was made in 1839[10] and studies carried out in the latter half of the 19th century placed its value as an antiseptic on a much firmer basis[4]. Since that time iodine has been used as an antiseptic for the skin[11], for the sterilization of the air[12] and of inanimate objects such as surgical instruments[3]; as a therapeutic agent in diseases caused by vegetative bacteria[5], spores, viruses and fungi, as well as for the disinfection of drinking water and swimming pools[10]. Generally, free iodine is the active agent[13] which means that it must be presented as the element and not, as in the case of chlorine, in the form of organic or inorganic derivatives. Traditionally, iodine is formulated either in alcohol, or in an aqueous solution of potassium iodide. In the latter case, the tri-iodide formed has only a low activity against both bacterial spores[14] and vegetative cells[15], and this is clearly a disadvantage. Furthermore when these solutions are used as antiseptics they stain badly and, on storing, lose strength by the volatilisation of iodine. Although relatively non-toxic, solutions of iodine in these solvents are harsh and irritant to some skins and may even cause severe blistering. For these reasons, such iodine formulations have tended to fall into disuse. Efforts to overcome their disadvantages have resulted in the introduction of iodophors, which are the products of the interaction of iodine with certain types of cationic, anionic or preferably, non-ionic surface active agents[16]. These latter compounds consist of a hydrophobic portion which is normally a long alkyl chain, and a hydrophilic portion which may be, for example, a carboxylic acid ester group or a polyoxyethylene chain. In solution, above a certain concentration, they will form micelles, i.e. aggregates of molecules which in aqueous solution have the alkyl chains turned inward so that they only interact with each other. The hydrophilic portion on the outside of the micelle is then enabled to interact with the aqueous phase. In an iodophor the iodine is dissolved in the hydrocarbon portion of the micelle structure and partitioning of the iodine occurs between this and the aqueous phase[17]. Iodophors may solubilize up to 30% by weight of iodine, of which 70-80% may be released as available iodine on dilution of a concentrated solution[16]. Thus iodophors have at least the range of uses that iodine has, but as the solutions are more stable, non-staining and virtually non-irritating to the eyes, nose, skin and mouth[18] they have largely supplanted iodine itself.

In summary, it may be said that of the halogens, chlorine and iodine have a long history of use as germicides. Iodine suffers from some disadvantages when presented in solution and attempts to overcome these have resulted in the production of iodophors. Because of its different mode of action and properties, chlorine has not been formulated in this way.

Iodophors have been employed successfully in preoperative skin treatment and for the sterilization of instruments and blankets. Further uses have been found and iodophors are now widely used in the food processing industries - particularly the dairy industry and increasingly in agricultural premises such as piggeries and broiler houses where intensive methods of production make animal hygiene extremely important.

In spite of the fact that iodine has been in use as a biocidal agent for some 150 years, attempts are still being made to provide more acceptable iodine formulations. One such attempt, by the personnel of Glasby Pharmaceuticals Ltd., initiated the work described in this thesis. The identification of the biocidal principle in the commercial formulation and the elucidation of the effect of structure on the biocidal activity of the system employed was the main aim of this part of the work.

CHAPTER ONE: B. DISCUSSION

INVESTIGATION OF THE COMMERCIAL DISINFECTANT

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1. The Characterisation of the Biocidal Principle in the N-Alkyldiethanolamine - Iodine System.

As outlined in the previous section, iodophors have come to occupy an important place in the spectrum of antiseptics and disinfectants. For this reason, Glasby Pharmaceuticals Ltd. attempted to develop their own iodophor by the interaction, under a variety of conditions, of iodine with various commercially available long chain amines and amine derivatives. Their approach to this project was empirical in nature, but nevertheless a formulation with useful biocidal properties was obtained from the interaction of iodine with 'Ethomeen C 12' under certain conditions (see later).

'Ethomeen C 12' is a commercial product manufactured by Armour Hess and Co. Ltd. and comprises of a mixture of N-alkylated-diethanolamines of the general formula $R.N(CH_2.CH_2\ OH)_2$. The hydrocarbon residue R, is derived from cocoa oil and, consists, chiefly of a mixture of saturated normal alkyl chains ranging from 8 to 18 carbon atoms in length, and of these, about 50% is n-dodecyl[19]. 'Ethomeen C 12' is manufactured by converting cocoa oil into a mixture of primary amines (RNH_2), the cocoa amines, which are subsequently treated with ethylene oxide until an average of 2 ethylene oxide molecules per primary amine molecule has been consumed. Thus, to a first apprximation, the commercial material may be regarded as N-(n-dodecyl)-diethanolamine, $C_{12}H_{25}N(CH_2CH_2OH)_2$.

The commercial biocidal product is prepared as follows: solid iodine is added with vigorous stirring to the liquid amine heated to 70°C, the molar ratio of amine:iodine used being 2:1. On interaction, heat is evolved and the temperature rises to about 140°. On cooling, a dark-brown, sticky, viscous liquid is obtained, which is dissolved in water or water-alcohol mixtures and these solutions are sold as disinfectant concentrates. Sometimes, as is usual with iodophors mineral acid is added to the formulation.

When moderately concentrated solutions of iodophors are treated with starch solution the characteristic blue colour of the starch-iodine complex is not obtained because the iodine is strongly retained by the hydrocarbon portion of the micelles. However, iodophors release iodine on dilution to below the critical micelle concentration. Using this technique, elemental iodine was detected in the product formed when iodine was used in excess of a molar ratio of amine: iodine of 2:1, respectively. When the molar ratio of the reactants was 2:1, iodine could not be detected in the product and an aqueous solution of this was acidic with a pH of about 4. In contrast, when amine was used in excess of this ratio the solution of the product in water was alkaline. These observations suggest that the commercial product is not an iodophor and that a chemical reaction occurred with a stoichiometry of 2 moles of base to 1 mole of iodine. It was thus decided to investigate the reaction thoroughly, and isolate and identify the biocidal agent in the commercial product. It must be mentioned in this connection, that although positive identification of the biocidal principle was subsequently made using pure synthetic C12DEA, the commercial mixture itself was used initially for this purpose.

The crude commercial product was systematically examined using thin layer chromatography which revealed that it contained two major, as well as, several very minor components. One of the major spots on the chromatogram had the same R_F value and appearance as 'Ethomeen C 12' and was assigned to unreacted starting material. The other major spot, at R_F 0.9, was originally thought to be due to the active component and an attempt was made to isolate it by dry-column chromatography using the technique devised by Loev and Snader[20]. Of the various systems employed, the best results were obtained with silica gel as the adsorbent and water as the mobile phase. Each dry column was monitored by t.l.c. and by bulking the appropriate fractions from a number of runs, 0.8 g. of material was obtained from the total of 4.4 g. of the crude reaction product which was processed in this way. Examination of this material showed that it consisted mainly of an unidentified inorganic material (assumed to be derived from the thin layer adsorbent) and iodide ion. Further, it was found to be biologically inactive. A re-examination of the t.l.c. system showed that when potassium iodide and hydriodic acid are each subjected to chromatography, they too give a spot at high R_F (R_F 0.9) which was shown to be due to iodide ions. A probable explanation for this phenomenon is that ion exchange occurs on the thin layer plate and the counter ion to the iodide is derived from the silica gel or the binding agent.

This work showed that iodide is produced in the reaction, and this was further indicated by using an iodide sensitive electrode and by ultra-violet absorption measurements at 226 nm. where the iodide ion has an absorption band. Attempts were also made to quantify these observations. Thus it was established that the use of silver nitrate and copper sulphate solutions did not give the expected precipitates of the insoluble iodides, presumably because of the surfactant properties of the amine present in the mixture. Attempts were made to estimate the iodide by potentiometric titration using various oxidants. Of these, sodium hypochlorite did not given an end point with the solution of the reaction product although it gave satisfactory results with a potassium iodide solution. Results obtained with (a) potassium dichromate, and (b) potassium iodate in dilute acid solution indicated that only 73% of the iodine used was present in the product as iodide. But further work using the industrial product demonstrated, that in spite of the fact that silver iodide is not precipitated in the process, silver nitrate is a suitable titrant for the estimation of iodide, provided that the end point is determined potentiometrically using a silver electrode. By this method, it was shown that 96% of the iodine used in the reaction was reduced to iodide.

When iodine changes from the elemental state to iodide ion, it is reduced and thus some other component of the reaction system (e.g. amine) must be oxidised. At the same time, the reaction must produce a cation as a counter ion to the iodide. A reaction pathway which complies with these requirements is the oxidation of the amine accompanied by the formation of protons which combine with any available base to form salts. The fact that an aqueous solution of the commercial product is acidic (pH $\sim$ 4) is in agreement with this hypothesis as the product from such a reaction would be a mixture of salts of weak bases and a strong acid. This hypothesis was further substantiated by taking a known weight of the commercial product, basifying it and extracting the oil so liberated with chloroform. The infra-red spectrum of the extract was very similar to that of the free amine. The aqueous phase was then titrated with silver nitrate, without any possibility of interference in this case from the surface active amines, and it was thus confirmed again that 96% of the iodine used was reduced to iodide.

Efforts to isolate and characterise base hydroiodides from the commercial product were unsuccessful and further work was carried out using pure long chain amines as starting materials. However, because of the experimental difficulties encountered whilst working with these surfactants, pure diethanolamines containing short alkyl chains (R) were employed instead. Accordingly the first three members of the homologous series CnDEA (n = 1,2,3) were synthesized by standard methods using diethanolamine (HDEA). Each amine was reacted with iodine under conditions employed industrially but the crude products so obtained were found to contain some elemental iodine. In an attempt to obtain products free from iodine each reaction was carried out in methylene chloride at room temperature for 16 hours. Although base hydroiodides could not be isolated from these reactions the crude products were found to contain iodide ion which was determined by titration with silver nitrate (Table 1).

TABLE I REACTION OF CnDEA (n=1,2,3) WITH IODINE IN METHYLENE CHLORIDE AT ROOM TEMPERATURE

Amine	% Conversion of Iodine to Iodide
C1DEA	91.6
C2DEA	97.1
C3DEA	99.8

Spectroscopic examination of these crude products also tended to support the theory that they were mixture of hydroiodides. In the p.m.r. spectra, the peaks assigned to the absorption of the methylene groups adjacent to the nitrogen in the starting materials shifted down field (from 2.6 to 3.6 δ) in the products, as would be expected for amine salts. The infra-red spectra of the crude products also showed absorptions typical of amine salts at 2700 $cm.^{-1}$.

Triethanolamine was also treated with iodine according to the industrial method, and at room-temperature in methylene chloride solution; it gave a brown granular product which on trituration with methanol yielded a white crystalline solid. That this was triethanolamine hydroiodide was proved by the estimation of iodide ion using three different titrants, each of which gave a result in good agreement with the theoretical figure. Elemental analysis, also gave values in good agreement with those required for this salt. The reaction product was identical with an authentic specimen of triethanolamine hydroiodide as regards p.m.r. and infra-red spectra, and melting point.

Additional evidence as to the nature of the product of the industrial procedure was obtained when pure synthetic C12DEA was reacted with solid iodine to give a brown, slightly sticky solid, free from elemental iodine. This product, when recrystallised from carbon tetrachloride, gave a yellow-brown powder which was identical as regards infra-red and p.m.r. spectra and melting point, with an authentic specimen of N-dodecyldiethanolamine hydroiodide, prepared from the amine and iodine free hydriodic acid (see later, p 181)

Triethylamine hydroiodide and N,N-dimethyldodecylamine hydroiodide were isolated from the reaction of iodine and the corresponding amine in refluxing tetrachloroethylene. These reactions were carried out in this manner in an attempt to modify the extremely vigorous conditions of the commercial reaction. Ethomeen C 12 and C12DEA were similarly reacted with iodine both in tetrachloroethylene and isopropanol solutions under reflux, but the products (although biologically active) proved to be intractable.

The isolation of the corresponding amine hydroiodide from several reactions indicates that the interaction of elemental iodine with tertiary amines applies to amines of the type RCH_2NR_2, and, assuming that the oxidation product of the amine is basic in nature, may be formulated as

$$\text{x moles amine} + \text{y moles } I_2 \longrightarrow \text{z moles } [\text{oxidised amine}]\, H^{\oplus} I^{\ominus}$$
$$+ (x - z) \text{ moles amine } H^{\oplus} I^{\ominus}$$

By inspection, $x = 2y$

and this is in agreement with the stoichiometry of the industrial reaction which is 2 moles of amine to 1 mole of iodine. However, this is the stoichiometry of the overall reaction and not that of the actual redox process which, if it were 1:1, would give a reaction product consisting of 50% oxidised amine hydroiodide and 50% non oxidised amine hydroiodide. But the crude product from the reaction of solid iodine and neat C12DEA was demonstrated to contain at least 69% of C12DEA.HI, which indicates that at <u>least</u> 2 moles of iodine a e involved in the oxidation, and the further oxidation, of each C12DEA moiety i.e.

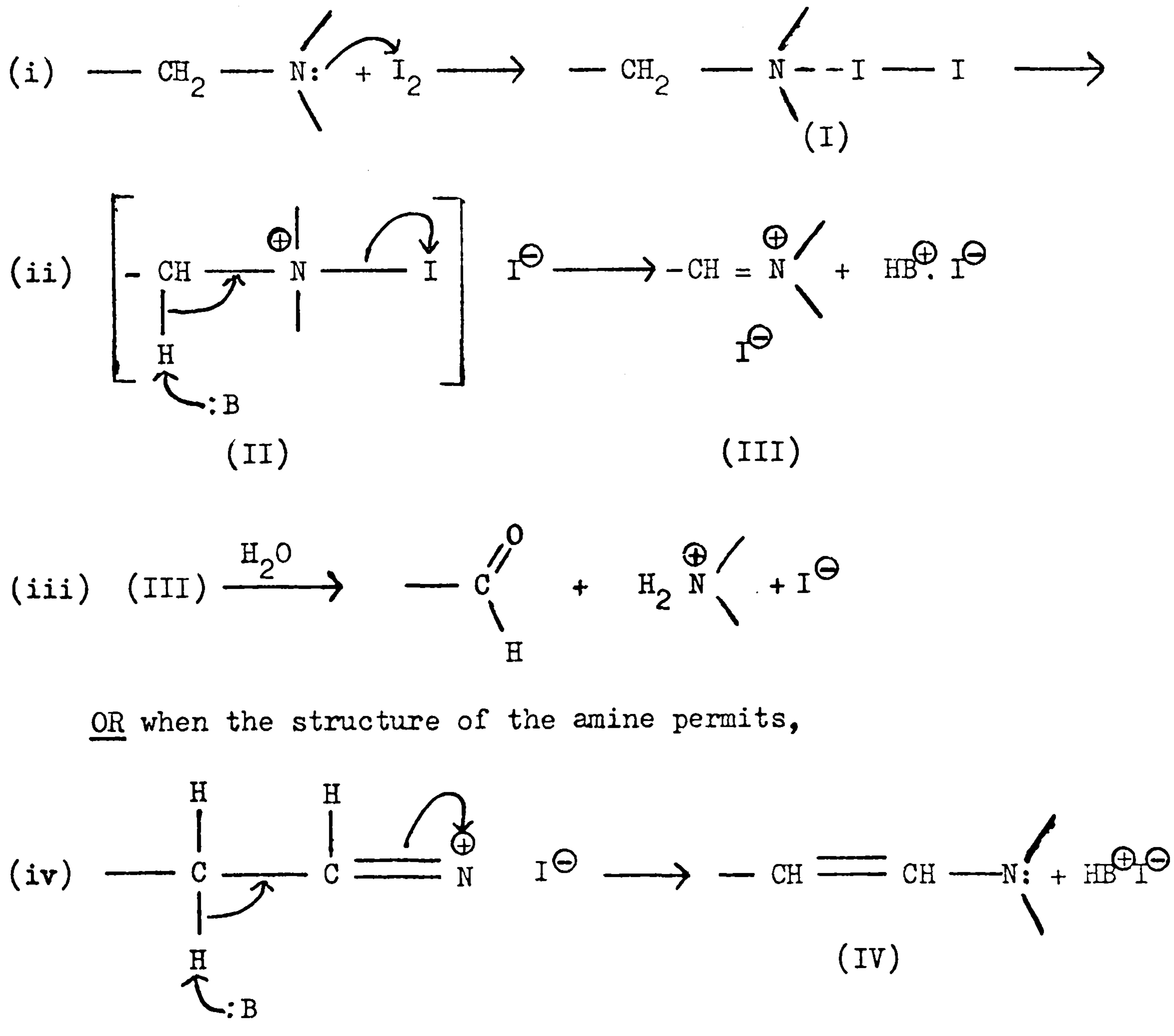
$$2I_2 + \text{C12DEA} \longrightarrow [\text{oxidised C12DEA}] + 4\ \text{HI};$$

the hydriodic acid is neutralised and thus the overall reaction becomes:

$$2I_2 + 4\ \text{C12DEA} \longrightarrow [\text{oxidised C12DEA}]\ \text{HI} + 3\ \text{C12DEA.HI}$$

Such a stoichiometry would give a product containing approximately 75% C12DEA.HI.

Attempts to isolate and identify the oxidation product formed in the reaction of solid iodine with pure C12DEA proved unsuccessful. The method employed involved recrystallisation of the crude product in order to remove as much as possible of the C12DEA.H , and evaporation of the mother liquors to dryness. The residue was rendered basic and the mixture of amines so obtained was subjected to repetetive dry column chromatography and preparative thin layer chromatography. But owing to the large number of oxidation products present, separation could not be effected. However, evidence of the nature of the redox process was gained from a study of various model systems (see later) and this led to the postulation of a reaction pathway which may be usefully outlined here. (Scheme 1)



Scheme 1

The formation of a charge-transfer complex (I) is a well documented interaction[21] which is attributed, in this case, to donation of the nitrogen lone pair to the halogen acceptor.

Immediately upon mixing, solutions of iodine with N-alkyldiethanolamines exhibit the characteristic charge-transfer absorption band in the ultra violet region at 293 nm. The spectrum also contains absorptions at λ max. 360 and 510 nm. attributable to complexed and free iodine, respectively. Therefore, there is no doubt that a charge-transfer complex is formed between an N-alkyldiethanolamine and iodine. In solutions, there appears to exist an equilibrium between the 'free' donor and acceptor, and the resultant complex - hence the band at λ max. 510 nm.

When allowed to stand, a solution of iodine with an N-alkyldiethanolamine undergoes chemical change and, eventually, the corresponding diethanolamine hydroiodide is isolated as the main product. In the course of this reaction, the intensity of the bands at λ max. 293 and 360 nm. first increases with time, reaching a maximum and then decreases (Figure 1). Over the same period, the intensity of the absorption at λ max. 510 nm. for free iodine, shows a corresponding continuous decrease. The variation with time observed in the relative intensities of the bands in the electronic spectra of these systems is due to formation of tri-iodide ions from 'free' iodine in solution and iodide ions produced during the reaction. Absorptions due to the tri-iodide species coincide with those of the amine/iodine complex. In the course of the reaction the concentration of tri-iodide ions at first increases, reaches a maximum, and thereafter decreases as it takes part in the changes

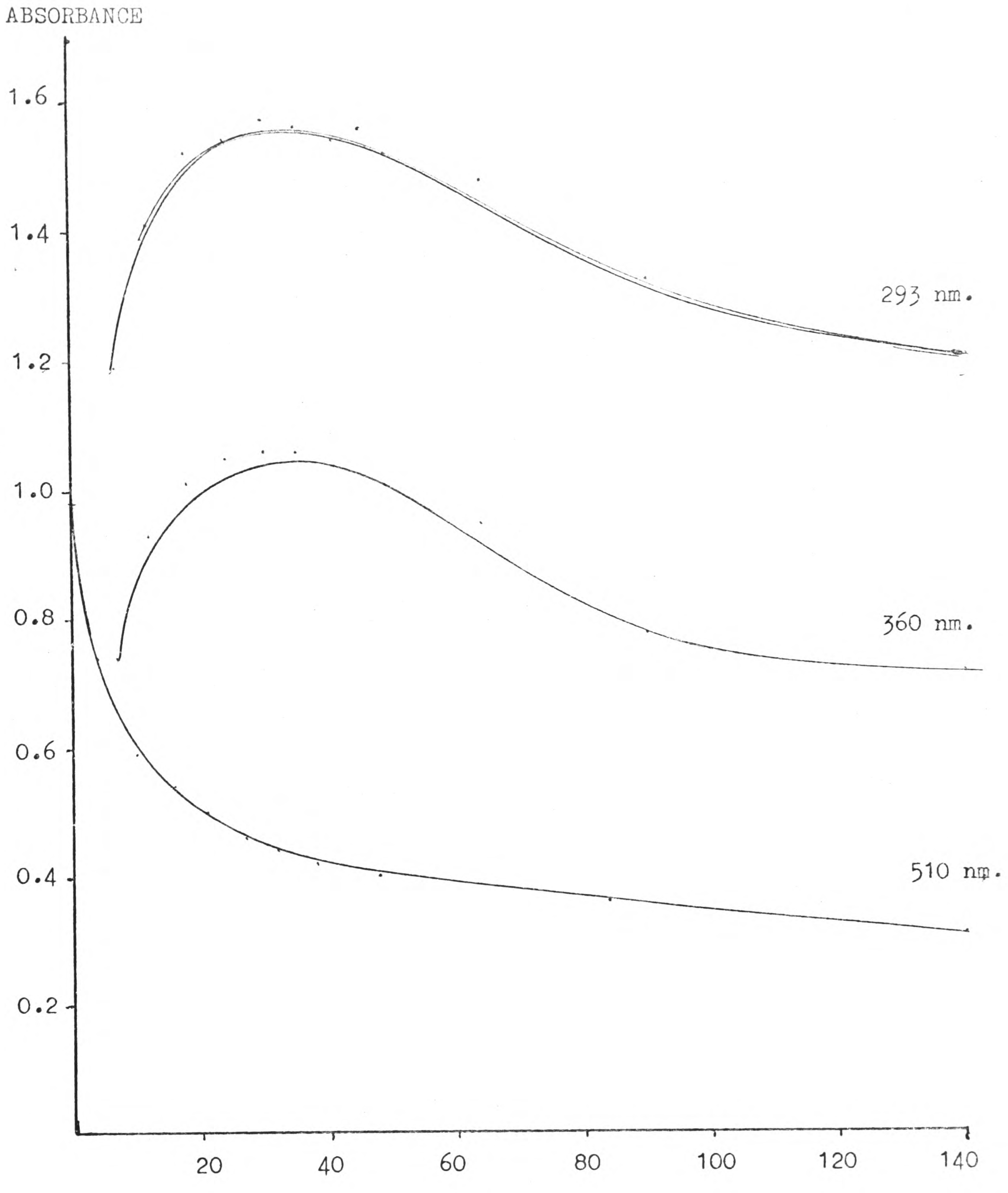
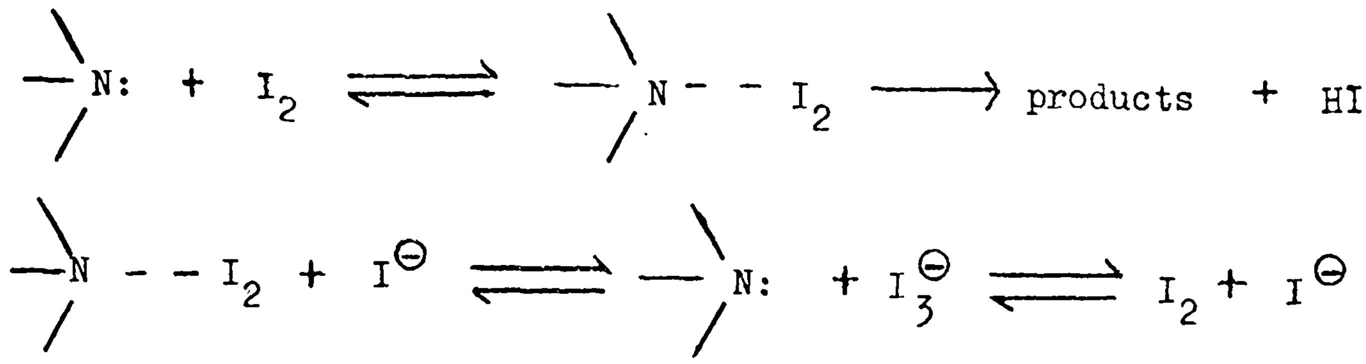


FIGURE 1 VARIATION WITH TIME AFTER MIXING OF THE ABSORBANCE (AT 293, 360 & 510 nm.) OF SOLUTIONS OF IODINE AND C12DEA IN CHLOROFORM



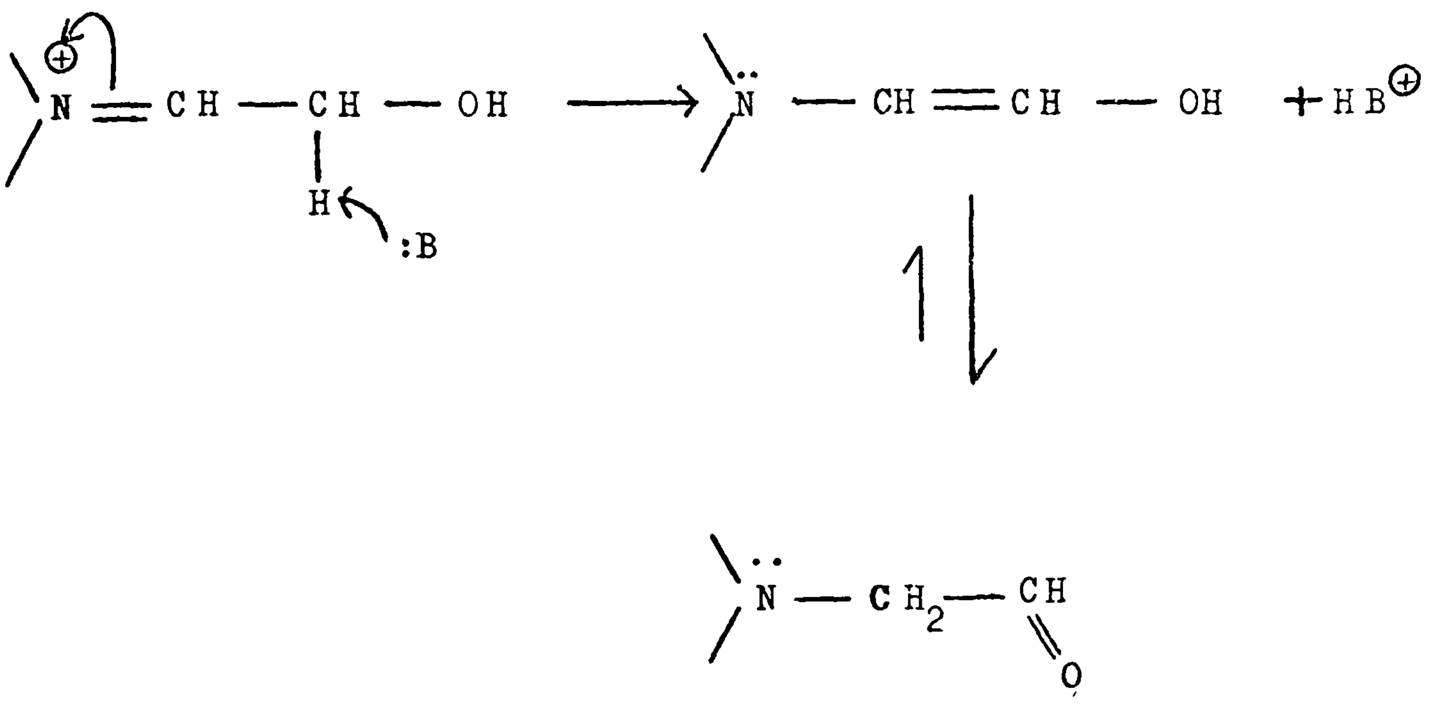
$$-N: + I_2 \rightleftharpoons -N--I_2 \longrightarrow \text{products} + HI$$

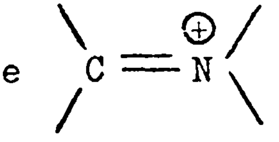
$$-N--I_2 + I^{\ominus} \rightleftharpoons -N: + I_3^{\ominus} \rightleftharpoons I_2 + I^{\ominus}$$

The addition compounds which were isolated by other workers from the interaction of halogens and certain amines and which were originally thought[22] to be N-halotrialkylammonium halides (II), were subsequently characterised as charge-transfer complexes. Following Mulliken's work[23], they were shown[24] by means of X-ray crystallography to possess a linear N-I-I group, thus precluding the ionic structure (II). Their possible role as intermediates has been investigated by the author and will also be discussed later.

The formation of immonium salts (III) and their subsequent hydrolysis has been postulated for the reaction of bromine with simple amines[25] and for the Decker alkylation method[26] used for the synthesis of secondary amines.

The formation of enamines (IV) from immonium salts has been described by a number of workers[27] for various systems, and evidence for their formation during the oxidation of certain amines by iodine was obtained by the author (p70). The infrared spectra of all the crude products obtained from the reaction of the various N-alkyldiethanolamines and triethanolamine with iodine exhibited absorption bands at about 1720 and 1630 cm^{-1} i.e. in the double bond region, which were not present in the spectra of the corresponding free amines. The band at 1630 cm^{-1} is at a wavelength typical of enamine double-bond absorption, and the band at 1720 cm^{-1} is in the carbonyl region. Aldehydes could be formed by two possible routes in accordance with Scheme 1; firstly hydrolysis of an intermediate immonium salt by moisture present in the reaction mixture, and secondly by an Amadori rearrangement of the enamine group produced, by the participation of a hydroxyethyl group as shown below.



Here, and in all other cases, the base :B, is the free amine. The absence of an absorption, which may be assigned to the  group, at 1690 cm^{-1} may be explained by its readiness to undergo hydrolysis and/or, lose a proton to excess amine present in the reaction mixture to give an enamine.

It is possible that under the extremely vigorous conditions of the 'commercial type' reaction, oxidation of the hydroxethyl groups may take place directly and not <u>via</u> the nitrogen. For example, bromine is known to oxidise alcohols to aldehydes, which may react further to give esters.

The p.m.r. spectra of the crude products obtained from the reaction of pure amines with iodine also supported Scheme 1 as in addition to absorptions which are assigned to the protonated amines, they contained a number of other peaks in the low field region (ca. 5 to 7.5 δ) i.e. where protons attached to unsaturated systems are expected to absorb.

The remainder of the work described in this chapter was directed towards elucidating the nature of the biocidal principle. Unless otherwise stated, all tests for biocidal activity were carried out by Personnel of Glasby Pharmaceuticals Ltd. using the Kelsey-Sykes technique[28].

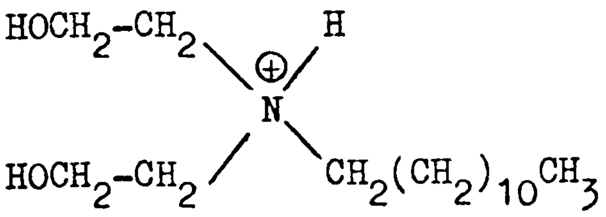
None of the crude, iodine-free products from C1, C2 and C3DEA described above, were biologically active and authentic C3DEA hydroiodide was also found to be inactive. When Ethomeen C12 and C12DEA were reacted with iodine in solution in both isopropanol and tetrachloroethylene at reflux temperature, the products were all biologically active, but no pure materials could be isolated from these reactions. As mentioned previously, when the reaction between C12DEA and iodine was carried out according to the industrial method, C12DEA hydroiodide was isolated. This recrystallised product and the authentic hydroiodide were tested for biological activity and were found to be as active as the commercial material. That the biological activity of the commercial product due to C12DEA.H1 and not to any oxidation product was further substantiated as follows The crude reaction product from pure C12DEA and solid iodine was recrystallised and the motherliquor evaporated to dryness and all traces of solvent removed by prolonged drying in vacuo. The biological activity of this residue, which would contain some C12DEA.H1 together with the oxidised 'amine' hydroiodide, was compared on a weight to weight basis with that of the recrystallised C12DEA.H1. It was thus established that the recrystallised product and the authentic hydroiodide are equally active and each of these is more active than the residue from the mother liquor. The activity of the disinfectant can thus be attributed to the base hydroiodide.

The low activity of the residue from the mother liquor is probably partly due to the fact that it contains some base hydroiodide.

The lack of biological activity in the case of C3DEA hydroiodide raises the question of the dependence of biological activity on structure. This aspect is discussed in the following section.

2. Effect of Structure on Biological Activity

In investigating the effect of structure on the anti-microbial activity of N-alkyldiethanolamine salts, it was considered that activity might depend on both the nature of the anion and the structure of the cation. For this reason, the chloride, bromide, iodide, iodate, sulphate, nitrate, dimethylglutarate and acetate salts of C12DEA were prepared and tested. It was thus established that, in contrast to the corresponding potassium salts which are inactive, all the C12DEA salts exhibited a similar level of biological activity. On this basis it was concluded that the activity of the C12DEA salts studied is attributable to the N,N-bis(2'-hydroxyethyl)-N-dodecylammonium cation (V)



(V)

These findings suggest that any of the above C12DEA salts should be as effective as the hydroiodide as disinfectants. Yet this is not so in practice. Aqueous solutions of the hydroiodide salt are consistently more active than similar solutions of, for example, the chloride and bromide. This additional activity is generally attributed to iodine generated by the slow aerial oxidation of iodide ion in the presence of protons. It is interesting to note in this connection that (a) the pH of the commercial formulation is about 4, and (b) the biological activity of a solution of C12DEA.H1 increases with time, in a manner parallel to the rise in iodine content of the solution.

Industrially, the disinfectant might have been produced more conveniently, simply by neutralising 'Ethomeen C 12' with hydroiodic acid. However, the availability and relative cheapness of commercial grades of iodine make it possible to prepare hydroiodide salts more economically by the interaction of C12DEA with iodine rather than by the neutralisation of the amine with hydriodic acid.

The effect of the structure of the amine cation on activity was also investigated and it was shown that the hydroiodide and hydrochloride salts of N,N-diethyldodecylamine were as active as the corresponding diethanolamine species. Hence, it seems that an advantage derived from the use of the latter compounds in the commercial process under discussion is their higher solubility in water, and this is obviously the result of the presence of the hydroxyethyl groups in the molecule. Clearly, the C12DEA/iodine system is related to the important group of quaternary ammonium type of disinfectants, of which trimethyltetradecylammonium bromide (Cetrimide, B.P.) is a prominent member. In fact, the level of biological activity of C12DEA.H1 is comparable to that exhibited by a solution of Cetrimide of equivalent concentration. For a quaternary ammonium cation, the length of the longest alkyl chain in the cation determines whether or not biological activity is exhibited, and, in the former case, the level of activity. Thus, for example, in contrast to the activity exhibited by C12DEA.H1 and HCl, the corresponding salts of triethanolamine and triethylamine are biologically inactive. For this reason a systematic study was undertaken of the effect of the size of the group R upon the biocidal properties of homologous N-alkyldiethanolamines, $RN(CH_2CH_2OH)_2$ (RDEA).

In view of the fact that the commercial amine mixture, 'Ethomeen C 12', contains alkyl groups, R, ranging in length from 8 to 18 carbon atoms, the following members of the series were synthesized by standard methods:- C1 to C10 inclusive, C12, C14, C16 and C18. The purity of each compound was established by chromatography (g.l.c. for up to C10; t.l.c. for C12 to 18). Further purification, when required, was effected by redistillation or recrystallisation according to the physical state of the particular amine at room temperature. All the bases were assayed by potentiometric titration against standard acid and, where necessary, were again redistilled or recrystallised to a purity of at least 98% prior to their being used in the chain length activity study. Each product was identified by infrared and p.m.r. spectroscopy. The i.r. spectra confirmed the presence of -OH and saturated -CH, whilst the p.m.r. spectra showed the presence of hydroxethyl groups and indicated the length of the alkyl chain.

The variation of biocidal activity with chain length (R) was determined[29] by measuring the MINIMUM INHIBITORY CONCENTRATION (M.I.C.) for each member of the series. This is defined as the lowest concentration of a solution of a given substance which inhibits the growth of a particular micro-organism under certain prescribed conditions such as the number of organisms used, the nature of the growth medium, temperature and pH.

For this thesis, the amines, as their acetate salts, were tested using nutrient broth No. 2 at pH 6.5 against Escherichia Coli 8277 (2 x 10^7 cells). The presence or absence of growth after 24 h at 37° was visually assessed from the turbidity of the cultures. The results are given in Table 2

TABLE 2 THE MINIMUM INHIBITORY CONCENTRATIONS (M.I.C.) OF MEMBERS OF THE HOMOLOGOUS SERIES RDEA

R	M.I.C.(mM)	R	M.I.C.(mM)
C1	10	C8	0.5
C2	10	C9	0.3
C3	10	C10	0.2
C4	10	C12	0.1
C5	10	C14	0.1
C6	10	C16	0.1
C7	2	C18	1.0

Thus under the prescribed comditions, it may be seen (Figure 2), that antimicrobial activity to any degree, is exhibited only by those compounds having a group, R, consisting of more than six carbon atoms. This activity reaches a maximum with the C12, C14 and C16 members and then decreases with a further increase in the size of R.

Similar results have been obtained by other authors for various homologous series such as the n-alkylamines[30,31], quaternary ammonium compounds[32,33], aliphatic sulphonic acids[34, 35], alkyl sulphates[36] and fatty acids and their derivatives[37]. Thus for example, Cummings et al[30] showed that of a series of primary n-alkylamines, compounds with less than 10 carbon atoms were not active against tubercule bacilli and certain pathogenic fungi. The activity of

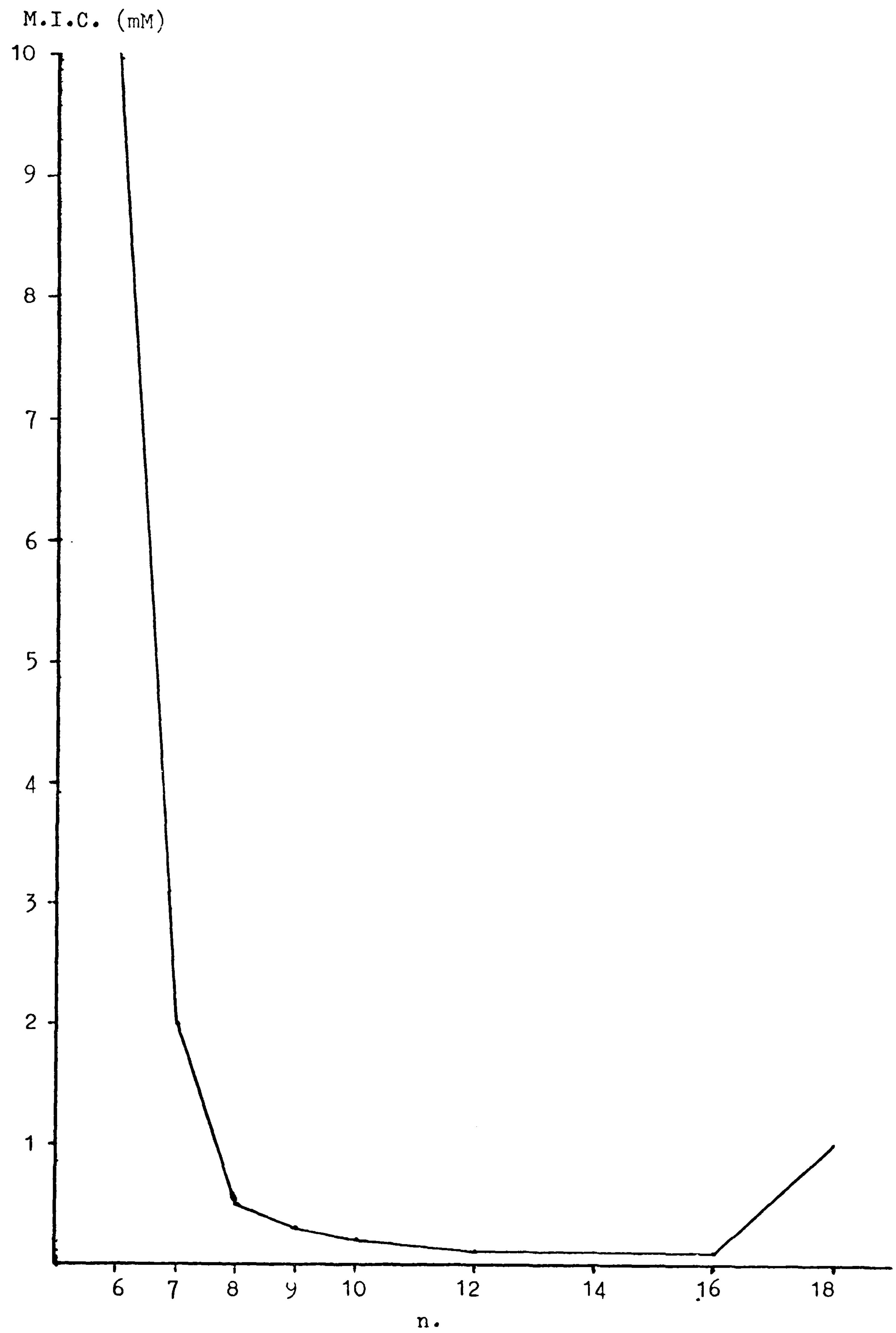


FIGURE 2 VARIATION OF M.I.C. WITH n (the no. of C atoms in the alkyl chain) FOR THE HOMOLOGOUS SERIES CnDEA

alkylamines increased with increasing chain length reaching a maximum at 12 to 15 carbon atoms and decreased at longer chain lengths.

It would appear, therefore, that the relationship between alkyl chain length and antimicrobial activity shown by the alkyldiethanolamine series is a general property of antimicrobial compounds which contain a normal alkyl chain and a terminal functional group. The functional group referred to may be cationic (quaternary ammonium compounds), anionic (fatty acids) or neutral (alcohols or esters). It was found[38,39] that in each of these types of compounds, anti-microbial activity is associated with surface activity, a fact which was shown to apply also to the alkyldiethanolamine (RDEA) series. Detergency, demonstrated by the formation of a foam lasting for 2 minutes, was exhibited only by C7DEA and the higher homologues.

A surface active compound may be defined as one which lowers the boundary tension prevailing at an interface[40]. Surface active molecules are composed of hydrophobic and hydrophilic portions, and the degree of surface activity exhibited depends on the balance between the associated lipophilic and hydrophilic properties[40,41,42] However, not all surface active compounds possess biocidal properties, for example phospholipids[38] and polyesters[43] are biologically inactive. It is clear, therefore, that although surface activity by itself does not necessarily result in antimicrobial activity, it appears that, at least in the case of the alkyldiethanolamines and other similar groups of compounds, the level of detergency and also that of antimicrobial activity depend on the same molecular characteristics.

In order to penetrate the envelope of a microbial cell, a molecule must pass through a hydrophobic zone consisting largely of lipid[44]; the penetration of this is facilitated by the presence in the molecule of a large non-polar portion. In addition the molecule must also possess sufficient hydrophilic character in order to be able to pass through an aqueous enviroment to the site where it exerts its toxic action; this point is well illustrated by the lower antimicrobial activity associated with the less soluble C18DEA.

Bacteria themselves are particulate and act as adsorbents. Absorption, may, therefore, constitute the stage before the actual process of disinfection begins. In this connection a surface-active compound which becomes preferentially adsorbed on the surface of a bacterial cell has a greater chance of killing the bacterium than a compound which does not.

In the course of an investigation into the mode of antimicrobial action of the C12DEA system, P. Lambert[29] studied the effect of varying the concentration of C12DEA, (at pH 4.6), on the percent survivors of micro-organisms after a 1 minute exposure to the disinfectant. The results (Figure 3) show a marked decrease in the bactericidal activity of C12DEA at concentrations between 0.7 and 1.6 mM.

It has been shown that the maximum at A in Figure 3, is associated with micellization. For this purpose, the critical micelle concentration of C12DEA was determined by two independent methods: (a) the capillary rise, and (b) the dye titration method of Corrin and Harkins[45] and was found to be 1.6 and 1.5 mM respectively. These results are in good agreement with the maximum shown in Figure 3 which corresponds to a concentration of 1.4 M.

The observed decrease in bactericidal potency at concentrations around the C.M.C. may be due to a competition between the micelles

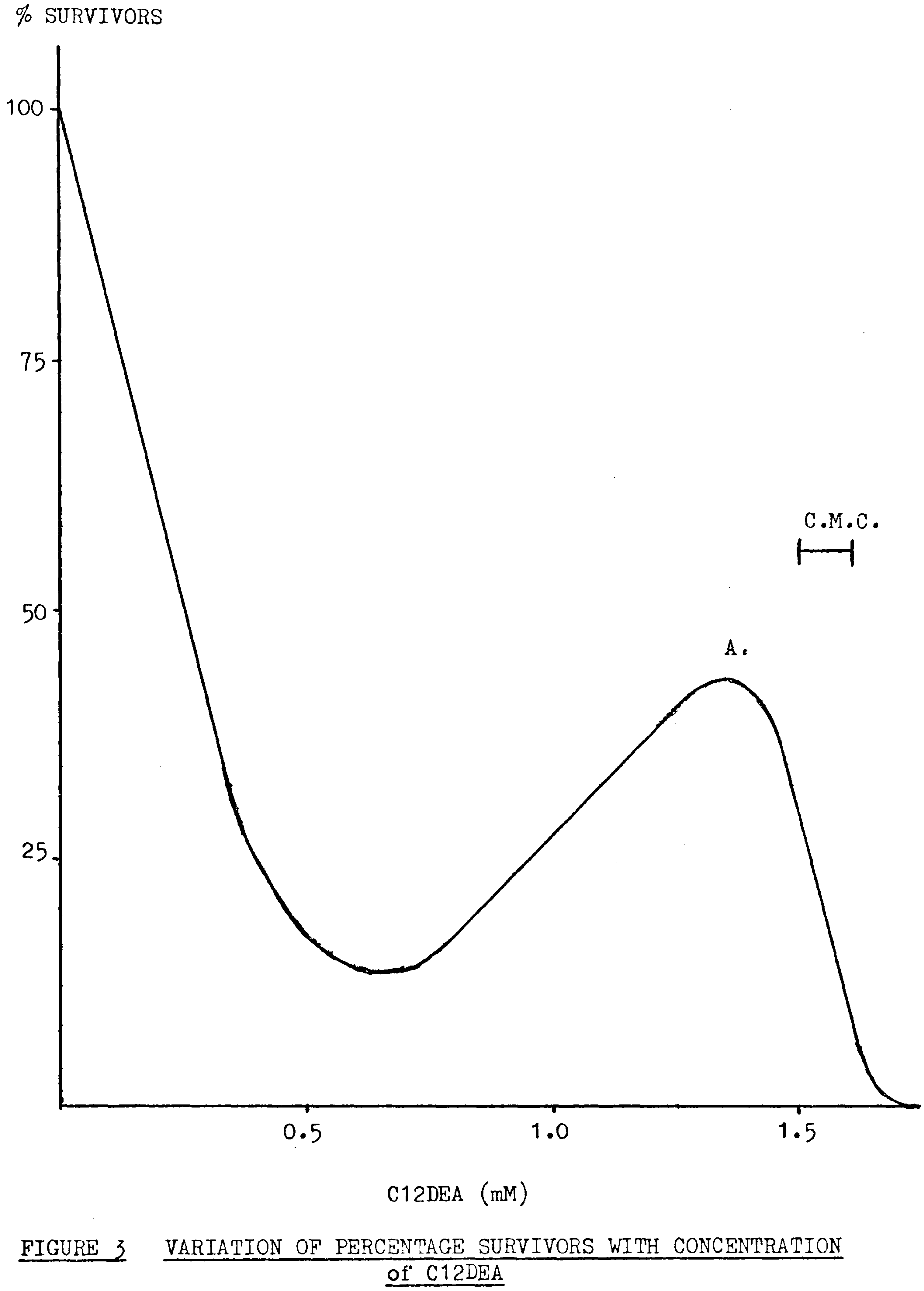


FIGURE 3 VARIATION OF PERCENTAGE SURVIVORS WITH CONCENTRATION of C12DEA

(10^4 cells of E. Coli 8277, exposed for 1 minute at 25° to various concentrations of C12DEA in acetate buffer, pH 4.6).

and the bacterial cells for free C12DEA molecules in solution. This in turn reduces the number of molecules of C12DEA hydroiodide available to exert toxic action upon the bacterial cells. At higher concentrations (i.e. above 1.8 mM C12DEA), the bactericidal potency is restored and since it is considered[46] that after the micelles are formed, the addition of more surfactant leads to an increase in the number of micelles, but, little, if any increase in the number of non-aggregated molecules or ions, the micelles themselves must exert a toxic effect possibly by some mechanism other than that associated with the free C12DEA molecules.

It has been demonstrated that the bis (2-hydroxyethyl)-dodecylammonium ion behaves as a typical surface active antimicrobial agent; in this respect it behaves like certain active quaternary ammonium salts. But, whereas quaternary ammonium compounds exist as such in solution irrespective of the pH, the extent of protonation of a tertiary amine in solution depends on the pKa of the amine and the pH of the solution. Thus, investigations revealed that C12DEA would be protonated only to the extent of 22% at pH 6.8 - the pH of the cytoplasmic fluid of a typical bacterium[44]. On this basis, it is conceivable that in the cell the lethal agent is the free C12DEA molecule rather than the corresponding protonated species. Similar observations have been made[47] in relation to other antimicrobial agents. Hence, it would seem that comparison of the biological activity of C12DEA with that of other biocidal tertiary amines, rather than with quaternary ammonium salts would be more meaningful in this case. In this connection, although various studies have demonstrated the biocidal activity of long chain primary amines[31], and of primary, secondary and tertiary dodecylamines[30], the great success of the quaternary ammonium salts as disinfectants has tended to overshadow the biological activity of primary, secondary and tertiary amine salts, despite the fact that quaternary ammonium compounds such as trimethyltetradecylammonium bromide and the alkyldimethylbenzylammonium chlorides were developed as biocidal agents following the discovery of the antimicrobial activity of dodecylamine hydrochloride[48,39].

CHAPTER TWO

THE OXIDATION OF AMINES BY IODINE

CHAPTER TWO: A. INTRODUCTION

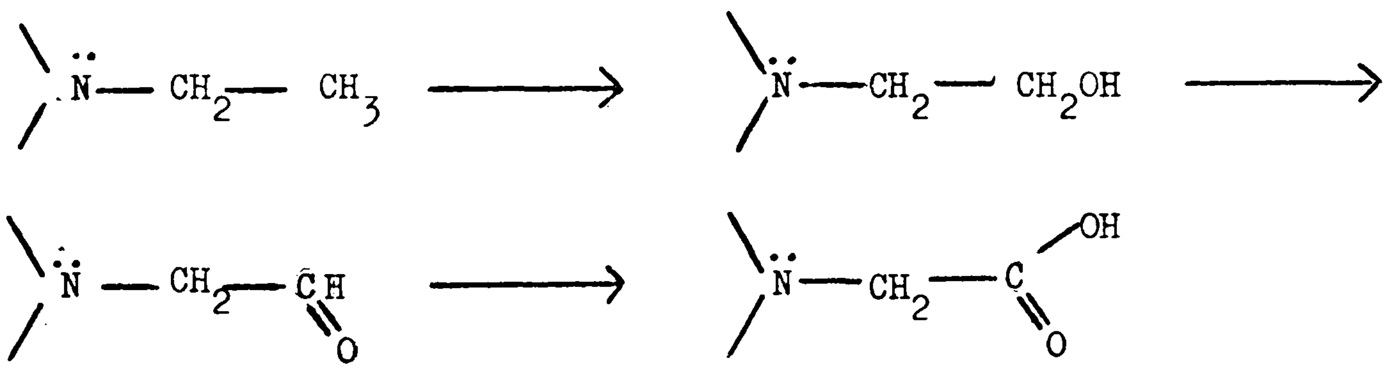
OXIDATION OF AMINES

OXIDATION OF AMINES

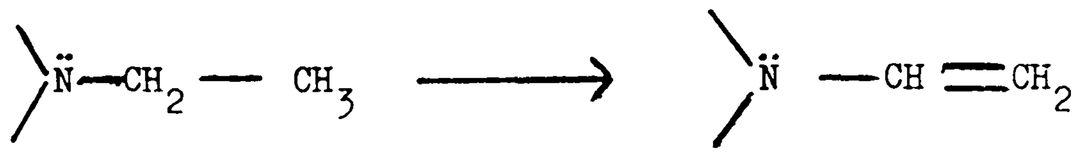
1. The oxidation reaction

It was noted in the preceding chapter that when an N-alkyldiethanolamine $RN(CH_2CH_2OH)_2$ is treated with iodine a redox reaction occurs during which iodine is reduced to iodide ions and the amine is oxidised. By definition, oxidation is a reaction which involves loss of electrons and, consequently, the atom which is oxidised is raised to a higher oxidation state.

The oxidation number of the nitrogen atom in amines is -3, in amine oxides ($R_3\overset{\oplus}{N}-\overset{\ominus}{O}$ $_0$ and azo compounds ($\rangle N=N\langle$) -1 and in the nitro group ($-\overset{\oplus}{N}\langle{}^{O}_{O}\ominus$) +3.. Hence the conversion of an amine to any of the above classes of compounds is, by definition, an oxdiation[49]. However, oxidation of amines is not limited to changes at the nitrogen; alkyl groups may be oxidised without any overall change in the amino function, as, for example, in the series



in which the oxidation number of the terminal carbon atom changes from -3 in the alkyl group to +3 in the carboxyl group. A further example of this latter type of oxidation is provided by the conversion of an amine to an enamine (VI)



(VI)

The oxidation of amines may follow a variety of courses depending on the nature of (a) the amine, and (b) the oxidising agent employed[50]. Thus, features such as the type (aliphatic or aromatic) and the degree of substitution on the nitrogen, and the presence and nature of other functional groups in the molecule may affect the rate and mode of oxidation of the amine. Furthermore, amines are usually resistant to oxidation in acid solution[25], but are easily attacked by oxidants in neutral or alkaline solution. This is in accord with the suggestion[51] that the susceptibility of an amine to oxidation depends on the availability of the nitrogen lone pair. An interesting illustration of this point is provided by the alleged inertness of tertiary aliphatic amines towards nitrous acid in strongly acidic solution[52,53]. But according to Geuther[54] such amines are cleaved by nitrous acid in the weaker acidic medium, aqueous acetic acid. Here, the hydrolysis of the salt to free amine molecules, makes it possible for nitrous acid to attack the nitrogen lone pair[52].

In general, the first step in the oxidation of an amine involves the transfer of one or both electrons of the lone pair to the oxidant, and this may be followed by the elimination of a proton or a hydrogen atom to give an intermediate (radical or ion) which reacts further. The products[55] which may arise in this way from one amine molecule include aldimines, ketimines, enamines and nitriles, and, when two amine molecules are involved, hydrazines, azo compounds or azines are formed. The addition of oxygen to amines gives hydroxylamines or amine oxides. Combinations of these processes yield nitroso, nitro and azoxy compounds, oximes and hydroxamic acids, or the products of their subsequent hydrolysis such as aldehydes, ketones, acids and amides. Aromatic amines on oxidation give polymeric products.

2. Types of oxidants for amine oxidation

Oxidants may be classified according to the nature of the products of their reactions with amines as

(a) those which oxidise the amine by the addition of oxygen to the nitrogen, and

(b) those which attack the amine oxidatively at a carbon site.

(a) This class of oxidants includes peroxy acids, acyl peroxides, ozone and hydrogen peroxide; their initial action involves addition of oxygen to the nitrogen atom of the amino group with the formation of amine oxide. Tertiary amine oxides are reasonably stable and can often be obtained in good yield by allowing the reactants to stand in solution at room temperature for a few hours[50]. This reaction is subject to steric interference, and thus amines which are not quaternised readily are generally difficult to convert to amine oxides. Secondary amines are for the most part easily converted to N,N-dialkylhydroxylamines in sufficient yield for the reaction to be of synthetic value[50]. It is considered that the secondary amine oxide formed initially rapidly rearranges to the corresponding hydroxylamine

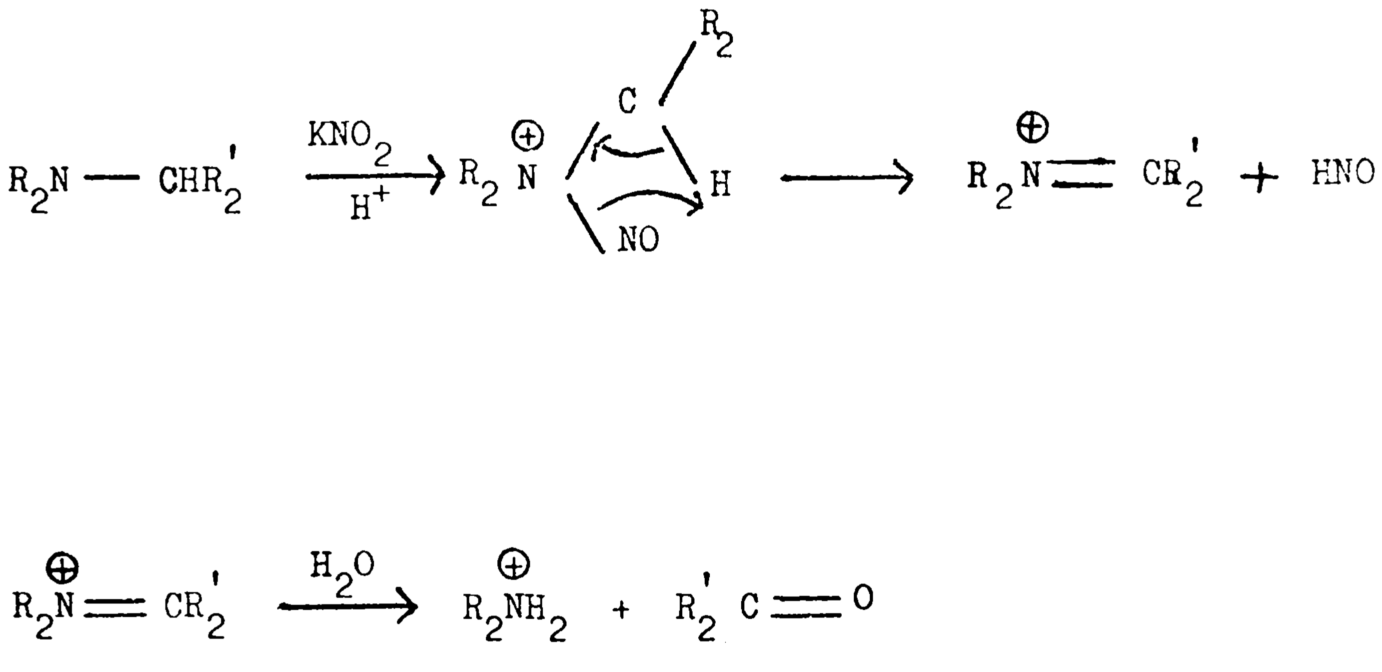
$$R_2\overset{\oplus}{H}N-\overset{\ominus}{O} \longrightarrow R_2N-OH$$

The oxidation of primary amines by hydrogen peroxide is often complicated by the fact that it may involve several stages. The primary amine oxide which is first formed also undergoes rearrangement to the hydroxylamine (RNHOH). The latter may sometimes be isolated in small yield but, in most cases, it is oxidised further to various products, the nature of which varies according to the nature of the alkyl group present in the amine. In a primary amine some hydroxamic acid (R.CO.NHOH) is always formed[56]. Nitroso-compounds are formed by the oxidation of the hydroxylamine, and these rearrange to an aldoxime in those cases when the alkyl group is primary, or a ketoxime in those cases where the alkyl group is secondary. The oximes may also undergo further oxidation. When the alkyl group is tertiary nitro compounds may be formed (Scheme 2).

$$\begin{array}{lllllll}
RCH_2NH_2 & \longrightarrow & RCH_2NHOH & \longrightarrow & RCH_2NO & \longrightarrow & RCH{=}NOH \\
R_2CHNH_2 & \longrightarrow & R_2CHNHOH & \longrightarrow & R_2CHNO & \longrightarrow & R_2C{=}NOH \\
R_3CNH_2 & \longrightarrow & R_3CNHOH & \longrightarrow & R_3CNO & \longrightarrow & R_3CNO_2
\end{array}$$

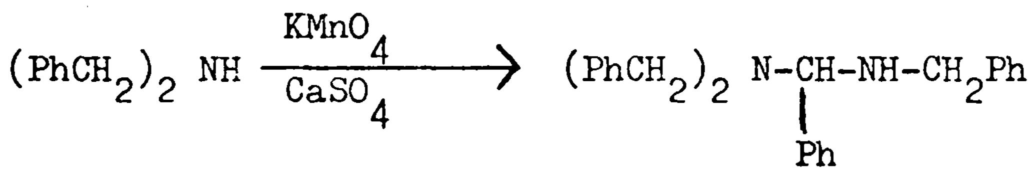
Scheme 2

(b) This class of oxidising agents includes manganese dioxide, lead tetra-acetate,chlorine dioxide and mercuric acetate; these oxidants remove hydrogens from the amine molecule either by an ionic or a radical process. An example of the latter process is provided by the removal of an α-hydrogen from a tertiary amine by t-butyl perioxide under more vigorous conditions than would be needed for amine oxide formation; the radicals so produced dimerise spontaneously to give ethylene diamine derivatives[57]. Other members of this series cause the loss of a hydrogen from a tertiary amine to form an immonium salt, the protonated form of an enamine[58]. Further oxidation and hydrolyis results in the oxidative cleavage of an alkyl group from the nitrogen. A typical example is given in Scheme 3.



Scheme 3

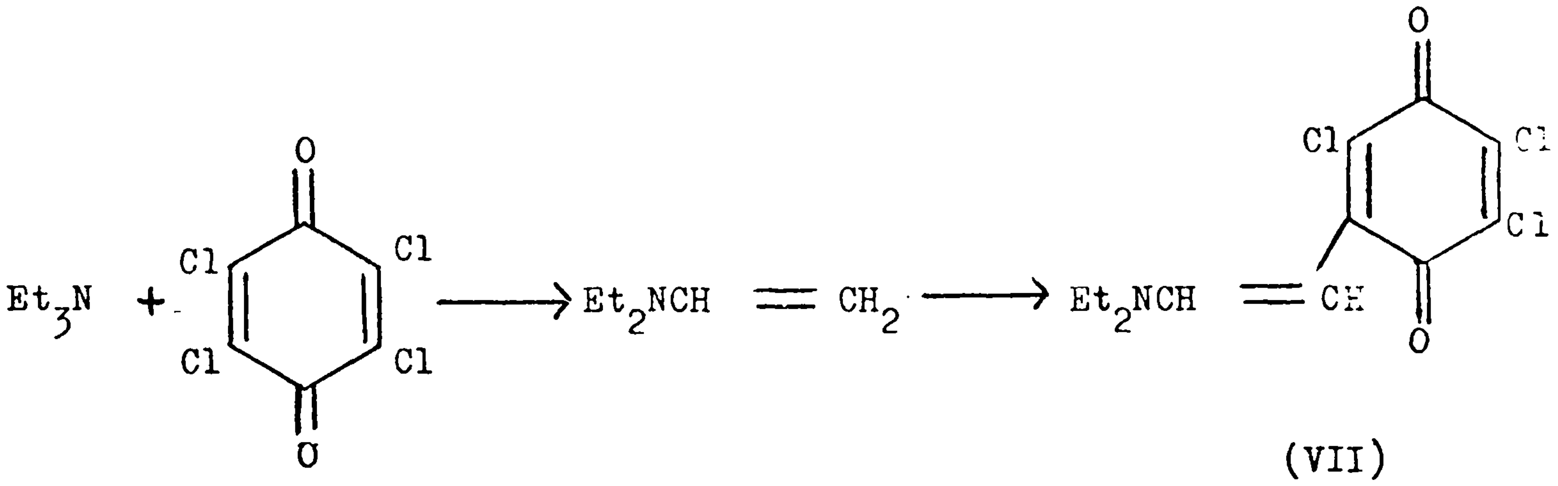
Secondary amines are oxidised much as tertiary amines with the added factor of the removal of a hydrogen atom from the nitrogen to give an aldimine or ketimine which, reacts readily with free amine to give *gem*-diamine derivatives, e.g.[59]



$$(PhCH_2)_2\ NH \xrightarrow[CaSO_4]{KMnO_4} (PhCH_2)_2\ N\text{-}\underset{\displaystyle Ph}{\underset{|}{CH}}\text{-}NH\text{-}CH_2Ph$$

The oxidation of primary amines involves the same initial steps as with the secondary and tertiary amines but the nature of the final product depends on the nature of the alkyl group present. When the alkyl group is primary, the imine which is first formed is further dehydrogenated to a nitrile[60]. When the alkyl group is secondary, ketimines or their transformation products such as ketones, are formed[61]. When the alkyl group is tertiary there is no α-hydrogen to be attacked and oxidation can occur readily only on the nitrogen to give products similar to those formed with peroxides. Thus tertiarybutylamine (t-BuNH$_2$) is oxidised to the corresponding nitro compound (t-Bu-NO$_2$) in good yield by permanganate[62]. When the same amine is treated under anhydrous conditions with iodine pentafluoride, azo-isobutane ($(CH_3)_3C-N=N-C(CH_3)_3$) is formed[63].

In addition to the above inorganic oxidants, there are a number of organic oxidants which have been shown to attack certain tertiary amines by dehydrogenation of an alkyl group[64]. Thus, chloranil oxidises triethylamine in benzene at room-temperature to diethylvinylamine which reacts further with more chloranil to give the diethylamino-vinylquinone VII.



(VII)

Benzoyl peroxide and N-bromosuccinimide have been shown to act similarly. When the reaction with the latter oxidant is carried out in aqueous solution one of the alkyl groups is split off as the aldehyde in a manner similar to the oxidative cleavage mentioned previously.

3. Mechanisms of amine oxidation

As regards the mechanisms of these oxidations, the evidence for radical intermediates comes mainly from the behaviour of oxidising agents towards aromatic amines. But clearly, when a one electron oxidant, such as hexacyanoferrate (III) is used, radicals must be formed by the initial removal of one electron as shown below[65] (Scheme 4). Such a scheme is applicable to both aromatic and aliphatic amines.

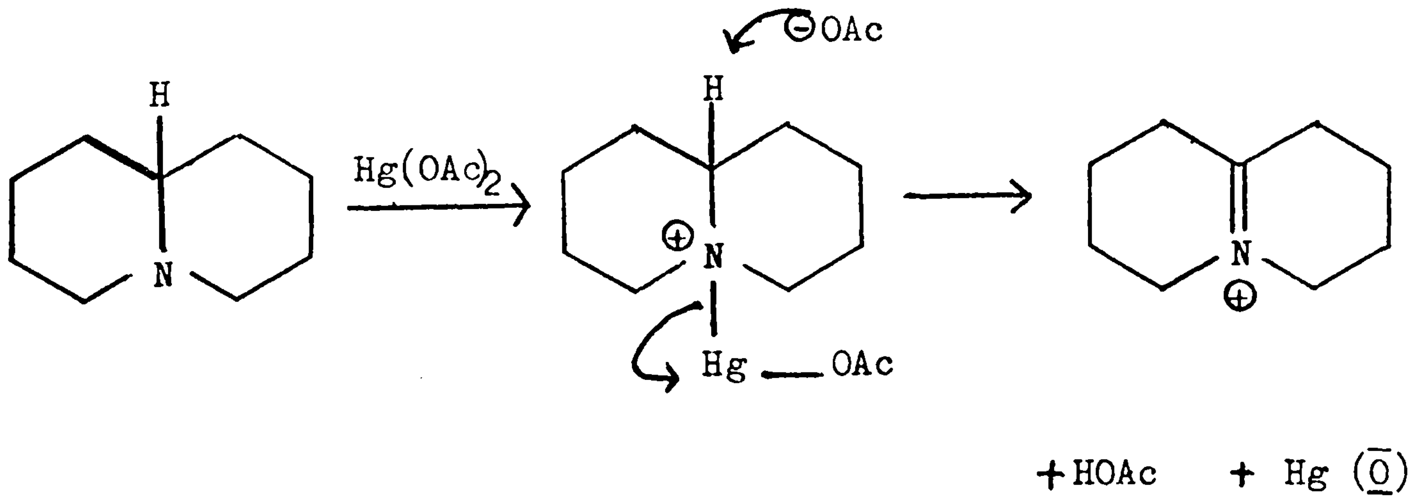
$$R'CH_2\ddot{N}R_2 + Fe(CN)_6^{3\ominus} \longrightarrow R'CH_2\overset{\oplus}{\dot{N}}R_2 + Fe(CN)_6^{4\ominus}$$

$$R'CH_2\overset{\oplus}{\dot{N}}R_2 \longrightarrow R'\dot{C}H\ddot{N}R_2 + H^{\oplus}$$

$$R'.\dot{C}H\ddot{N}R_2 + Fe(CN)_6^{3\ominus} \longrightarrow R'CH{=}\overset{\oplus}{N}R_2 + Fe(CN)_6^{4\ominus}$$

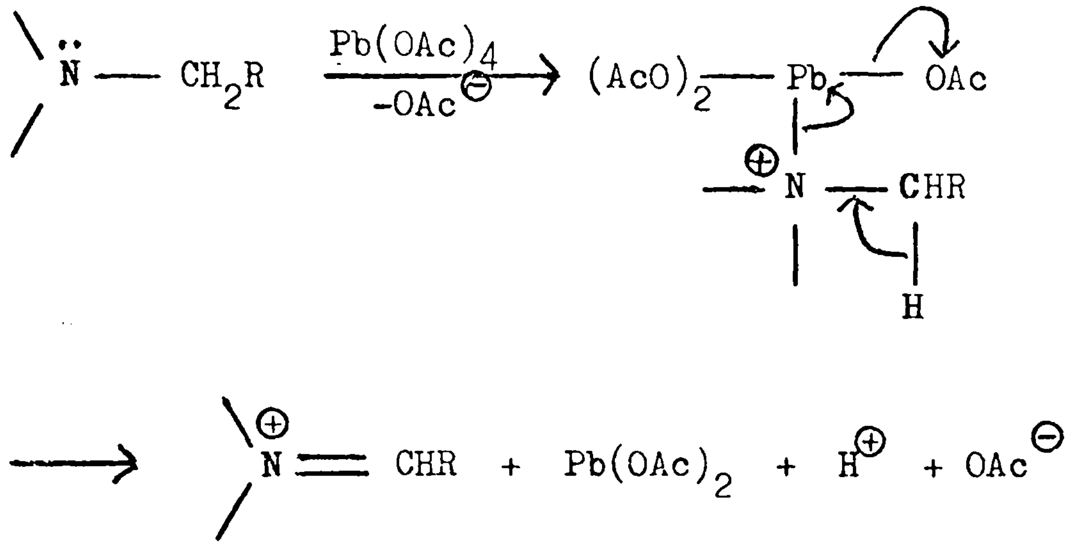
Scheme 4

For two electron oxidants similar schemes have been proposed, e.g. Scheme 3 for nitrous acid and Scheme 5 for the oxidation of quinoziline (VIII) by mercuric acetate[66]. This latter scheme also involves the initial formation of a complex through the nitrogen lone-pair followed by concerted removal of a proton from an α carbon and cleavage of the nitrogen - mercury bond.



Scheme 5

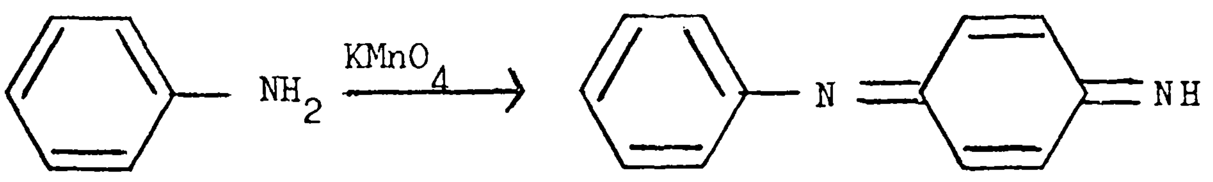
In accord with the dominant feature of amine chemistry, namely the availability of the nitrogen lone pair, it has been proposed that for oxidants such as potassium permanganate[67], chromium trioxide[68] and lead tetra-acetate[69] the initial step in the oxidation of an amine would also involve the formation of a quaternary nitrogen compound, e.g. Scheme 6[69].



Scheme 6

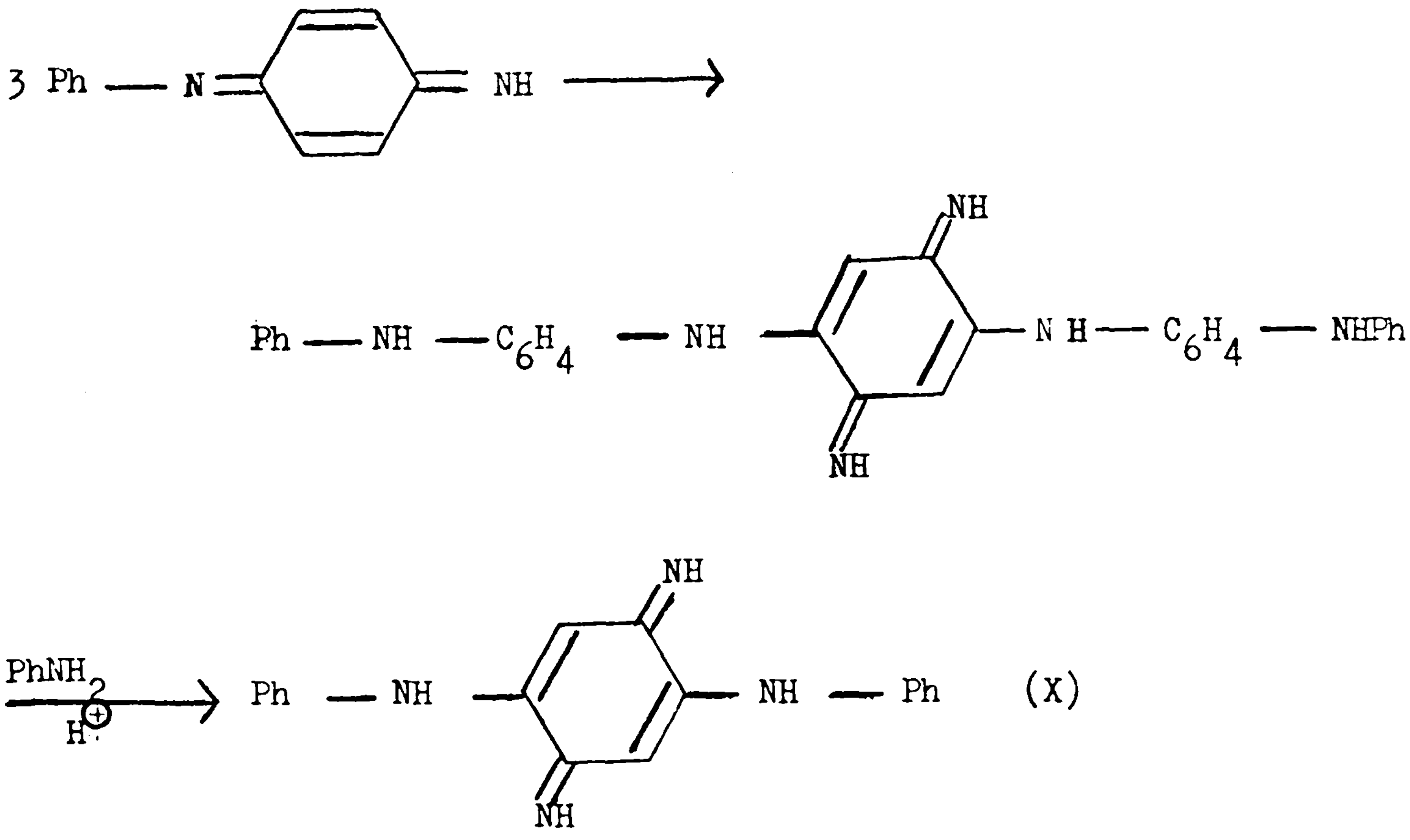
In general, aromatic amines are weaker bases than aliphatic amines but are readily oxidised to a variety of compounds of different structural types depending on the oxidising agent and the conditions of the oxidation. Here again, using agents such as peroxide, the amine oxide is formed initially and this undergoes rearrangement to the corresponding hydroxylamine. In the case of aniline, the phenylhydroxylamine so formed[70] is converted to nitrosobenzene and, under more vigorous conditions, to nitrobenzene. Nitrosobenzene condenses with phenylhydroxylamine and with aniline to produce azoxybenzene and azobenzene, respectively[71]. The same products may be obtained by the oxidative dealkylation of secondary amines (N-alkylanilines) with peroxymonosulphuric acid, pertrifluoroacetic acid and other similar reagents. Tertiary amines are converted to amine oxides[62].

Oxidising agents other than oxygen-donating peroxides often give complex mixtures resulting from attack on the ring. In the simplest structural case, aniline, the products are very varied, but their occurrence can be accounted for by the intermediacy of N-phenylquinonediimine (IX)[72] which has actually been isolated from the product of oxidation of aniline by permanganate.



(IX)

It has been suggested that formation of (IX) involves an azene intermediate. N-phenylquinonediimine is easily trimerised by acid, and in the presence of aniline, the trimer is converted into azophenine (bis-2,4-(phenylamino)quinone diimine) (X).



(X)

Under slightly differnt pH conditions, dimerization of (IX) occurs, which is followed by further oxidations and dimerizations - leading eventually to the formation of perinigraniline, a polymeric quinonediimine; further transformations yield other compounds including the polymer known as aniline black.

Strong oxidising agents may attack, and sometimes cleave, an alkyl group of mono- and dialkylanilines. For example, using manganese dioxide[73] the course of the reaction depends on the structure of the amine and the conditions, methyl and dimethylaniline give formanilides whereas the main products from diethylaniline are acetaldehyde and formanilide.

$$\mathrm{Ph\ NHMe} \xrightarrow{\mathrm{MnO_2}} \mathrm{PhNHCHO}$$

$$\mathrm{Ph\ NMe_2} \xrightarrow{\mathrm{MnO_2}} \mathrm{PhNMeCHO}$$

Cleavage of the N-alkyl group and formation of the oorresponding aldehyde also occurs when parasubstituted N-alkylanilines are treated with potassium chromate in acid solution[74].

4. Reactions of amines with halogens

It has been known for a considerable time that primary, secondary and tertiary amines react with halogens. The use of fluorine leads to the complete destruction of organic molecules and this is also the case with amines[55]. The chlorination of primary amines occurs in stages and either N-chloro or N,N-dichloro compounds may be prepared by using the appropriate amounts of reactants. Unlike C-chlorination, N-chlorination generally follows an ionic path and hence requires a source of 'positive' chlorine, such as the element, hypochlorite salts[55] and tertiary alkyl hypophalites[55].

$$R\ddot{N}H_2 + NaOCl \longrightarrow R\ddot{N}HCl \longrightarrow R\ddot{N}Cl_2$$

Chlorination, when accompanied by base catalysed elimination, provides a useful route to imines and thence to ketones[30], (Scheme 7)

$$R_2CH\ddot{N}H_2.HCl \quad + \quad \underline{t}\text{- BuOCl} \longrightarrow R_2C\overset{\oplus}{H}NH\ \overset{\ominus}{Cl} \xrightarrow{NaOE_t}$$

$$R_2C = \ddot{N}H \xrightarrow{H_2O} R_2C = O$$

Scheme 7

Secondary amines react with free chlorine in aqueous solution buffered to a pH of about 7, and the corresponding hydrochlorides react with aqueous hypohalite solution in the cold as follows:

$$R_2\overset{\oplus}{N}H_2\ \overset{\ominus}{Cl} + NaOCl \longrightarrow R_2\ddot{N}Cl + NaCl + H_2O$$

Monochloroamines and dichloroamines are also formed by the action of aqueous chlorine on tertiary amines, one or two alkyl groups, respectively being eliminated in the process as aldehydes.

In aromatic amines, the benzene nucleus is activated by the amino group towards attack by electrophiles and, hence, nuclear halogenation is exceptionally easy. N-Chlorination of aniline has been accomplished by treating it with hypochlorous acid in cold ether[76]; the product, N,N-dichloroaniline, is very unstable and is rapidly converted into various ring chlorinated compounds.

The studies on the reactions of bromine with amines suggest that it behaves in a similar manner to chlorine. In contrast, very little is known about the reactions of iodine with amines. Thus, a closer study of the reaction of tertiary amines with iodine was undertaken in the present work and is reported in this thesis. It was deemed essential to gain sufficient data to enable the postulation of a reaction pathway, and thus an investigation of the reaction of tertiary amines with iodine under both aqueous and non-aqueous conditions was carried out. Additionally it was considered necessary to isolate and identify any oxidation products, to study their formation in relation to any proposed oxidative scheme and to explore the possibility of adapting the reaction for synthetic purposes.

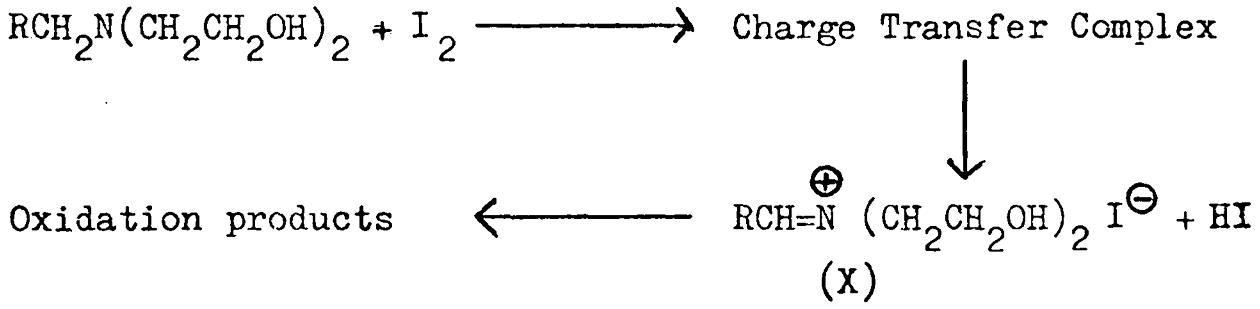
CHAPTER TWO: B. DISCUSSION

OXIDATION OF TERTIARY AMINES AND N-ALKYLDIETHANOLAMINES BY IODINE

OXIDATION OF TERTIARY AMINES AND N-ALKYLDIETHANOLAMINES BY IODINE

1. Immonium ion intermediates

The reaction of an N-alkyldiethanolamine with iodine (Chapter One) yields only small amounts of oxidation products (see later), the main product being the corresponding amine hydroidide. Clearly, formation of the latter involves hydrogen iodide and this must result from the oxidation of some of the amine by iodine. For this reason a reaction scheme was proposed for the reaction (Scheme 1; p 24)

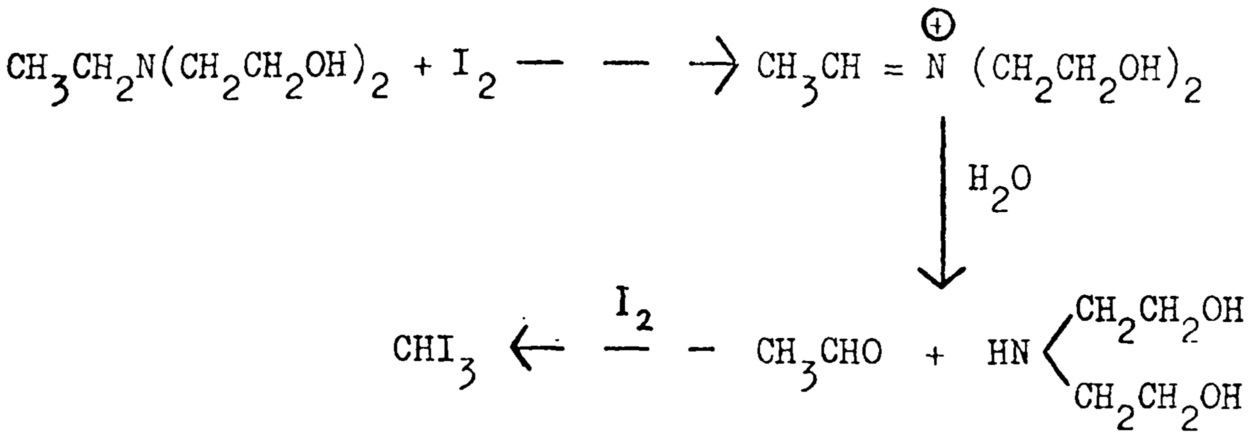


In the course of this investigation, several different types of amines were subjected to the reaction under various conditions. In all cases, the corresponding hydroiodide was isolated as the main product and it was thus concluded, that the reaction scheme above is applicable to all amines which possess an α-hydrogen. Consequently, model amines have been used in a study designed to examine the feasibility of the various aspects of the proposed pathway.

In the proposed reaction sequence, the charge transfer complex initially formed between the amine and iodine, liberates hydrogen iodide and is converted into an immonium salt (X).

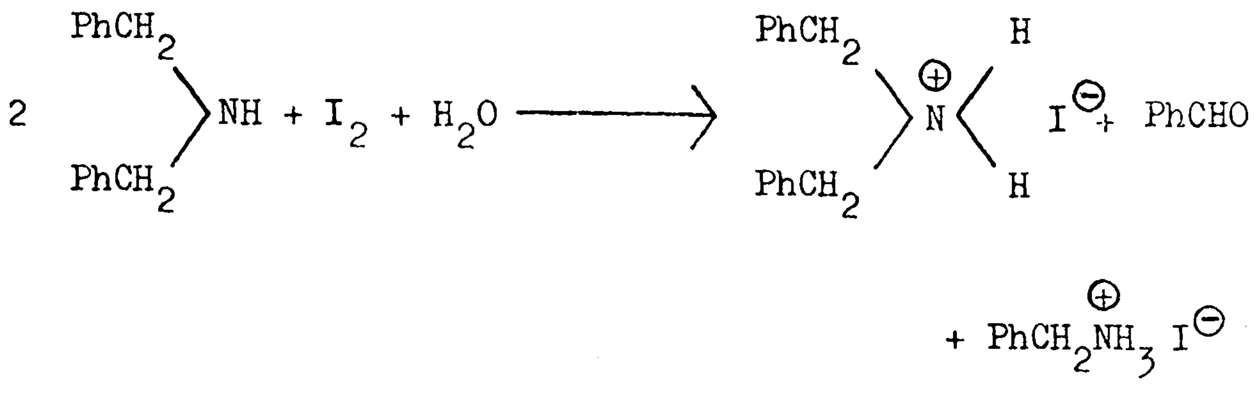
Immonium salts have been postulated by several authors[35,77] as intermediates in the oxidation of tertiary amines by a variety of chemical agents and also in their electrochemical dealkylation[78]. However, immonium salts have rarely been isolated or trapped[79]; and their intermediacy has been inferred from product studies. For example, reactions have been carried out in a suitable solvent and the product isolated characterised as either the derived enamine[27] or a product formed from the enamine, such as the trimer of the enamine obtained from 1-methylpyrrolidine[81]. More usually, the intermediacy of an immonium salt was inferred by isolation of the products on hydrolysis, namely, the corresponding secondary amine and carbonyl compound. It was considered, therefore, that isolation of such products from the oxidation of an amine by iodine under aqueous conditions would provide good evidence for the intermediacy of an immonium ion in this reaction.

It has been reported[82] that amines containing the $>N-CH_2-CH_3$ group undergo the iodoform reaction; this is generally regarded as being a qualitative test for the CH_3-CO- group, or for compounds which on oxidation give molecules containing that group. With amines, the reaction proceeds without the addition of sodium hydroxide and thus, in this case, the active agent must be molecular iodine. No mechanism has ever been given, but a simple explanation for this observation in the light of the postulated reaction scheme (p. 24) is that iodine oxidatively dealkylates the tertiary amine to give, in the case of (say) triethylamine, diethylamine and acetaldehyde; the latter then undergoes the normal iodoform reaction. Thus, when C2DEA was caused to react with aqueous potassium tri-iodide, a small amount of acetaldehyde, trapped as its DNP derivative, and iodoform were isolated. These results are consistent with the postulated formation of an immonium salt as an intermediate in the reaction and the formation of iodoform may be rationalised as follows (Scheme 8)



Scheme 8

Similar conclusions were drawn from the oxidation of tribenzylamine by iodine under aqueous conditions which gave a mixture of equimolar amounts of benzaldehyde and the hydroiodide salts of tribenzylamine and dibenzylamine. The reaction requires a molar ratio of reactants amine:iodine = 2:1; iodine in excess of this ratio is not utilised. Halogenated by-products (cf. iodoform in the previous case) were not formed during the tribenzylamine/iodine reaction as the resulting aldehyde, benzaldehyde, does not possess α-hydrogens. Under the same conditions, tribenzylamine hydroiodide did not react with iodine. This observation indicates that the initial step of the reaction involves the nitrogen lone pair and not attack on an α-carbon atom. For the same reason, dibenzylbenzamide was found to be inert towards iodine, in contrast to dibenzylamine which gave an equimolar mixture of dibenzylamine and the Schiff's base, benzylidene-benzylamine. It is considered that the initial oxidative dealkylation of dibenzylamine gives benzylamine and benzaldehyde and these condense, under the conditions used on working up the reaction mixture, to the observed product. Confirmation was provided by the fact that benzylidene-benzylamine was obtained in excellent yield by treating a solution of a mixture of benzaldehyde and benzylamine with a drying agent. Thus the oxidation reaction may be formulated as in Scheme 9



and during work-up

$$PhCHO + PhCH_2NH_2 \xrightarrow{-H_2O} Ph\text{-}CH{=}N\text{-}CH_2\text{-}Ph$$

Scheme 9

Benzylamine, when treated with iodine in the same manner, gave benzylidene-benzylamine in steps analagous to those shown above for dibenzylamine.

It will be recalled that tribenzylamine was cleaved by iodine to dibenzylamine and benzaldehyde. The former was not cleaved further and was in fact isolated as the hydroiodide. In contrast, dibenzylamine itself reacts with iodine. This observation confirms the view that the availability of the nitrogen lone pair for complexation with iodine is the deciding factor in this reaction. In agreement with this is the failure of an excess of iodine to be consumed in the oxidation of tribenzylamine.

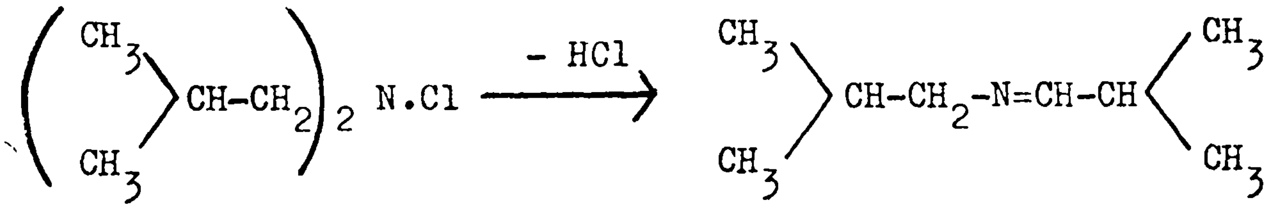
A survey of the literature concerning reactions of tertiary amines shows that dealkylation (in particular demethylation) by the action of hypochlorous acid and hypochlorites was observed by Wilstätter and Iglauer[83] in 1900. They stated that the amine moiety gives an N-chlorodialkylamine, but they supposed that the alkyl group was lost as an alcohol. However, in 1913, Meisenheimer[22] identified the products from the reaction of trimethylamine with hypochlorous acid as being dimethylamine (which reacted with excess reagent to give the observed product, N-chlorodimethylamine) and formaldehyde. This author postulated that the active oxidising species was molecular chlorine, which reacted with the amine to form a 'trialkylamin-dihalogenid', according to the equation

$$(CH_3)_3\,N + Cl_2 = (CH_3)_3N.Cl_2;$$

the latter then loses hydrogen chloride to give dimethylmethylene ammonium chloride

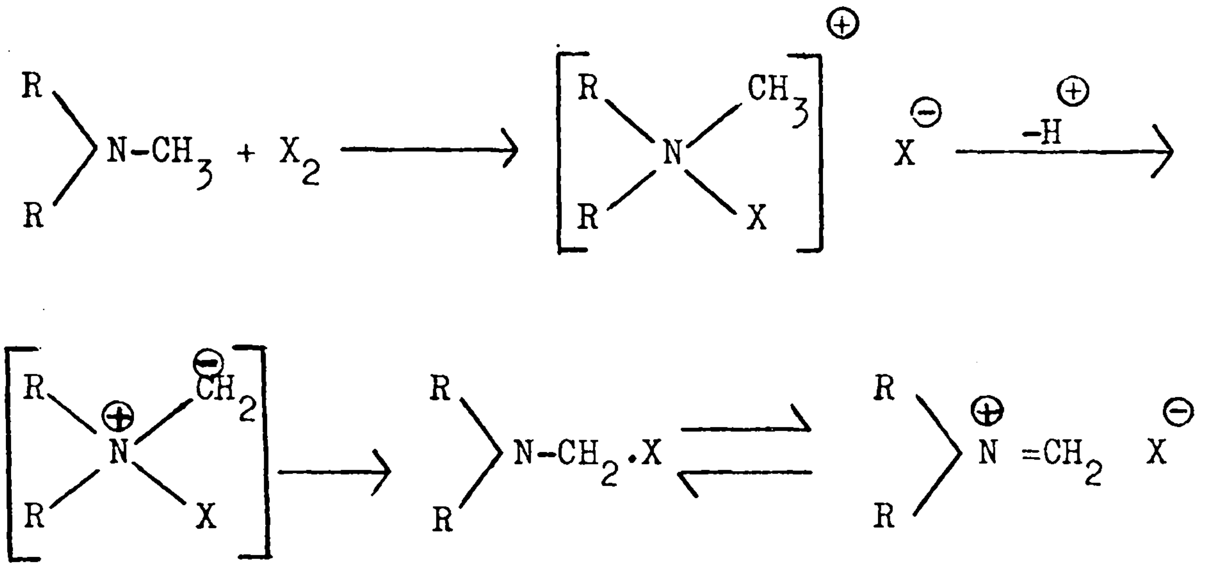
$$(CH_3)_3N.Cl_2 \longrightarrow (CH_3)_2\overset{\oplus}{N} = CH_2\ Cl^{\ominus} + HCl$$

Meisenheimer based his proposals on the fact that (a) N-chloro di-isobutylamine loses hydrogen chloride to give isobutylidene-isobutylamine,



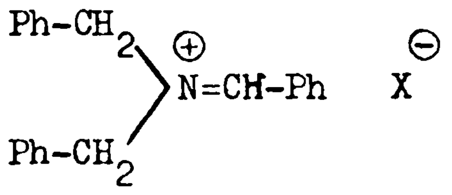
(b) the products of the reaction could be regarded as arising from the hydrolysis of an intermediate immonium salt and (c) halogen-amine addition compounds were, at that time, known[84]. However, Meisenheimer, who also obtained N-chlorodiethylamine and acetaldehyde from triethylamine by the same reaction did not offer direct evidence for his scheme.

Böhme and his coworkers[85,86] studied the action of chlorine, bromine and iodine on trimethylamine and tribenzylamine. They postulated a generalised scheme for these reactions, which involved an intermediate immonium salt considered to be in equilibrium with an α-haloamine



It must be emphasised, however, that although the **overall conclusions** reached by Böhme et al. are in agreement with the present author's findings, as in the case of Meisenheimer, no compelling evidence for their reaction scheme was presented. Furthermore, both Meisenheimer and Böhme formulated the amine-halogen addition compound as a salt - a view which is now unacceptable (see Chapter Three).

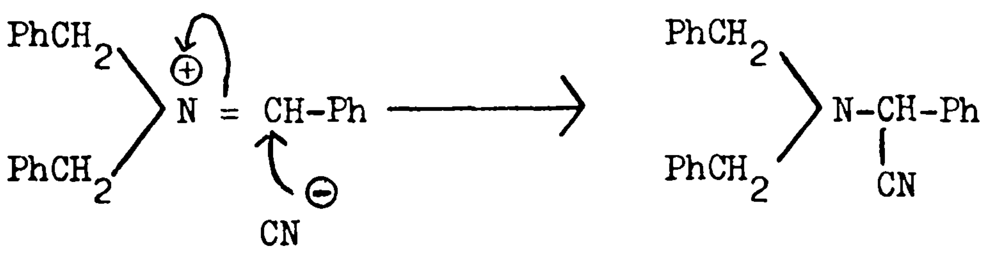
In an attempt to isolate the postulated immonium salt intermediate (XI) formed during the oxidation of tribenzylamine by iodine, the reaction was carried out



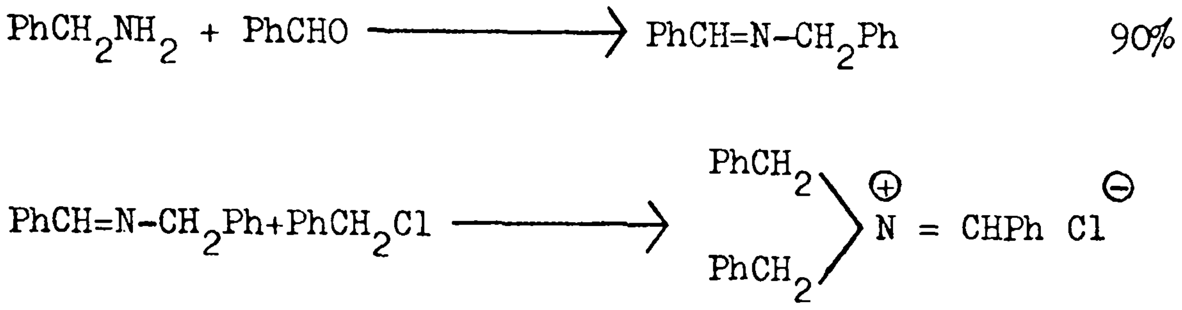
(XI) X=I

under anhydrous conditions in tetrachloroethylene. The product, a brown crystalline solid, gave on prolonged treatment with water a trace of benzaldehyde and approximately equimolar quantities of tribenzylamine and dibenzylamine. Examination of the reaction mixture before work up by chemical and spectroscopic means showed that it consisted entirely of a mixture of dibenzylamine and tribenzylamine hydroiodides. It was thus concluded that the benzaldehyde referred to above was produced by the hydrolysis of tri-iodide salts present in small amount. For example, the crude product did not show absorption in the infrared region at ca. 1690 cm^{-1} reported to be typical of immonium salts[87], or at 1650 cm^{-1} reported[52] for (XI). Furthermore, the infrared spectrum of the crude product was very similar to a spectrum of a mixture of tribenzyl and dibenzylamine hydroiodides. The p.m.r. spectrum did not contain the absorptions at δ 9.50, 5.22 and 5.39 reported by Smith and Leoppky[52], who isolated the crude immonium salt (XI) ($\overset{\ominus}{X}$ = tetrafluoroborate) from the reaction of tribenzylamine with nitrosyltetrafluoroborate.

Additional evidence that the product obtained by the present author was not the immonium salt was provided by the failure of the product to react with potassium cyanide in dimethyl sulphoxide solution to give α-cyanotribenzylamine, expected to be formed by nucleophilic attack by the cyanide ion on the electron deficient α carbon atom



Further attempts to isolate the immonium salt from the reaction of tribenzylamine with iodine were unsuccessful even when rigorously anhydrous conditions were employed. In each case, the the products of hydrolysis of the salt were isolated. Similar results were obtained during the attempted preparation of the salt by an unambiguous and well established route, namely the procedure of Decker and Becker[26] outlined below, (Scheme 10).

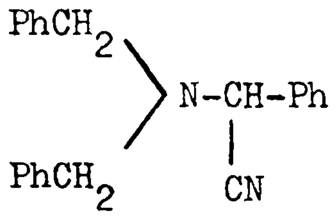


$$\mathrm{PhCH_2NH_2 + PhCHO} \longrightarrow \mathrm{PhCH{=}N{-}CH_2Ph} \qquad 90\%$$

$$\mathrm{PhCH{=}N{-}CH_2Ph{+}PhCH_2Cl} \longrightarrow \left.\begin{matrix}\mathrm{PhCH_2}\\ \mathrm{PhCH_2}\end{matrix}\right\rangle \overset{\oplus}{\mathrm{N}} = \mathrm{CHPh}\ \overset{\ominus}{\mathrm{Cl}}$$

Scheme 10

The outcome of these attempts confirms the view that the immonium salt (XI) is very sensitive to hydrolysis by even traces of water. In this context, it is worth noting that when the literature procedures[88,89] which were claimed to yield the immonium salt were repeated in these laboratories, only hydrolysis products were obtained. For these reasons, it was considered that a more appropriate approach to this problem might be one which entailed generation of the immonium salt in the presence of a nucleophile with which it would react faster than with traces of water. Of the nucleophiles, which are known to react with immonium ions[58], none would appear suitable except the cyanide ion - particularly since the expected product, α-cyano-tribenzylamine (XII), has been characterised[52]

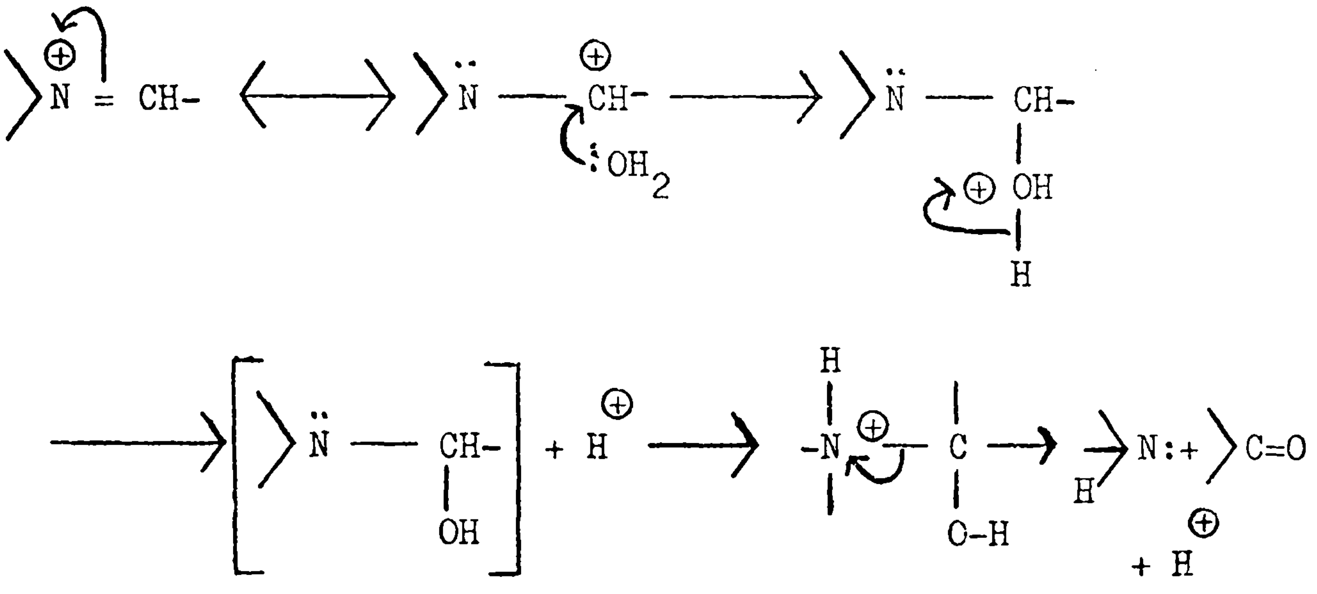


(XII)

Application of this trapping technique to the system tribenzylamine-iodine in isopropanol gave a mixture which was shown by chromatography to consist mainly of recovered tribenzylamine and the desired product (XII). Separation was effected by dissolving the mixture of the two amines in ether and passing hydrogen chloride gas through until no more precipitate was formed. Under these conditions, the very weak base α-cyanotribenzylamine did not form a hydrochloride and, thus, was not precipitated. The identity of the product was confirmed by comparison with an authentic sample of XII prepared unambiguously[90]

The isolation of α-cyanotribenzylamine certainly confirms the view that an immonium salt is formed as in intermediate in the reaction of amines with iodine. This conclusion is further substantiated by the isolation of the predicted hydrolysis products in each case studied. Hydrolysis of an immonium salt to an amine and a carbonyl compound is a well established reaction[58] thought to proceed via the following mechanistic steps (Scheme 11)

(Scheme overleaf)



Scheme 11

2. Preparation of carbonyl compounds by the oxidation of amines with iodine in aqueous media

During the investigation of the oxidation of amines by iodine in aqueous solution, reactions were monitored by chromatography and it was thus noted that certain reactions proceed very cleanly, e.g., the oxidation of tribenzylamine gave product mixtures consisting of equimolar quantities of tribenzylamine, dibenzylamine and benzaldehyde only. In addition, this reaction is fast (15-30 minutes) and easy to perform. It was therefore felt desirable to investigate the possibility of adapting the amine-iodine system for synthetic and for degradative purposes. For exa~ple, it could be used as a method of preparing secondary amines from tertiary amines, or carbonyl compounds for amines; or as a method for the dealkylation of N-alkyl systems.

Oxidative dealkylation by halogens has occasionally been investigated since Wilstätter's original observation that the alkaloids tropidine and tropane are demethylated on treatment with hypochlorous acid[83]. In 1968, Deno and Fruit[91] found that dealkylation could be accomplished efficiently and conveniently by aqueous bromine in acetate buffer. These latter workers stated that the details of the mechanism are not clear, and suggested that the mechanism postulated by Meisenheimer (p. 59) for the action of chlorine on tertiary amines may also apply to aqueous bromine. In contrast, the use of iodine for similar purposes has not been explored.

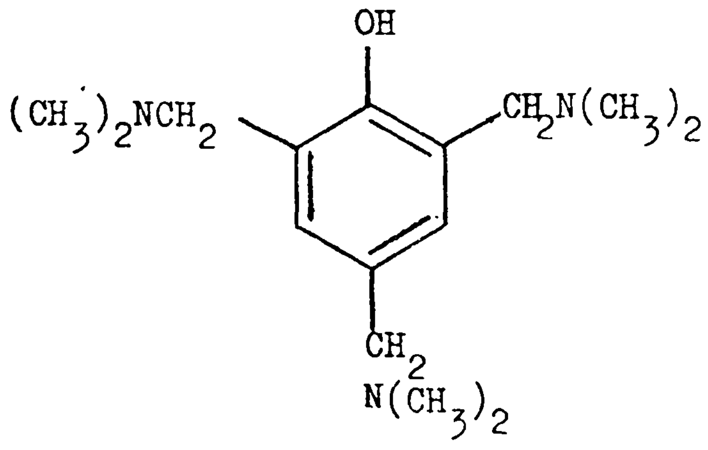
Reference has already been made to the fact that the major product of the reaction of iodine with various amines (C12DEA, C3DEA, etc., triethylamine and N,N-dimethyldodecylamine) under anhydrous conditions is the corresponding amine hydroiodide. Similarly, the products obtained by the treatment of benzylamines with iodine under aqueous conditions showed that the hydriodic acid produced in the redox reaction is neutralised by unreacted amine. As the salts produced cannot be oxidised by iodine a viable preparative procedure would have to cater for the removal of the hydriodic acid in order to ensure that the reaction goes to completion. The obvious way to accomplish this is by carrying out the reaction in the presence of another base, which must be unaffected by iodine (this excludes most amines), and should not itself be sufficiently basic to convert iodine to iodate.

As a model reaction system, the oxidation of tribenzylamine by iodine was studied and it was shown that when the reaction was carried out in the presence of sodium carbonate the tribenzylamine was not oxidised. Aqueous sodium carbonate was subsequently shown to convert iodine to iodate and it was also established that iodates have no oxidising action on amines under the conditions employed in these reactions. But with sodium bicarbonate or calcium carbonate as the competing bases in vigorously stirred suspension, tribenzylamine was oxidised and benzaldehyde was isolated in 53 and

72% yield respectively, based on the reaction

$$(PhCH_2)_3N + 3H_2O + 3I_2 \longrightarrow 3PhCHO + NH_4I + 5HI$$

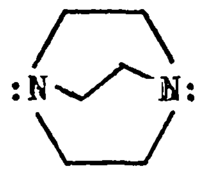
Similarly, using sodium bicarbonate as the base, dimethylbenzylamine gave a 27% yield of benzaldehyde and the Mannich base (XIII) formed a product, which was shown to be a carbonyl compound by its reaction with 2,4-dinitrophenyl-hydrazine reagent, but was not fully characterised.

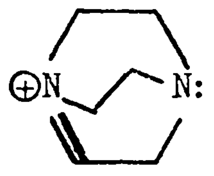


(XIII)

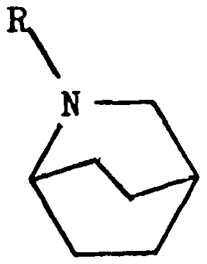
However, the above method has severe limitations in use. It will be of value only for amines which are converted to carbonyl compounds not possessing α-hydrogens. For example, very little n-butyraldehyde was isolated from the reaction of tri-n-butylamine with iodine under aqueous conditions in the presence of calcium carbonate, because in this case a competing reaction, namely iodination of the aldehyde on the α-carbon, proceeds quite easily.

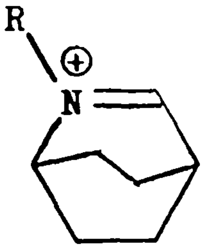
But some amines which do possess α-hydrogens, for example triethylenediamine (XIV) are not oxidised by iodine under the conditions employed. They owe their resistance to oxidation by iodine to the fact that a double bond cannot be established at the bridgehead in the corresponding immonium salt intermediate (XV) (Bredt's rule,[92])


(XIV)


(XV)

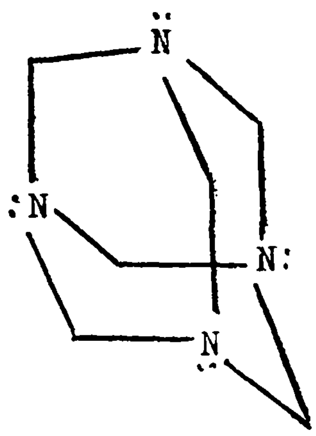
However pyridines and the triethylenediamine type of amines give charge-transfer complexes with iodine, but unlike other amines, for example; tribenzylamine and C2DEA, these complexes are not converted to the corresponding immonium salts for the reason already stated. Similarly other workers have shown that triethylenediamine is recovered to the extent of 80% from attempted oxidation with mercuric acetate[93], whereas under the same conditions amines of the type (XVI) readily form the immonium salt (XVII)[94]


(XVI)


(XVII)

It should be noted that the charge-transfer complexes formed by the interaction of triethylenediamine and related amines with iodine are readily isolated as solids and correspond to the 'trimethylamindihalogenid' which was described by Meisenheimer as N-halotrimethylammonium halide. The characterisation of these and other similar complexes and their role in amine oxidation is discussed in the next chaper.

One of the amines found to be resistant to oxidation by iodine and which forms charge-transfer complexes is hexamine (hexamethylenetetramine) (XVIII); this, like triethylenediamine, is a 'bridge-head' amine. The availability of the iodine present in its charge-transfer complex with this halogen for oxidations, led to it being used as the competing base in the reactions of iodine with amines under aqueous conditions. In a typical experiment benzaldehyde was obtained in 83% yield from tribenzylamine by this method.



(XVIII)

As an alternative to the use of a base such as calcium carbonate or hexamine for the removal of the hydrogen iodide formed during the reaction, the neutralization of unreacted amine may be prevented by oxidizing the acid in situ back to iodine, using an oxidizing agent such as potassium iodate which itself does not attack the amine. With this procedure only a fraction of the required amount of iodine need be added to the amine as it is constantly regenerated by the dropwise addition of aqueous potassium iodate. Alternatively, aqueous potassium iodate may be added slowly to an aqueous solution of the amine hydroiodide or potassium iodide and amine hydrochloride. For example, dropwise addition of aqueous potassium iodate to a suspension of tribenzylamine hydroiodide in the molar ratio 1:3, respectively, would be expected to give benzaldehyde and dibenzylammonium iodide according to the equations

$$6(PhCH_2)_3N.HI + KIO_3 \longrightarrow 6(PhCH_2)_3N + 3H_2O + KI + 3I_2$$

$$6(PhCH_2)_3N + 3I_2 \longrightarrow 3(PhCH_2)_3N.HI + 3(PhCH_2)_2\overset{\oplus}{N}{=}CHPh.\ I^{\ominus}$$

$$3(PhCH_2)_2\overset{\oplus}{N}{=}CHPh\ I^{\ominus} + 3H_2O \longrightarrow 3(PhCH_2)_2\overset{\oplus}{N}H_2\ I^{\ominus} + 3PhCHO$$

or overall

$$3(PhCH_2)_3N.HI + KIO_3 \longrightarrow KI + 3(PhCH_2)_2\overset{\oplus}{N}H_2\ \overset{\ominus}{I} + 3PhCHO$$

Instead, the product was found to be an approximately equimolar mixture of tribenzylamine, benzylidene-benzylamine and benzaldehyde. This may be due to preferential participation of dibenzylammonium iodide (once formed) in the first stage of the reaction, and is attributed to the greater solubility of this salt in an aqueous reaction medium.

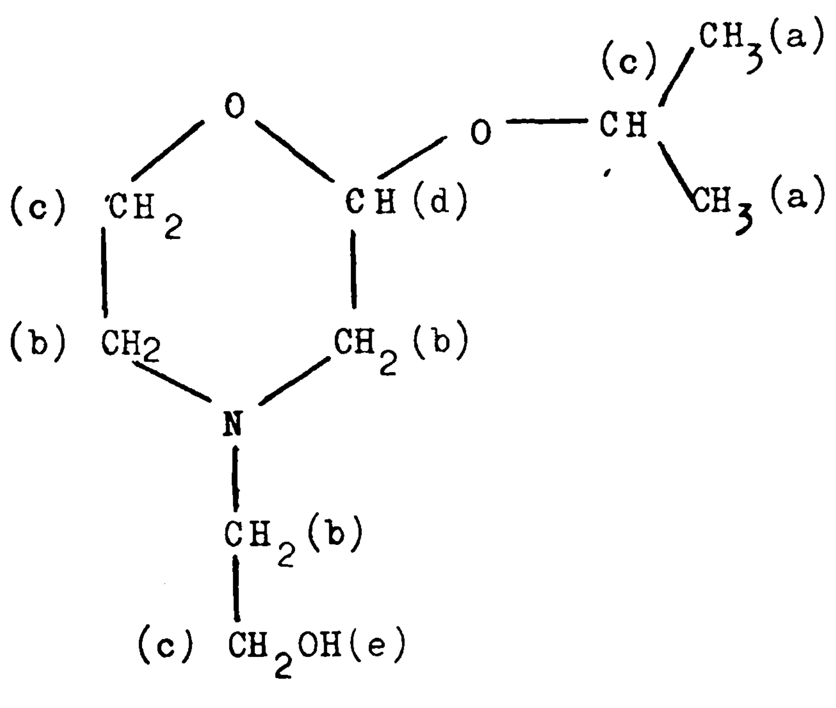
The reaction of tribenzylamine hydroiodide, produced in situ from the readily available hydrochloride and potassium iodide, with an equimolar quantity of potassium iodate gave an equimolar mixture of benzylidene-benzylamine and benzaldehyde, which corresponds to a 67% yield of benzaldehyde based upon the reaction

$$(PhCH_2)_3N.HI + KIO_3 \longrightarrow 3PhCHO + KI + NH_4I$$

Finally, tribenzylamine hydrochloride was oxidised by an equimolar quantity of potassium iodate in the presence of a catalytic amount of potassium iodide. The product was a 2:1 molar mixture of benzylidene-benzylamine and benzaldehyde, equivalent to a 60% yield of benzaldehyde. It was hoped that this latter variation of the potassium iodate - iodine method, which ensures that only a small amount of iodine is present in the reaction mixture at any given instant and the acidic nature of the reaction medium - which would tend to slow iodination at the α-carbon of the resulting carbonyl compound - would make it possible for amines like, for extrample tri-n-butylamine, to be oxidized in good yield to the corresponding aldehyde. However, these expectations did not materialise in practice. Only a trace of n-butyraldehyde was produced even when simultaneous dropwise addition of the potassium iodate solution to the reaction mixture and distillation of the volatile product was used. Thus it would seem that the limitations referred to earlier in relation to the oxidation of amines by iodine in the presence of a competing base also apply to the potassium iodate-iodide modification of the method.

3. Oxidation of aliphatic amines by iodine in organic solvents

The reaction of amines with iodine under non-aqueous conditions was also further investigated with particular emphasis on the isolation and characterisation of amine oxidation products. The amines used for this purpose were C2DEA and C3DEA which are chemically analogous to the C12DEA of the industrial system and reactions were carried out in solvents such as isopropyl alcohol, light petroleum, carbon tetrachloride and tetrachloroethylene. The products isolated using the latter three solvents were tarry materials and could not be studied further. In contrast, for the reaction of C2DEA with iodine is isopropanol solution, chromatography indicated that the crude material contained relatively small amounts of three oxidation products - one of which was by far the major component, and a lot of C2DEA. Isolation of the major oxidation product was effected and a study of its chemical and spectroscopic properties (see below) led to it being assigned the structure XIX, which corresponds to 2-isopropoxy-4-(2'-hydroxyethyl)morpholine

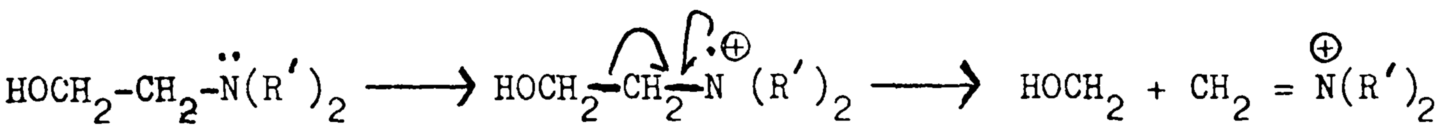


(XIX)

High resolution mass-spectrometry gave a molecular weight for XIX of 189.1372 which corresponds to the molecular formula $C_9H_{19}NO_3$ (calculated mass 189.1365), indicating gain of the unit C_3H_4O by the N-ethyldiethanolamine molecule. The obvious source of this three carbon entity is the solvent, isopropanol. The molecular formula points to a structure which may contain either a double bond or a ring. The former possibility is excluded by the absence from the infrared spectrum of the product of olefinic absorption. As hydrogen iodide is also produced (viz. the formation of hydroiodides), the reaction may be formulated as

$$C_6H_{15}NO_2 + C_3H_7OH \xrightarrow{2I_2} C_9H_{19}NO_3 + 4H^{\oplus} + 4I^{\ominus}$$

According to this formulation, two molecules of iodine are involved in the oxidation of one molecule of amine. The presence of an isopropoxy group in the product was confirmed by the low resolution mass spectrum which exhibited peaks at $^m/e$ 146 and 130, corresponding to loss of isopropyl and isopropoxy groups, from the molecular ion, respectively. The base peak at $^m/e$ 158, formed by loss of a CH_2OH unit (i.e. 189-31) provides strong evidence for the presence of the $N-CH_2-CH_2OH$ group, since tertiary amines fragment by α-fission



$$HOCH_2-CH_2-\ddot{N}(R')_2 \longrightarrow HOCH_2-CH_2-\overset{\cdot\oplus}{N}(R')_2 \longrightarrow HOCH_2 + CH_2=\overset{\oplus}{N}(R')_2$$

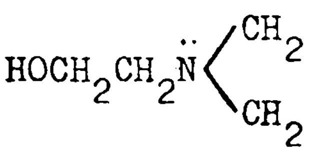
The presence of the hydroxyl group in the product is confirmed by the infrared spectrum.

Examination of the p.m.r. spectrum of the oxidation product (P.M.R. No. 1) confirms that it containes one proton exchangeable with deuterium oxide (i.e. the hydroxyl group), and the integration of the spectrum shows there to be a total of 19 protons, in agreement with the mass spectrum. The p.m.r. spectrum consists of several groups of multiplets, the chemical shifts and relative intensities of which led to the assignments listed in Table 3

Table 3. P.M.R. SPECTRUM OF 2-ISOPROPOXY-4-(2'-HYDROXYETHYL) MORPHOLINE

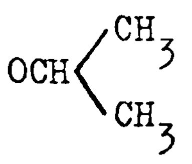
chemical shift (δ)	No. of H	assignment	position in structure (IXX)
1.2	6	$OCH(\underline{CH}_3)_2$	(a)
2.5	6	$N\underline{CH}_2$	(b)
3.8	5	$O\text{-}\underline{CH}$	(c)
4.45 (exchangeable)	1	$O\underline{H}$	(e)
4.7	1	$O\text{-}\underline{CH}\text{-}O$	(d)

These indicate the presence of the groups



$HOCH_2CH_2\ddot{N}\left\langle\begin{matrix}CH_2\\ CH_2\end{matrix}\right.$

and



$OCH\left\langle\begin{matrix}CH_3\\ CH_3\end{matrix}\right.$

which together with a residual portion, C_2H_3O, clearly constitute the proposed structure (XIX) for the substituted morpholine, which is thus seen to accommodate all the available spectroscopic evidence.

It will be noted that this oxidation product is formulated as a cyclic acetal. Chemical confirmation for this structure was based on the detection, by gas-liquid chromatography of isopropanol formed by the hydrolysis of XIX under acid conditions. Furthermore, on treatment with benzoylchloride the oxidation product gave the corresponding benzoate hydrochloride, the p.m.r. spectrum of which (Table 4) is compatible with its derivation from the postulated structure (XIX).

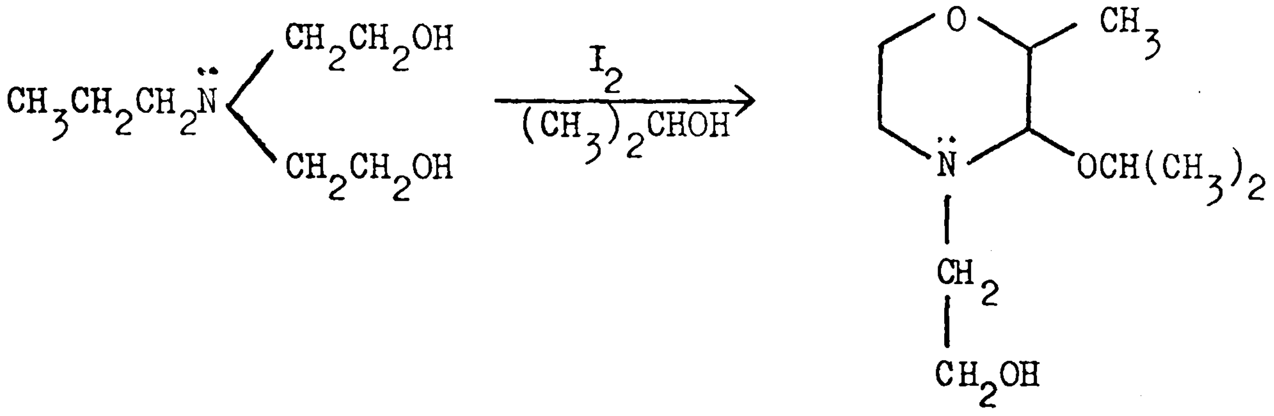
Table 4. P.M.R. SPECTRUM OF THE BENZOATE HYDROCHLORIDE OF XIX

chemical shift (δ)	no. of H	assignment
1.2	6	$OCH(\underline{CH}_3)_2$
3.1	1	$\overset{\oplus}{\underline{H}N}$
3.5	6	$\overset{\oplus}{N}\underline{CH}_2$
4.1	3	$O\underline{CH}$
4.9	2	$\underline{CH}_2$-O-CO
5.2	1	O-$\underline{CH}$-O
7.8	5	$-\phi$

The downfield shift of the multiplets attributable to six protons from 2.5 in XIX to 3.8 δ in the salt, is due to the deshielding of the protons α- to the nitrogen by the positive charge on the nitrogen in the substituted ammonium ion. The shift in absorption, due to the hydrogens of the methylene group adjacent to the hydroxyl group on esterification is typical and confirms the assignment of the absorption centred at 3.8 δ as being due to protons adjacent to an oxygen in XIX. In addition the low-field multiplet at 4.78 δ which is observed in both spectra is typical of a methine group positioned between two oxygen atoms. This multiplet may in fact be regarded as a doublet of doublets which arises from the splitting of the methine hydrogen by the protons of the adjacent methylene group; the latter thus appear to be non-equivalent, presumably because of the rigidity imposed upon the morpholine ring by the bulky isopropoxy and hydroxyethyl substituents. These assignments were confirmed by comparing the p.m.r. spectra of N-(2'-hydroxyethyl)morpholine and its benzoate hydrochloride which was prepared in the same manner as the corresponding derivative of the oxidation product XIX.

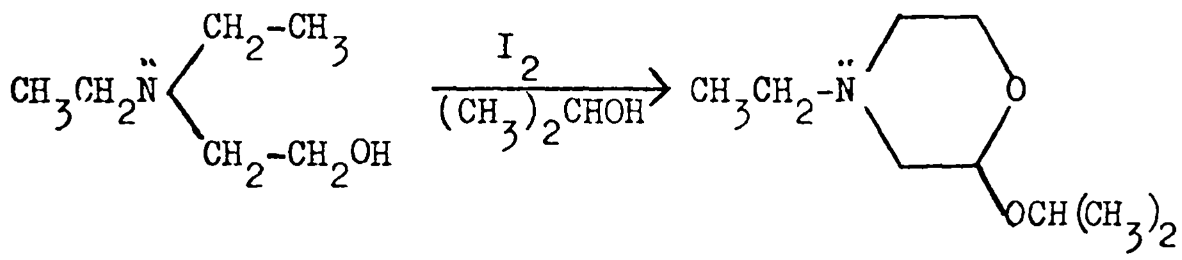
The amines C3DEA, diethylaminoethanol and triethylamine were each treated with iodine in the same manner as C2DEA and the structures assigned to the products isolated from these reactions are as follows:

N-propyldiethanolamine, C3DEA



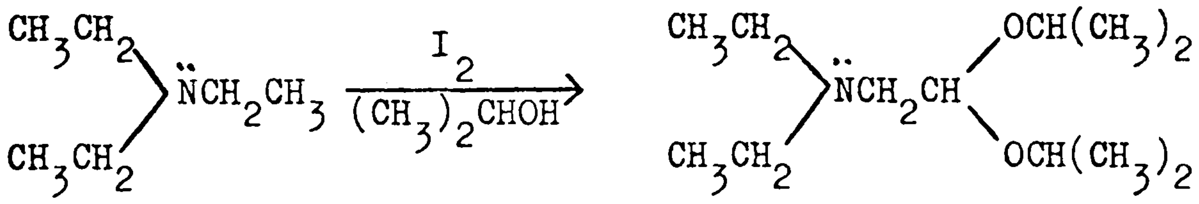
(XX)

Diethylaminoethanol



(XXI)

Triethylamine



(XXII)

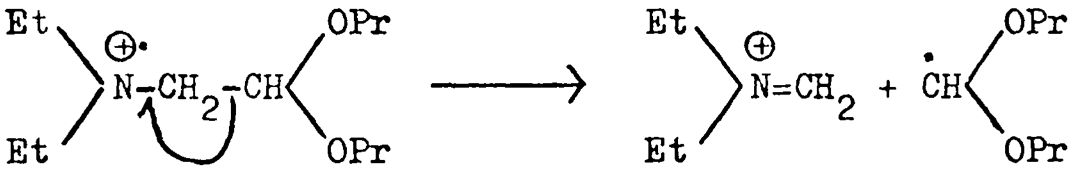
These products were isolated in very small yield using a combination of dry-column and gas-liquid chromatography and it was not possible, therefore, to examine them by chemical means. For this reason, characterisation and structure elucidation was accomplished entirely by spectroscopic means.

Comparison of the spectra of the products from C2DEA (XIX) and diethylaminoethanol (XXI) show the differences one would expect for the substitution of a hydroxyethyl group by an ethyl group. For example, the infrared spectrum of XXI does not show an absorption due to -OH and its p.m.r. spectrum does not contain an absorption due to an exchangeable proton. The p.m.r. spectrum (PMR No. 2), however, indicates that there are nine protons in a typically aliphatic environment; six protons which show a marked downfield shift on addition of trifluoroacetic acid, thus confirming the presence of three methylene groups attached to the nitrogen and one proton at lower field attributable to the methine group positioned between two oxygen atoms. In this case too, this absorption appears as a doublet of doublets.

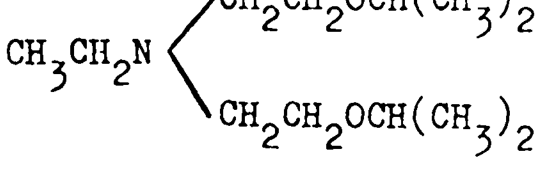
The low resolution mass spectrum of XXI has peaks at 158 ($M^+ - CH_3$), 130 (M^+ - Pr) and 114 (M^+- OPr) but no peak at 142 ($M^+ - CH_2OH$). The base peak has a mass of 57; this peak is also present in the mass spectrum of XIX. The mass spectrum of XX has peaks at 203 (M^+), 172 ($M^+ - CH_2OH$), 160 (M^+ - Pr) and 144 (M^+ - OPr), indicating the presence of the hydroxyethyl and isopropoxy groups, with a base peak of mass 56. As the base peak of these morpholine derivatives is undoubtedly due to a substituted ammonium ion, the fact that in the case of XX it has a mass of one unit less than the base peaks of XIX and XXI, is indicative of having a substituent α-to the nitrogen i.e. the isopropoxy group, which is lost during the formation of the base peak.

The p.m.r. spectrum of XX confirms the presence of the -OH group, and of protons in an aliphatic environment, adjacent to a nitrogen and to oxygen. The doublet at 4.6 δ is attributable to the proton on the carbon between the nitrogen and the propoxy group, whilst the doublet of the methine adjacent to the methyl group is lost in the complex of absorptions centred about 4

All the above products contain the morpholine ring system, which has obviously been formed by intramolecular attack of a hydroxyethyl group upon the β-carbon of the oxidised chain. Triethylamine does not contain hydroxyethyl groups and hence cannot react in this manner; consequently, the corresponding oxidation product would not be expected to be a morpholine derivative. This was confirmed by the isolation of an acyclic compound, the mass spectrum of which has peaks at 217 (M^+), 202 ($M^+ - CH_3$), 159 ($M^+ - CH_3 - Pr$), 131 ($M^+ - 2\ Pr$) - the latter indicating the presence of two isopropoxy groups - and a base peak at $^m/e$ 86 which may be attributed to the diethylmethylene immonium ion, formed probably as follows



The p.m.r. spectrum of XII (PMR No. 4) provides confirmatory evidence for the postulated structure. It clearly precludes possible alternatives such as XXII by virtue of the markedly different ratios of protons in various environments that such a structure would require (see Table 5)



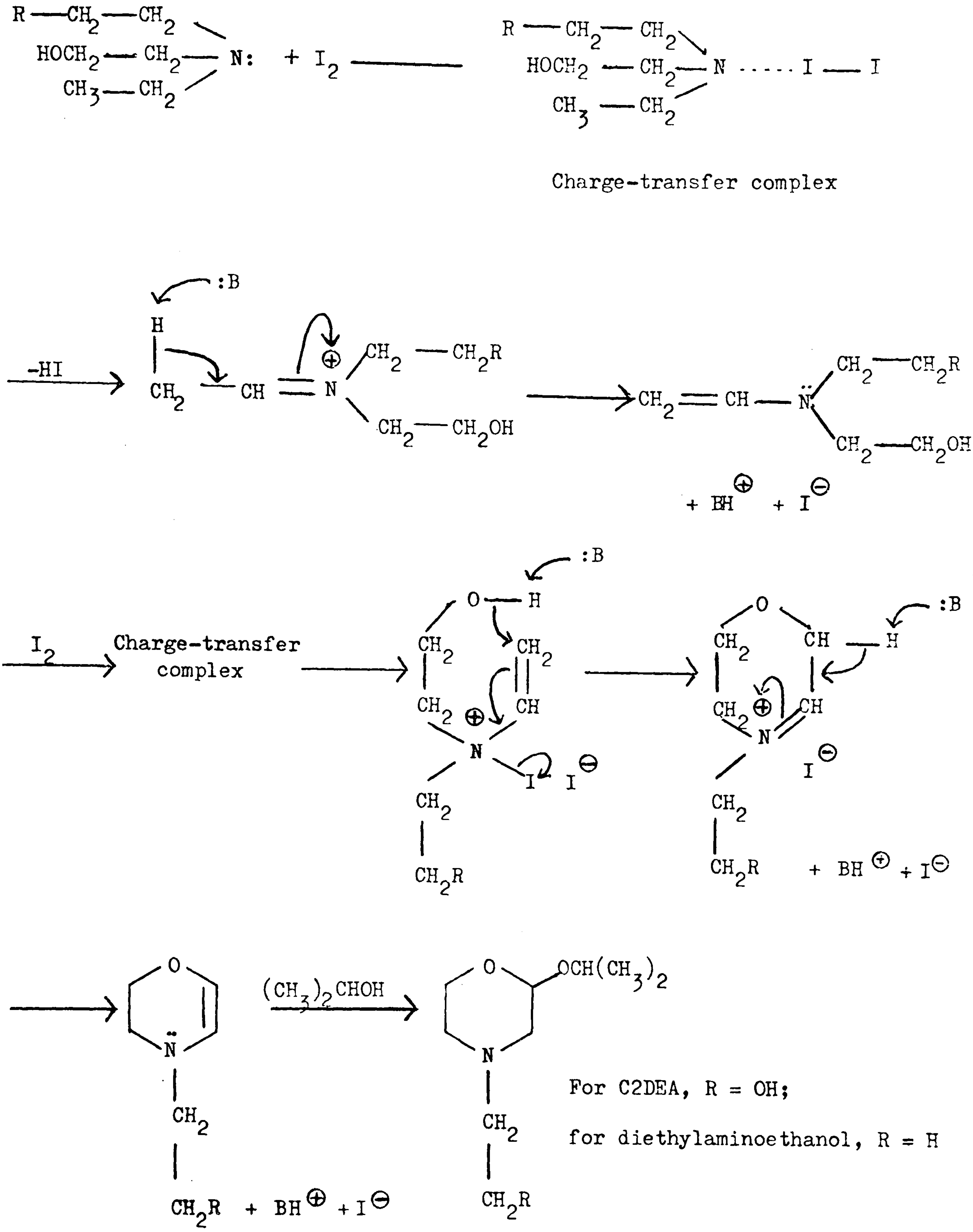
$$CH_3CH_2N\begin{cases}CH_2CH_2OCH(CH_3)_2\\CH_2CH_2OCH(CH_3)_2\end{cases}$$

(XXIII)

TABLE 5. P.M.R. SPECTRUM OF DI-ISOPROPYL 2-(DIETHYLAMINO)-ACETALDEHYDE DI-ISOPROPYL ACETAL (XXII)

Environment of protons	Expected number of protons for		Observed spectrum	
	Structure XXII	Structure XXIII	No. of protons	Chemical shift (δ)
Aliphatic	18	15	18	1.2
Adjacent to nitrogen	6	6	6	2.65
Adjacent to oxygen	2	6	2	3.9
Between 2 oxygens	1	Nil	1	4.70

In the light of the structures deduced for these products, and in view of the evidence presented earlier in this section - which confirms the formation of immonium ion intermediates in oxidations of tertiary amines by iodine, pathways leading to these structures must involve the corresponding immonium salts. Thus, 2-isopropoxy-4-(2'-hydroxyethyl)morpholine (XIX) and 2-isopropoxy-4-ethylmorpholine (XXI) are probably formed by the oxidation of C2DEA and diethylaminoethanol respectively, by iodine in isopropanol as depicted in the generalised Scheme 12 which accounts for ring closure to a morpholine derivative and the attachment of the nucleophile - isopropanol - at the β rather than the α-carbon of the postulated 'vinyl ether like' intermediate. It should be noted that in both cases the products are formed by the addition of isopropanol and the loss of 4 protons - thus two separate oxidations by molecular iodine must have taken place. On account of the hydrogen iodide liberated the scheme also explains the fact that the corresponding amine hydroiodide is in each case the major product.

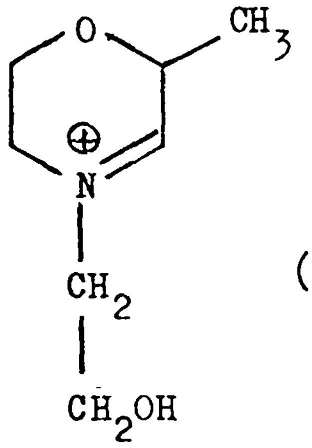


For C2DEA, R = OH;

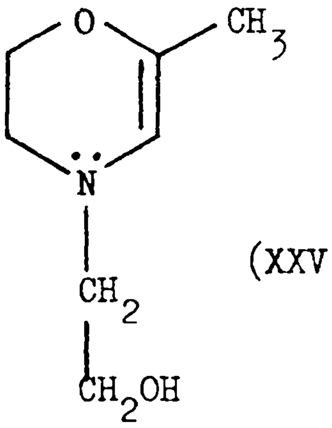
for diethylaminoethanol, R = H

Scheme 12 OXIDATION OF C2DEA AND DIETHYLAMINOETHANOL BY IODINE IN ISOPROPANOL SOLUTION

In the case of C3DEA, either steric factors prevent the addition of the isopropoxy group at the β carbon which already has a methyl substituent, or the greater stability of the immonium ion XXIV, due to the electron donating methyl group, prevents formation of the 'enamine' XXV. Hence, in this case, formation of 2-methyl-3-isopropoxy-4-(2'-hydroxyethyl) morpholine (XIX) is seen as being the result of nucleophilic attack by isopropanol at the α carbon atom of the immonium ion.



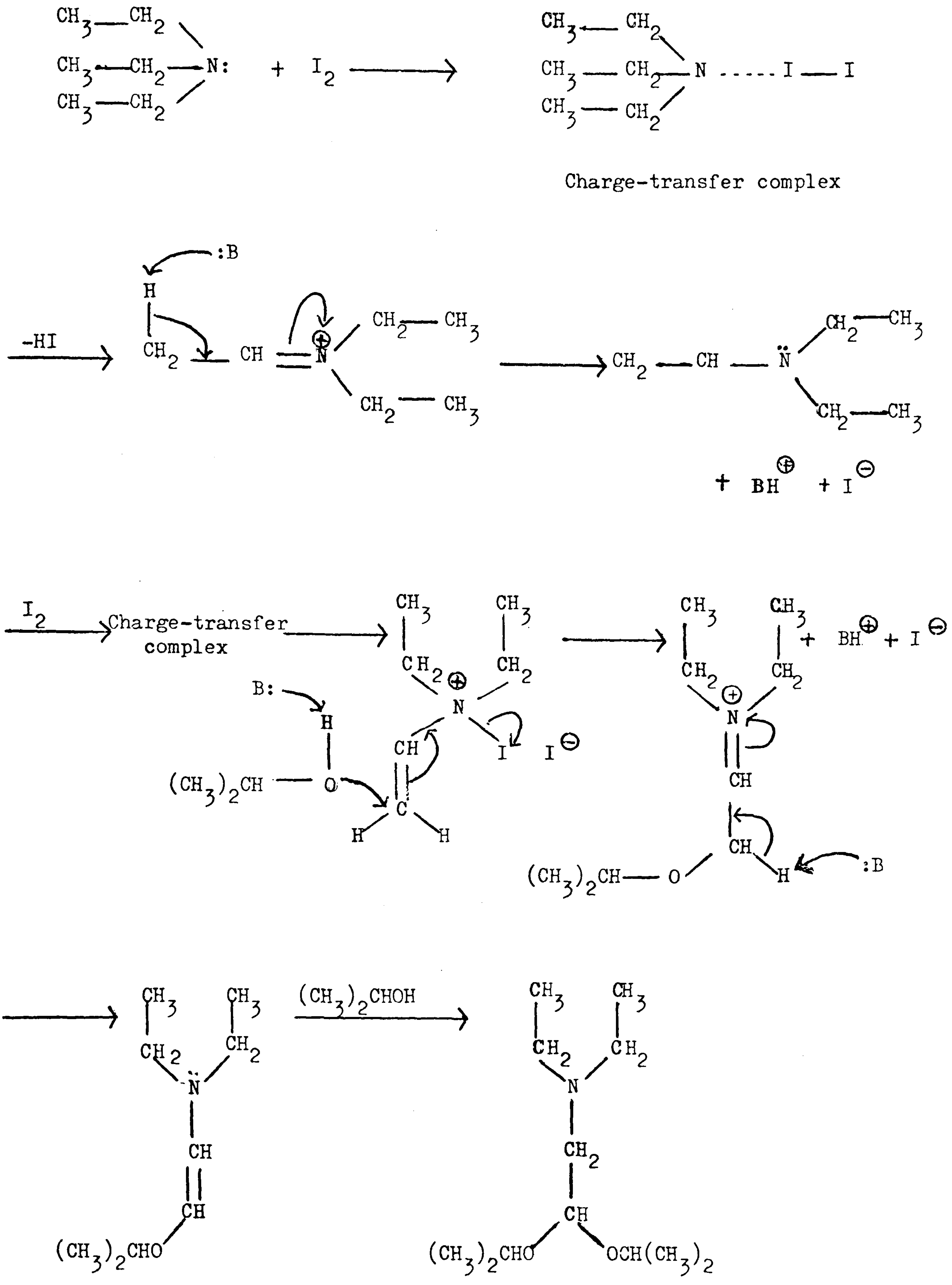
(XXIV)



(XXV)

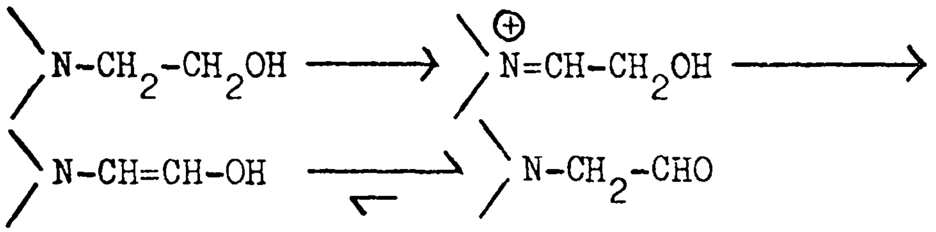
The triethylamine reaction may be formulated in a similar manner to the oxidation of C2DEA, except that the product results from addition of two moles of isopropanol as depicted in Scheme 13.

The product obtained from the oxidation of triethanolamine by iodine in isopropanol has not been characterised but high resolution mass spectrometry points to a molecular formula $C_{10}H_{20}N_2O_4$. A compound corresponding to this molecular formula could result from the combination of two oxidised triethanolamine molecules and the loss of a two carbon unit. Calculation shows that the product has two double bond equivalents and could possibly contain two cyclic groups. Examination of the low resolution mass spectrum shows that the base peak has a mass of 116 i.e. half the molecular weight. The structure of this molecule must therefore account for this cleavage and, in addition, its formation should



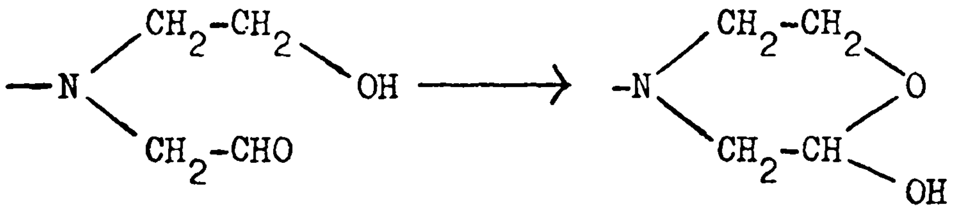
Scheme 13 OXIDATION OF TRIETHYLAMINE BY IODINE IN ISOPROPANOL

be rationalised by a scheme similar to those postulated for the oxidation of the other amino-alcohols. Triethanolamine contains no alkyl groups; therefore a hydroxyethyl group must be oxidised, but if an 'enamine' (XXVI) were to be formed via an immonium salt, it would tautomerise to an aldehyde

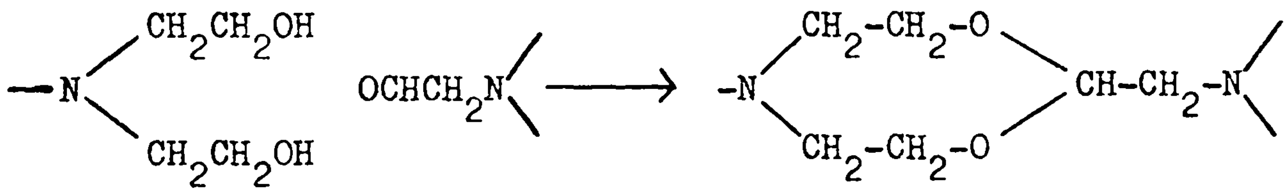


(XXVI)

The latter could reasonably be expected to react with alcoholic functions to give (i) a cyclic hemiacetal (XXVII) by intramolecular attack and (ii) a cyclic ketal (XXVIII) by intermolecular attack.

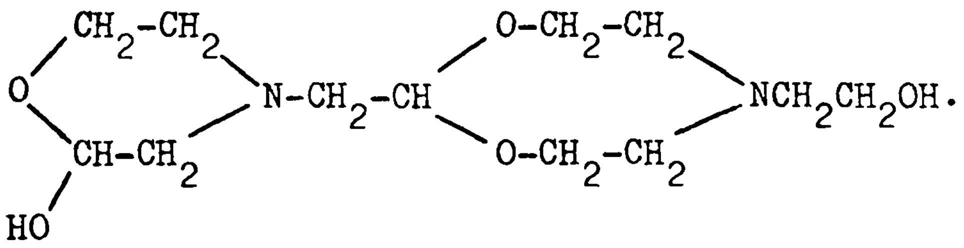


(XXVII)

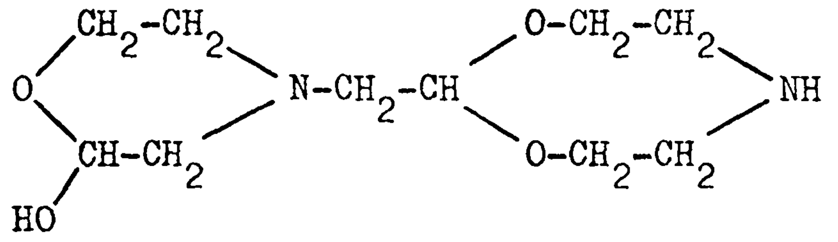


(XXVIII)

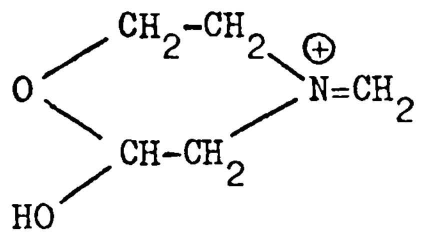
A combination of these two reactions would give



Oxidation of the remaining hydroxyethyl group and hydrolysis of the resulting immonium salt by water produced in the formation of the ketals could lead to

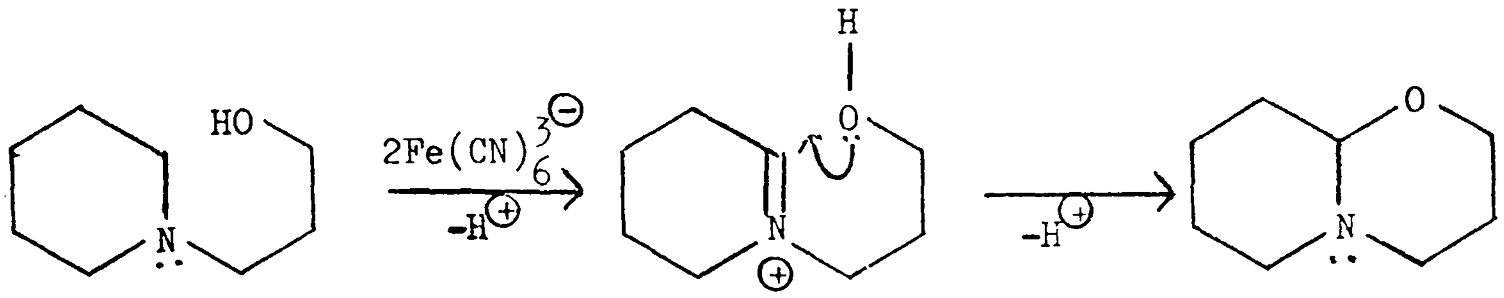


The low resolution mass spectrum of the product is in accord with this structure, in so far as the base peak with a mass of 116 would correspond to the fragment

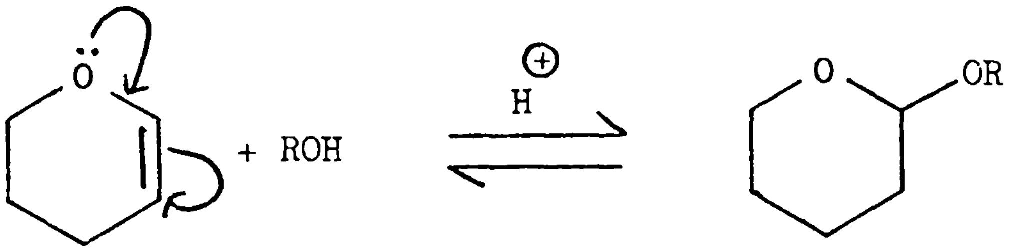


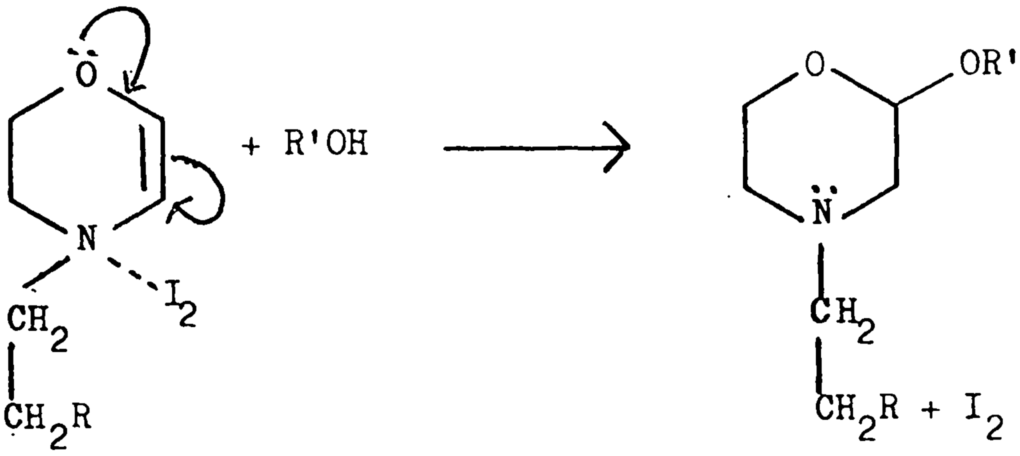
It must be stressed, however, that a definite characterisation of this product has not been achieved because the quantity of product isolated was insufficient for the determination of its p.m.r. spectrum and for other investigations. It should also be emphasized that only one of a number of oxidation products was actually isolated.

Oxidation of amino alcohols has been studied by other groups of workers, such as Leonard and Musker[95] who used mercuric acetate as the oxidant and Audeh and Lindsay-Smith[79] who studied the oxidation of tertiary amines by alkaline hexacyanoferrate (III). Both found, however, that intramolecular nucleophilic addition of an alcoholic oxygen occurred at the α-carbon atom of the immonium ion, which they postulated as an intermediate in their respective reactions e.g.



In this respect the structure of the product isolated from the oxidation of C3DEA by iodine in isopropanol is compatible with the above observations. By contrast, the compounds XIX and XXI obtained under the same conditions from C2DEA and diethylaminoethanol, respectively, appear to have been formed by attack of isopropanol on the carbon atom α-to the nitrogen function. It is conceivable that under the reaction conditions used, the nitrogen lone pair of the intermediate (XXIX) is partly involved in weak complexation with, for example, iodine and hence allows the orientation of addition of the isopropanol to occur in the same way as with the established reagent, dihydropyran[96].

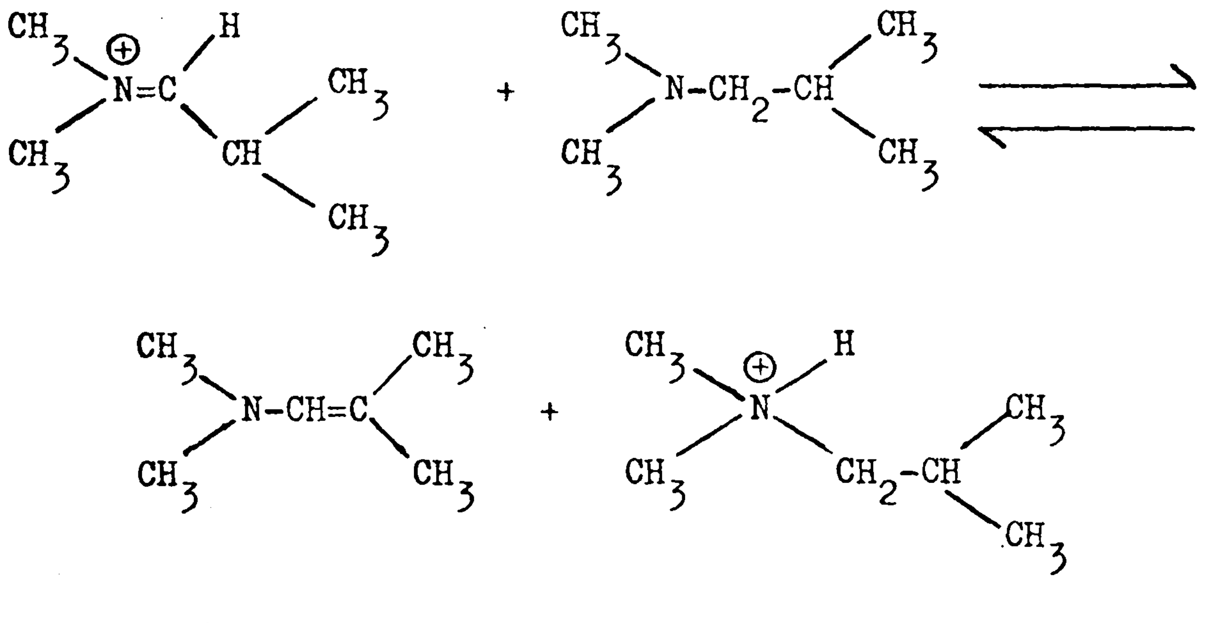




(R = H or OH)

(XXXII)

The proposed formation of enamines or enamine-like moieties by the loss of a α-proton from the corresponding immonium ion (see Schemes 12 and 13) may be attributed to the basic conditions in the reaction mixture, the base being the amine itself. This is borne out in the work of Damico and Broaddus[97] who investigated the oxidation of tertiary amines by trityl compounds. They postulated formation of immonium salts by the removal of a hydride ion from an α-carbon atom but in order to explain results such as the formation of (XXX), it was necessary to assume that immonium salts reacted with unreacted amine to give protonated amine and the corresponding enamine. Subsequently, they demonstrated the validity of this assumption by treating an immonium salt, which was synthesized unambiguously, with the corresponding tertiary amine; the products were an amine salt and an enamine (XXX).



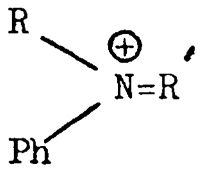
(XXX)

It should be noted that Leonard and Musker[95], used acid conditions, as is usual in mercuric acetate oxidations, (ca. pH 4) under which there would be little tendency for the immonium salt to lose a proton and give the enamine. In contrast, oxidation with hexacyanoferrate (III) was carried out in 2M aqueous potassium hydroxide. The intermediate immonium ion (XXXI) would be subject to attack by the nucleophilic hydroxide ion in a similar manner to that discussed above in connection with the oxidation of amines by iodine under aqueous conditions. Thus the action of the hydroxide ion is not to remove a proton from the β-carbon atom, but to add to the α-carbon atom of the immonium ion to give unstable α-hydroxyamines which then decompose to a secondary amine and a carbonyl compound; secondary amines were in fact isolated from these oxidations.

In order to compare results more directly with those obtained by other workers who oxidised amino alcohols derived from piperidine and pyrrolidine, the oxidation by iodine in isopropanol of N-ethylmorpholine, N-(2'-hydroxyethyl)morpholine, N-ethylpiperidine and N-(2'-hydroxyethyl)piperidine was also attempted. But although reduction of the iodine was noted, and the major product was, in each case, the corresponding amine hydroiodide; amine oxidation products could not be isolated in sufficient quantity and purity for identification.

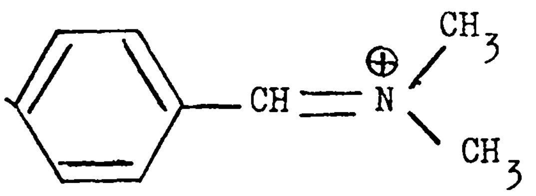
4. Oxidation of aromatic amines by iodine in organic solvents

In addition to the study of the reaction of tertiary aliphatic amines with iodine, a limited investigation was made of the oxidation of tertiary aromatic amines under the same conditions. The amines used were N,N-dimethylaniline, N,N-diethylamine and N-phenyldiethanolamine. As well as the hydroiodides of the starting materials other products obtained were N-methylaniline and crystal violet from N,N-dimethylaniline, N-ethylaniline from N,N-diethylaniline and N-(2'-hydroxyethyl)-N-iodoaniline from the aminoalcohol. The different nature of the 'oxidation' products isolated in these cases may be attributed to the intermediacy of an immonium ion (XXXII) which is stabilised by conjugation with the aromatic system



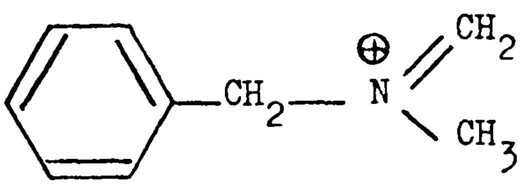
(XXXII)

The expected preferential formation of an immonium ion which is conjugated with the aromatic system has already been noted. Thus only benzaldehyde was isolated from the oxidation of N,N-dimethylbenzylamine by iodine under aqueous conditions. This product results from the hydrolysis of the immonium ion



;

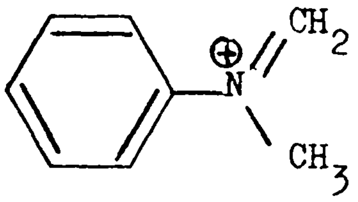
the less stable immonium ion



would be expected to give N-methylbenzylamine and formaldehyde, but none of the latter compounds were detected.

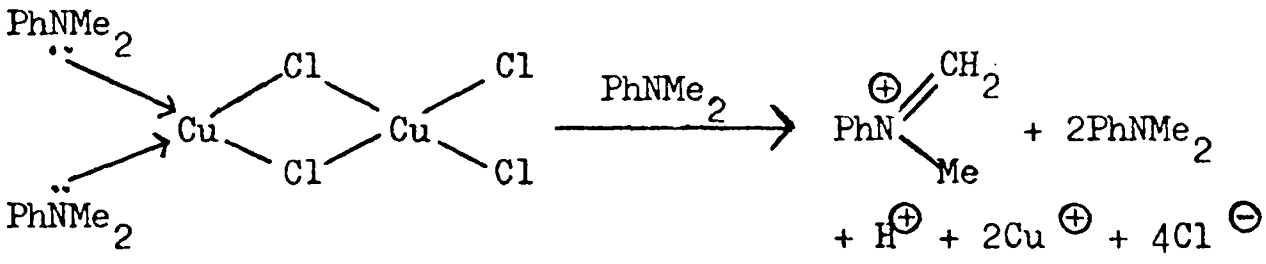
Hydrolysis of ion XXXII above, either during work up, or during the reaction by adventitous water would of course account for the isolation of secondary amines from the reaction mixtures. It should be noted that not only would such an immonium ion be more stable than an aliphatic immonium ion, but that the parent bases are weaker than aliphatic amines and hence less likely - as in the case of diethylaniline - to abstract β-hydrogens and form the corresponding enamine.

Formation of crystal violet by the oxidation of N,N-dimethylaniline with several agents including chloranil and cupric chloride[98], and aluminium chloride[99] has been noted by other workers who regard its formation as convincing evidence for the intermediacy of the immonium ion



in these reactions.

This is thought to be formed by the action of cupric chloride on N,N-dimethylaniline as follows



(XXXIII)

These authors stress that the products formed are those typical of a two electron oxidant and that cupric chloride, a one electron oxidant, reacts via the complex (XXXIII), with the result that a 'two electron' oxidation occurs, as is the case with other oxidants which are thought to form immonium salts.

For example $2e^{\ominus} + \text{Hg(II)} \longrightarrow \text{Hg}(\bar{0})$

$$2e^{\ominus} + \text{Pb(IV)(OAc)}_4 \longrightarrow \text{Pb(II)(OAc)}_2 + 2\text{OAc}^{\ominus}$$

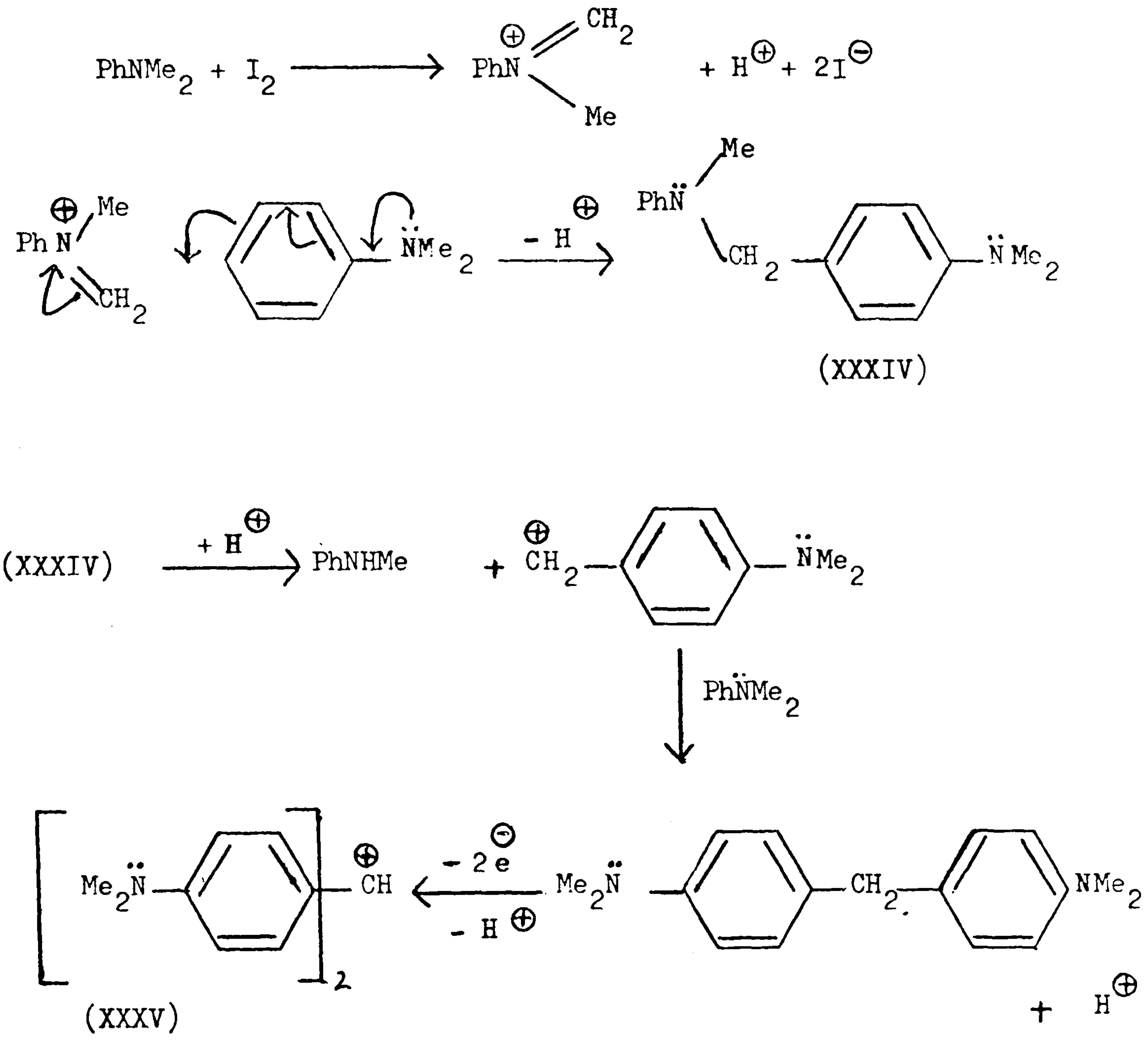
and by analogy iodine may be similarly regarded as

$$2e^{\ominus} + \text{I}_2 \longrightarrow 2\text{I}^{\ominus}$$

or more generally,

$$2e^{\ominus} + \text{X}^{\oplus} + \text{Y}^{\ominus} \longrightarrow \text{X}^{\ominus} + \text{Y}^{\ominus};$$

on this basis radical mechanisms for this reaction would thus seem unlikely. Formation of crystal violet may thus occur as follows (Scheme 14)

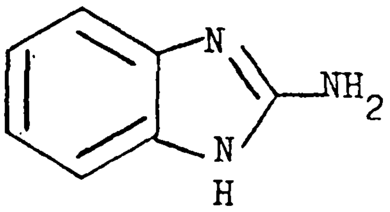


Scheme 14

The compound (XXXV) reacts with N-methylaniline and N,N-dimethylaniline to give methyl violet and crystal violet, respectively. Hence, this mechanism also accounts for the formation of small quantities of N-methylaniline.

5. Oxidation of amines with iodine in organic solvents as a preparative method

Although the oxidation and derived products from these reactions have been isolated in very small yield, a preliminary investigation was made of the synthetic potential of the oxidation of amines by iodine in non-aqueous media. During the investigations described above, the major product in each case was the corresponding amine hydroiodide. It would appear, therefore, that in order to increase the yield of the oxidation product(s) and hence transform the reaction into a potentially useful synthetic procedure, some means of removing the liberated hydrogen iodide would have to be devised. With this objective in mind, several bases and oxidising agents (of the type which are known not to affect the amine itself) were selected and accordingly, the following oxidations by iodine were attempted (see Table 6). In all cases, the products were found to contain appreciable amounts of unoxidised amine - and in some cases the outcome of the reaction was worse in the presence of the competing base, than in its absence. Calcium carbonate and hexamine were used because of their success in the oxidation of tribenzylamine by iodine under aqueous conditions, whilst 2-aminobenzimidazole was selected on account of its structural similarity to the very strong base guanidine; pyridine was used both as a competing base and a solvent.



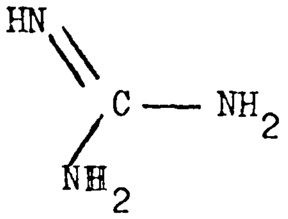
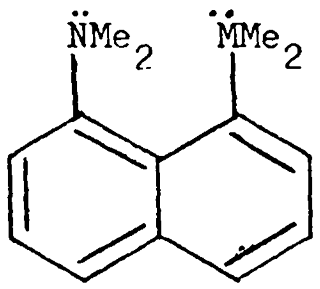


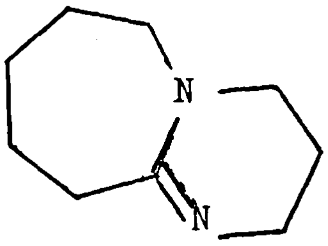
Table 6 OXIDATION OF AMINES IN ANHYDROUS MEDIA IN THE PRESENCE OF 'COMPETING' BASES OR OXIDISING AGENTS

Substrate	Solvent	Reagent (excess)
N,N-diethylaminoethanol	isopropanol	hexamine
C2DEA	"	"
C2DEA	"	calcium carbonate
Tribenzylamine	"	hexamine
"	"	calcium carbonate
"	"	potassium butoxide
"	"	2-aminobenzimidazole
"	pyridine	pyridine
"	dioxan	sodium acetate
"	isopropanol	pyridine-N-oxide
"	isopropanol	quinone

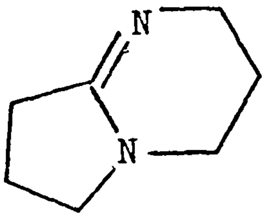
The use of sodium acetate as a base was founded on a report by Cava et al[100] on oxidative transformations in alkaloids, using iodine in dioxan in the presence of sodium acetate. These workers reported the conversion of an amine to an enamine in 80% yield and proposed a mechanism similar to Scheme 1, which involved the removal of protons by acetate ions. However, when these conditions were applied to tribenzylamine, 70% of the amine was not oxidised.

Other bases which were considered but not used were the 'Proton Sponges', 1,8-bis(dimethylamino)naphthalene, diazabicycloundecene (DBU) and diazabicyclononene (DBN)





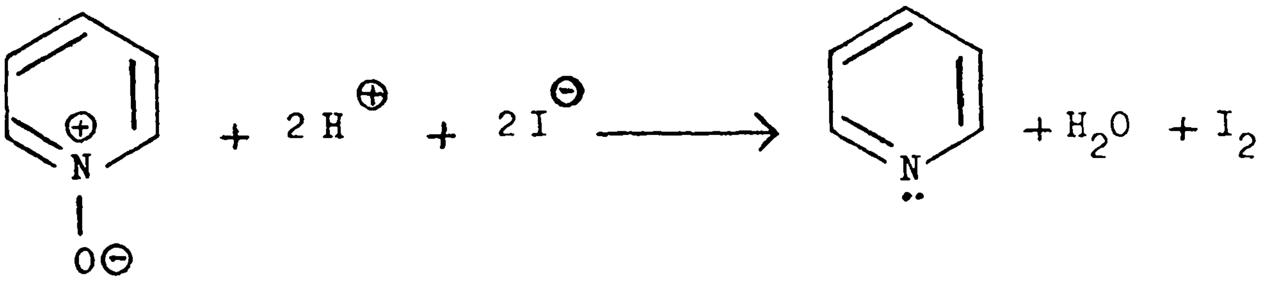
DBU

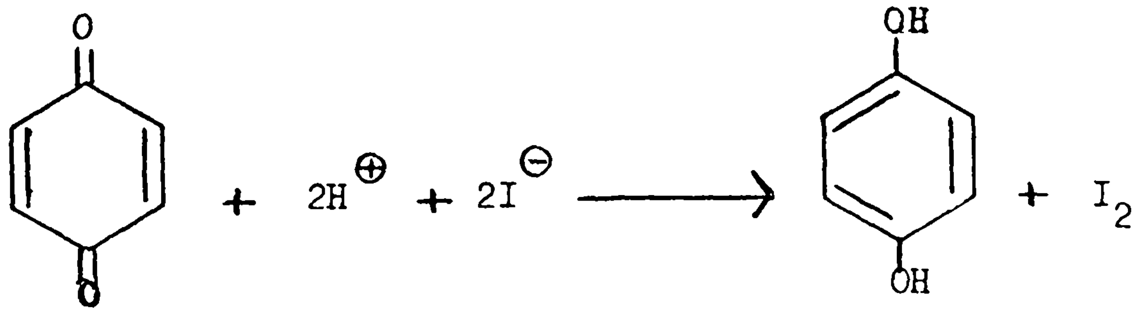


DBN

However, this system was not investigated further because of the difficulties associated with the separation of products.

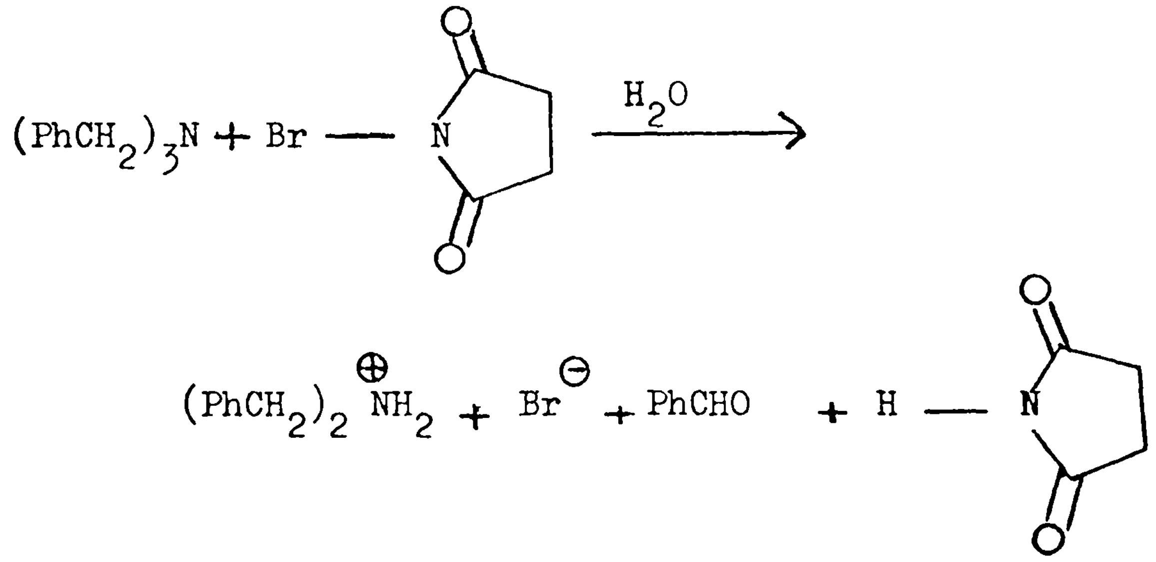
As in the investigation of the reaction in aqueous conditions, attempts were also made to remove the hydriodic acid by the addition of other oxidants, e.g. pyridine-N-oxide and quinone, but these attempts were also unsuccessful.





It is therefore concluded that the oxidation of amines by iodine under non-aqueous conditions does not have synthetic potential. It should be noted also, that whilst protonation reduces the yield of oxidation products considerably, it also acts as a protecting group. If the oxidised amine was present in the reaction medium as the free base, it too, would be prone to attack by iodine. The net result would then be total destruction of the amine molecule.

In this context, it is worth noting that Henbest and his school[64] have reported that when tribenzylamine was treated with an equimolar quantity of N-bromosuccinimide in non-aqueous solution, the products isolated were dibenzylamine and benzaldehyde with less than 2% of unreacted starting material. The reaction may be formulated as



It is considered by the present author that the oxidant is of the general type Br^+Y^- and i.e. a two electron oxidant similar to iodine, but the liberated acid, succinimide, is so weak that protonation of amine in this system does not occur. This modification, however, cannot be applied to the oxidation of amino alcohols in isopropanol, as NBS is known[101] to oxidise this solvent.

6. Summary and conclusions

The salient points of this discussion concerned with the scheme proposed for the oxidation of amines by iodine may now be summarised as follows:-

(a) Charge-transfer complex formation; (the detailed role of the charge-transfer complex will be considered in the next chapter)

It has been shown that for reaction availability of the nitrogen lone-pair is essential; amine salts do not react. In the case of amines such as hexamine and triethylenediamine these complexes are particularly strong donors but the resulting complex cannot be transformed to the corresponding immonium salt.

(b) Immonium ion formation

This has not been isolated but its intermediacy is supported by

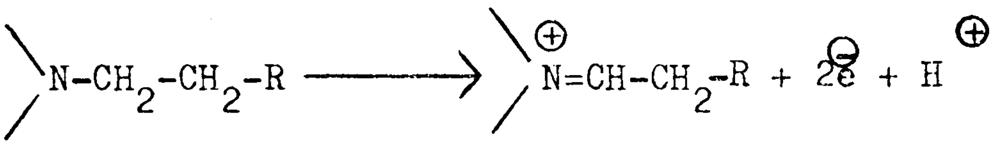
(i) the stability of certain charge-transfer complexes in which the donors amine cannot form the corresponding immonium ion (Bredt's rule)

(ii) isolation of its known hydrolysis products

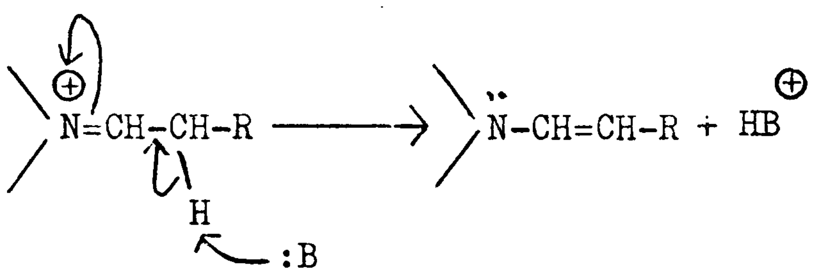
(iii) in situ conversion to a stable derivative by reaction with a nucleophile (cyanide ion)

and (iv) the indication that in certain cases the reaction goes via an 'enamine type' stage; enamines have been shown to be formed via immonium salts.

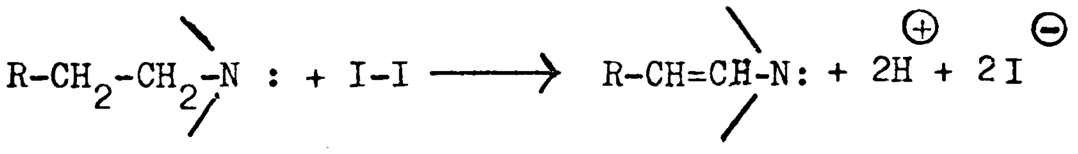
The scheme (Scheme 1, p.24) is thus similar to those proposed for the oxidation of amines by other 2 electron oxidants. Furthermore, the nature of the products obtained by the action of iodine on amines is compatible with an ionic process, which, by analogy with the Westheimer mechanism[51] for dehydrogenation may be depicted as follows



The loss of a second proton is then seen to be associated with enamine formation



Iodine clearly belongs to the class of oxidants which oxidise amines by dehydrogenation, which is the process of removing a pair of hydrogen atoms. An equivalent process is the elimination of two protons and the transfer of a pair of electrons (in this case the nitrogen lone-pair) from the molecule being oxidised to the oxidising agent i.e.



CHAPTER THREE

CHARGE TRANSFER COMPLEXES OF AMINES WITH HALOGENS AND THEIR ROLE IN AMINE OXIDATION

CHAPTER THREE: A. INTRODUCTION

CHARGE-TRANSFER COMPLEXES

CHARGE-TRANSFER COMPLEXES

1. Bonding in charge-transfer complexes

A molecular complex is defined[102] as 'a substance, formed by the interaction of two or more component molecules, which may have an independent crystal structure and which will reversibly dissociate into its components, at least partially, in the vapour phase and on dissolution'. Although such addition products have been known to chemists for many years, their constitution has been elucidated during the last 25 years. Thus, as a result of Mulliken's theory[103], which is in part, derived from earlier interpretations of observations made on seemingly disparate systems, many of these products may now be described as charge-transfer complexes.

Systems involving halogens and/or amines have played an important role in the development of the now generally accepted ideas about charge-transfer complexes. Thus, the brown colour of solutions of iodine in, for example, alcohol has been attributed to a complex formed between iodine and the donor solvent. Amongst the observations which led to this conclusion, the higher solubility, heat of solution and chemical reactivity of iodine in donor solvents[104], as well as the reversible colour change from brown to violet noted when such systems are heated, and the abnormally low freezing point depressions[105] given by solutions of iodine in mixed donor and non-donor solvents may be noted here.

Similarly, liquid amine/iodine systems are also brown, and furthermore, solid addition compounds were isolated from these solutions. Ammonia and iodine gave a compound formulated as as $NH_3.I_2$, and trimethylamine formed a solid complex with bromine to which the formula $(CH_3)_3N.Br_2$ was assigned. Hantzsch[9] realised that the nitrogen atom in such complexes should not be regarded as pentavalent and, by analogy with the addition products formed between amines and hydrogen halides, he formulated these substances as $[R_3N.I]I$ and $[(CH_3)_3N.Br]Br$. The latter formulation was in fact accepted by most chemists until the advent of the Mulliken theory (see later).

Alternative explanations of the nature of bonding between the two molecular species in such systems, were, however, put forward. Thus Pfeiffer[107] suggested that bonding occurred by the saturation of 'residual valencies'; as this did not account for the observed changes in colour, other workers[108] postulated the formation of a covalent bond between a DONOR and an ACCEPTOR species to give a compound which was responsible for the characteristic light absorption. This theory was criticised in turn; the apparently instantaneous attainment of equilibrium in solution disfavoured the contempt of covalent bonding. Further, X-ray diffraction studies[109] do not support the idea of a covalent bond because, in many cases, the determined interatomic distances between the components exceed the normal covalent bond lengths. Other equally unsuccessful explanations include Briegleb's[110] interpretation of the interaction in terms of dipole-dipole and dipole-induced dipole forces, Gibson and Loeffler [111], and Hammick and Yule [112] also formulated ideas, which attributed the spectroscopic changes observed on complex formation to some transfer of charge between the components during collisions.

The concept of complex formation through the interaction between electron donors and electron acceptors was developed by Weiss[113]. He described the interaction of nitro-compounds, and quinones (A) with aromatic substances (D), in terms of the transfer of a single electron, as represented by the following equation, leading to the formation of odd electron ions held together by electrostatic forces

$$D{:} + A \longrightarrow D\overset{\oplus}{\cdot} + A\overset{\ominus}{\cdot}$$

But the low heats of formation of such complexes are not compatible with the suggested formation of distinct ion pairs. Woodward[114] postulated the 'intermolecular semi-polar bond' formed by collisions resulting in a reversible electron transfer. This leads to formation of a dipolar aggregate held mainly by ionic forces, but possibly also stabilised by orbital overlap. In contrast, Brackmann[115] described the interaction of a donor and an acceptor by the term 'complex resonance' whereby a complex is formulated as a resonance hybrid of a no-bond structure and a single covalent bond,

$$D{:} + A \longleftrightarrow \overset{\oplus}{D} : \overset{\ominus}{A}$$

An important feature of this latter theory is that the observed colour is seen to be a function of the complex and not of the component molecules.

In 1949, the electronic absorption spectra of solutions of iodine in an aromatic hydrocarbon were examined by Benesi and Hildebrand[116] who observed absorption maxima not given by either of the pure components. Although they recognised that this was due to the formation of a complex, it was left to Mulliken to suggest[23] that the characteristic absorption of such solutions arises through an intermolecular charge-transfer transition. Mulliken's theoretical description of these weak interactions explained many of the observations and provided the impetus for much further work.

Mulliken[103] applied a quantum mechanical treatment to the formation of complexes via the interaction of an electron donor ($D{:}$) and an electron acceptor (A). He regarded the ground state of this complex as being a resonance interaction between a non-bonded ground state (D,A) and a dipolar excited state ($\dot{D}^{+}\dot{A}^{-}$). The nature of the components, $D{:}$ and A, is unimportant, i.e. they may be neutral molecules, atoms or ions, but both components must be in their totally symmetric ground state. In the no-bond structure the attraction between the two components is the result of classical intermolecular forces. In the excited state an electron is transferred from the donor to the acceptor; in this case some weak chemical binding and ion-ion attraction may be operative in addition to the classical cohesive forces.

The ground state of a complex is essentially 'no-bond' in character. Associated with this is an excited state, where the main contributor is mainly dipolar in nature. Hence the physical description of the complex is that of a no-bond ground state stabilised by admixture with a small proportion of a dipolar excited state. The characteristic new u.v./visible absorption band is, therefore, associated with an electronic transition from the ground to the excited state .

For a weakly interacting system which is nearly completely no-bond in character, the transition may be described as "intermolecular charge-transfer transition" since absorption of light causes an electron to be transferred from the donor to the acceptor and the resulting coordination entity is then referred to as a 'charge-transfer complex'.

Nagakura[118,119] studied the complexes formed between iodine and various aliphatic amines in solution in n-heptane and concluded that these are of the charge-transfer type and as such are best represented as resonance hybrids of

$$R_3N \;.....\; I_2 \text{ and } R_3\overset{\oplus}{N}-\overset{\ominus}{I_2}$$

and not as salts $[R_3NI]^{\oplus} \; I^{\ominus}$ Support for this formulation is provided by (a) the existence of an absorption band at ca. 250 - 280 nm. ascribable to the complex; and (b) the fact that the heats of formation of the complexes generally increase with decrease in the ionisation potential of the donor, an observation which is in accord with Mulliken's theory. Furthermore, the heats of formation (ca. 12 Kcal mol^{-1} for tertiary amines) indicate that these complexes are amongst the most stable charge-transfer complexes known.

Mulliken[117] has divided donors and acceptors into increvalent and sacrificial types. Increvalent donors are lone pair (n) donors such as aliphatic amines, ethers, phosphines and alcohols and these normally interact strongly with acceptors. In contrast, sacrificial donors such as cyclo alkanes donate an electron from a bonding orbital; thus only slight interaction is observed when σ-orbitals are involved, but π-orbitals lead to much stronger interaction. Increvalent acceptors are those of the vacant (ν) orbital type, and are often such strong acceptors that covalent bonding may occur rather than formation of a charge-transfer complex. Sacrificial acceptors may be of the σ- or π-type and the halogens and inter-halogens are considered as strong σ-acceptors.

Many attempts were made to test the validity of the proposed explanations and to quantify the observations made. To this end certain spectroscopic and other techniques were employed and a brief review of these attempts and of the results obtained will now be given.

2. Electronic spectra of charge-transfer complexes

Ultraviolet and visible spectroscopy feature prominently amongst the spectroscopic techniques used. Thus, Benesi and Hildebrand[116] studied complexes formed between methylbenzenes and iodine, and observed a new absorption band at ca. 300 nm. They assumed that this is due to a 1:1 iodine-hydrocarbon complex and derived a relationship (Equation 1) for the evaluation of the equilibrium constant for its formation

$$\frac{a}{O.D.} = \frac{1}{K.\varepsilon\ .\ d.} + \frac{1}{\varepsilon} \ \ldots\ldots\ldots\ldots \ \underline{\text{Equation (1)}}$$

(where d and a are the initial concentrations of the donor and
acceptor respectively,
K is the association constant,
O.D. is the optical density
and ε is the molar extinction coefficient of the complex)

Thus when $\frac{a}{O.D.}$ is plotted against $\frac{1}{d}$, a straight line is obtained of slope $(K\varepsilon)^{-1}$ and intercept $\varepsilon.^{-1}$ In this manner Benesi and Hildebrand made the first spectroscopic determination of association constants of charge-transfer complexes.

Although this approach was criticised and many modifications were suggested[102], Equation 1 has been much used, as for example by Nagakura and his coworkers in studying amine-iodine complexes by this technique. Some typical results are given below in Table 7.

Table 7. SPECTRAL CHARACTERISTICS AND FORMATION CONSTANTS FOR SOME AMINE-IODINE CHARGE-TRANSFER COMPLEXES

Amine	$\lambda^{max}_{I_2}$ nm	λ^{max}_{C-T} nm	ε_{C-T} $\times 10^{-4}$	K_{C-T} at 20°C $l\ mol^{-1}$	IP eV	Ref
NH_3	430	229	2.34	67	10.15	
$MeNH_2$	418	245	2.12	530	8.97	
Me_2NH	412	256	2.68	6800	8.24	
Me_3N	414	266	3.13	12100	7.82	
$EtNH_2$	417	246	2.26	720	8.86	
Et_2NH	410	260	2.50	7120	8.01	
Et_3N	414	278	2.56	6320	7.50	

These values of K are amongst the highest known for charge-transfer complexes. Furthermore, the variation of the association constant with temperature has been used to evaluate the changes in enthalpy and entropy on complex formation. The energies of the charge-transfer transitions $(h\nu_{C-T})$ have been correlated with the ionisation potential of the amine. A tendency for a decrease in the energy of the charge-transfer bond to accompany a decrease in the ionisation potential is in accord with the Mulliken theory, although it has been pointed out[120] that there is no theoretical reason to expect a linear relationship. The complementary variation of ν_{C-T} with the electron affinity of the acceptor has been much less widely studied, but estimates[121] of electron affinities for the halogens are in approximate accord with their accepted acceptor strengths i.e. $ICl \gg I_2 > Br_2 > Cl_2$.

Few attempts have been made to correlate the association constant, K, with the ability of the donor to donate an electron pair i.e. with the basicity of the amine. The strength of an amine as a Lewis base depends on electronic and steric features but estimates of absolute values and even of relative values depend largely on the solvent and the reference acid used. As most evaluations of charge-transfer associations constants (K_{C-T}) were made in non-polar solvents, such as n-heptane, it is not surprising that there is sometimes little or no correlation between K_{C-T} and the basic strength of the measured in aqueous solution using the proton, as the reference acid (Ka). When basic strengths of aliphatic amines are measured in non-polar solvents then the order of increasing base strength is ammonia $<$ primary amine $<$ secondary amine $<$ tertiary amine, which is in accord with the K_{C-T} values obtained for the complexes of methylamines and ammonia with iodine. For the ethylamines, the same pattern is followed except that for triethylamine, the association constant is low, a fact which may be attributed to enhancement of steric interactions. A good correlation of Ka with complexing ability was obtained by Popov and his coworkers[122] for equilibria involving molecular iodine and substituted pyridines

$$R-C_5H_4N + I_2 \rightleftharpoons R-C_5H_4N---I—I$$

An exception is the 2,6-dimethyl derivative where again steric hindrance causes the association constant for the charge-transfer complex to be less than could be expected from the corresponding Ka value.

3. The vibrational spectra of the complexes

In the infrared region, where there is only weak interaction between the components of a charge-transfer complex, the spectrum of the complex often shows only small differences compared with the sum of the spectra of the two components. Nevertheless changes in intensity and energy of the vibrational bands of both donor and acceptor may be observed, and these are generally larger in complexes involving σ-donors with σ-acceptors, such as amine-halogen complexes, than where only π-π interactions are operative. In some of the former cases, a low energy band associated with an intermolecular vibrational mode has been observed.

For homopolar diatomic acceptors, such as iodine, bromine or chlorine, the infrared forbidden stretching vibrations of the free molecules become active on interaction with an electron donor and decrease in frequency. Similarly, a decrease in frequency on complexation is observed with asymmetric acceptors, such as iodine monochloride, (Table 8).

Table 8. THE EFFECT OF COMPLEXING ON THE FUNDAMENTAL STRETCHING FREQUENCY OF SOME DIATOMIC ELECTRON-ACCEPTOR MOLECULES

System	State	ν (cm^{-1})	Type of Spectrum	Ref.
Br_2	gas	317	Raman	170
Br_2-py	py soln.	281	Raman	170
I_2	gas	213	Band	170
I_2-py	heptane soln.	184	Infrared	171
I_2-Me_3N	nujoll mull	185	Infrared	123
ICl	gas	382	Infrared	172
ICl-py	solid	274,276	Infrared	127

The weakening of the halogen-halogen band can be explained by Mulliken's theory, according to which some electron transfer from the nitrogen lone pair to an antibonding orbital of the iodine molecule occurs. This means that the halogen-halogen bond gains some anti-bonding character and is consequently lengthened and weakened. Changes in the vibrational spectrum of the donor on complexation have also been observed. Thus in the case of the trimethylamine-iodine complex, Nagakura[123] noted the (C-N) stretching frequency decreased and the (C-N) deformation increased in frequency, and the (C-H) deformation split into a triplet. Nagakura also noted a new band at 145 cm^{-1}, which he assigned to the nitrogen-iodine intermolecular stretching frequency. Corresponding absorptions have been observed in the far infrared spectra of the solid complexes of pyridine with iodine monochloride and iodine monobromide[124], and also in solutions of iodine[125,126], iodine monochloride[125] and iodine monobromide[125,127] in (a) pyridine and (b) substituted pyridines.

4. The application of resonance spectroscopy techniques to change-transfer complexes

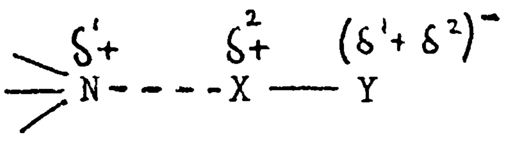
When the molecular environment of a nucleus undergoes rapid and reversible change, the position of the magnetic resonance absorption represents a time averaged resultant of its behaviour in the different environments[128]. Thus for a typical charge-transfer complex the p.m.r. absorptions due to the donor and the acceptor will each be shifted by an amount dependent on the strength of the charge-transfer interaction, as well as on the temperature and concentration. The changes in the chemical shifts associated with one of the components, with variation in the concentration of the other component was used by Hanna and

Ashbaugh[129] to obtain values for the association constants of several charge-transfer complexes by means of a relationship which was originally derived for the study of hydrogen-bonded systems, and which is analogous to the Benesi-Hildebrand equation (Equation 1; p.103). It does not, however, seem to have been applied to amine-halogen systems.

Qualitative measurements have been made by Fratiello[130] who noted that the p.m.r. signals of various solvents (including aliphatic amines and pyridine) were shifted downfield upon the addition of iodine. Yarwood[131] measured the methyl resonance signals of various methyl substituted pyridines dissolved in a number of different solvents both as the free base and as 1:1 charge-transfer complexes with iodine monochloride, and iodine, and found that these were shifted downfield on complexation. In accord with relative acceptor strengths, the shift was much greater in the case of the iodine monochloride complexes. The downfield shift is due to deshielding of the methyl protons as a result of some displacement of electrons on complexation.

Larsen and Allred[132] studied the interaction of iodine and 2,4,6-trimethylpyridine (TMP) in solution in carbon tetrachloride and nitrobenzene and correlated the dielectric constant of the solvent with relative amounts of the charge-transfer complex (observed as a time-averaged signal for the absorption of the free and complexed amine) and of a pyridinium cation described as $[(TMP)_2I]^{\oplus}.I_9^{\ominus}$

Amine-halogen complexes have also been studied by nuclear quadrupole resonance; Bowmaker and Hacobian[133] found that the charge-transfer is such that both the nitrogen atom and the halogen atom attached to it gain a partial positive charge, which is balanced by a partial negative charge on the terminal halogen atom



Interestingly they interpret their results both in terms of a slightly modified Mulliken theory, and a delocalised 3-centre σ-bond type similar to that proposed by Pimentel[134] for trihalide ions, and first applied to amine-halogen systems by Ginn and Wood[125].

5. Other techniques used in the study of charge-transfer complexes

Some electrical conductivity and magnetic susceptibility measurements on solid complexes have been carried out. A large number of solid charge-transfer complexes formed from weak electron donor or acceptor species are diagmanetic and poor electrical conductors as would be expected on the basis of Mulliken's valence bond description. However complexes involving strong donors and acceptor species may be paramagnetic and possess semi-conductor properties with high electrical conductivity in the solid state, and may also give e.s.r. signals.

The effectiveness of molecular halogens as electron acceptors is again demonstrated by the semi-conductors properties of halogen complexes, particularly those nonstoichiometric complexes of iodine with polynuclear aromatics and amines such as p-phenylenediamine, o-toluidine and poly-(4-vinylpyrrolidone). The generally high conductivity of these complexes is a reflection of the strong overlap of the appropriate orbitals of the donor and acceptor species.

Few measurements of magnetic susceptibility seem to have been carried out on amine-halogen complexes. The very strong donor, triethylenediamine, has been reported[135] to form a complex with iodine which is diamagnetic both in solution and as a solid. It has also been claimed that the paramagnetism associated with the triphenylamine-iodine system is due to the triphenylamine cation radical, but the e.s.r. spectrum of this system has since[136] been measured and found to be consistent with the formation of N,N,N',N'-tetraphenylbenzidine.

As a direct consequence of the Mulliken theory, a charge-transfer complex, in which each of the two components is non-polar, would be expected to have a dipole movement, the magnitude of which would be a measure of the participation of the polar form of the complex in the grand state. The determination of the dipole moment of a charge-transfer system has been used to estimate this dative contribution, but such estimates are, at best, only approximate. This is because the excited state would possess a dipole moment in any case, albeit less than expected for the pure polar form $D^{\oplus}-A^{\ominus}$, and, in addition, allowances must be made for the dipole of (a) the no-bond state arising from polarisation forces[137] and (b) the donor and/or acceptor. Such estimates have been made for amine-halogen systems despite the further possible complication that traces of water present may lead to ionic reactions[138] resulting in the formation of ion pairs. In certain solvents, this may occur even under extremely anhydrous conditions[139] and would then account for the abnormally high dipole moments (ca. 10-12D) of such systems[138]. At low temperatures, values more in accord with those expected for charge-transfer complexes have been obtained - 6.5 and 6.9 D, respectively, for the complexes of trimethylamine and triethylamine with iodine[140]. Other similar systems have also been studied[141] and the contribution of the dative form to the ground-state has been estimated to be of the order of 35% for aliphatic amines and ammonia and 25% for the pyridine/iodine system.

Amine-halogen systems have been studied conductiometrically and Mulliken[117] proposed that in the case of iodine and pyridine the observed slow increase in conductivity with time is due to the slow conversion of py. I_2 "the outer complex", to $[\text{py. I}]^+ I^-$, "the inner complex".

$$\text{py} + I_2 \rightleftharpoons \text{py}.I_2 \rightleftharpoons [\text{py I}]^{\oplus} I^{\ominus}$$

Support for this hypothesis was provided by the isolation[142] of two compounds from the γ-picoline/iodine system which were examined by X-ray crystallography and were assigned the structures $(\gamma\text{-pic}) \ldots\ldots I \leftarrow I$ for the 'outer complex species and $[(\gamma\text{-pic})_2 I]^{\oplus} I^{\ominus}$ for an ionic material which would be expected to form readily from Mulliken's "inner complex". As mentioned earlier p.m.r. measurements indicated the existence of both species in the trimethylpyridine-iodine system. Compounds analogous to the ionic picoline-iodine complex have not been isolated from systems containing alkylamines though the claim[143] has been made that these may exist in solution. Similarly no direct evidence has been obtained for the existence of the aliphatic amine analogues of Mulliken's "inner complexes", although it should be noted that aliphatic amine-halogen charge-transfer complexes were first formulated[84] as such ionic species.

X-ray diffraction studies[24] have led to the determination of the crystal structure of solid charge-transfer complexes. In the complexes of aliphatic amines with halogens the nitrogen is tetrahedrally coordinated by three alkyl groups and a halogen atom. The nitrogen and the two atoms of the acceptor are collinear, and the strength of the interaction is demonstrated by the fact that the nitrogen-halogen distance is substantially less than that of the van der Waals radii and only just in excess of that expected for a covalent bond. The halogen-halogen bond is slightly lengthened in accord with Mulliken's theory, and the observed decrease in the stretching frequency. The structure of the triethylamine-iodine complex is as given in Figure 4 below

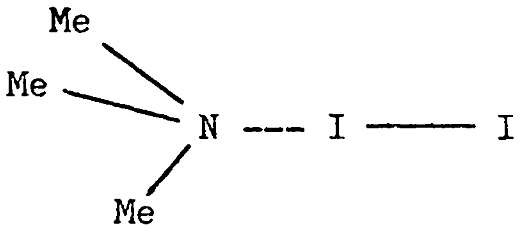


Figure 4

For complexes involving pyridines, the nitrogen and the halogen atoms are also collinear and are directed along the axis of the nitrogen lone-pair in the plane of the ring. It should be noted that the pyridine-iodine 'outer complex' has not been isolated in a crystalline state, but the equivalent pyridine-iodine monochloride complex has been examined. Some data for a number of complexes are given in Table 9. Of particular relevance to the present work is the fact that the hexamine:bromine 1:2 complex has a structure typical of aliphatic amine-halogen complexes and does not contain intermolecular bromine-bromine bridges.

TABLE 9. BOND LENGTHS (pm) IN HALOGEN ADDITION COMPOUNDS WITH AMINES

Compound	Charge-transfer bond	Bond length	Sum of v.d.W.radii	Hal-Hal bond length	Bond length in free hal.
Hex:2Br_2	N-Br	216	345	243	228
$Me_3N:I_2$	N-I	227	365	283	267
Me_3N:ICl	N-I	230	365	252	232
py:ICl	N-I	226	365	252	232
γ-pic:I_2	N-I	231	365	283	267

As may be seen from the foregoing discussion various techniques were employed to study charge-transfer complexes but a systematic investigation of a series of such complexes by a combination of techniques has never been attempted.

For this reason, and also for the purpose of obtaining evidence that such complexes are intermediates in reactions of amines possessing at least one α-hydrogen, with iodine (or bromine), the work described in the following section was undertaken.

CHAPTER THREE: B. DISCUSSION

AMINE-HALOGEN CHARGE-TRANSFER COMPLEXES AND THEIR ROLE IN THE OXIDATION OF AMINES

AMINE-HALOGEN CHARGE-TRANSFER COMPLEXES AND THEIR ROLE IN THE OXIDATION OF AMINES

1. Preparation of stable charge-transfer amine-halogen complexes

A systematic study of complexes of halogens with selected amines was undertaken for this thesis, in order to

(a) establish whether they are of the charge-transfer type, and if so,

(b) deduce the factors governing their stability,

(c) assess the strength of the donor-acceptor interaction in each case, and

(d) investigate the role that such complexes might play in the oxidation of amines by iodine.

The following substances were used in this investigation.

DONORS: triethylenediamine, hexamine, quinuclidine, Tröger's base, trimethylamine and tribenzylamine.

ACCEPTORS: iodine, bromine, chlorine, iodine monochloride and N-bromosuccinimide.

Some of the possible donor-acceptor combinations give a product which is either unstable, or of a composition which does not correspond to any simple, integral stoichiometric ratio of reactants. Such products were not used in this investigation.

The complexes which were prepared and actually investigated to a lesser or greater extent are listed in Table 10.

Triethylenediamine (XIV)and hexamine (XVIII) react readily with iodine, forming solid, easily isolable complexes. The molecular geometry of these two bases ensures that, at least at room temperature, the resultant complexes cannot be converted to the corresponding immonium ions. Their ease of formation was

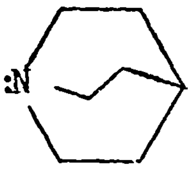
TABLE 10 MOLECULAR COMPLEXES PREPARED AND INVESTIGATED

DONOR (D)	MOLECULAR RATIO D:A IN Complex	ACCEPTOR (A)			
		Iodine	Bromine	Monochloride	NBS
TED	1:1	-	+	+	-
	1:2	+	+	+	+
Hexamine	1:1	+	+	+	-
	1:2	+	+	+	+
	1:3	+	-	+	-
	1:4	-	-	+	-
Quinuclidine	1:1	+	+	-	-
Trimethylamine	1:1	+	-	+	-
Tröger's base	1:1	-	-	-	-
	1:2	+	-	-	-

\+ denotes complex prepared and characterised
\- denotes complex not prepared

also noted by Halpern and Weiss[144] who reported that for the triethylenediamine-iodine complex, the formation constant obtained from measurements in the ultraviolet region using dilute solutions is exceptionally high.

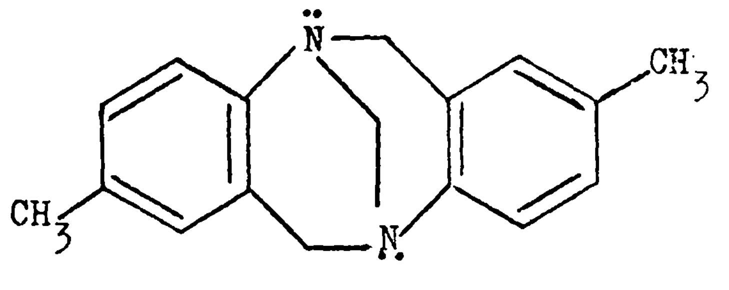
The structure of triethylenediamine is very similar to that of quinuclidine (1-azabicyclo[2,2,2]octane) (XXXVI) which was used by the present author as a model monobasic donor.



(XXXVI)

The reactions of the latter were studied extensively by H.C. Brown and his coworkers[145,146] who showed that it forms salts and quaternary ammonium compounds very readily. In spite of the fact that quinuclidine and triethylamine have similar basicities towards protons, the former reacts with methyl iodide fifty times, and with isopropyl iodide seven hundred times faster than the latter. This seeming anomaly is due to the fact that, in quinuclidine, the α- and β- carbon atoms are held well back and, hence the nitrogen lone-pair is unencumbered and readily accessible to electrophiles. In contrast, the lone-pair in triethylamine is flanked by the α- and, especially, the β- carbons of the groups bonded to the nitrogen. Therefore it is not surprising that, unlike the trimethylamine:iodine complex, the corresponding complex of triethylamine has never been isolated. Examination of molecular models readily demonstrates that these arguments also apply to triethylenediamine and to hexamine, and they also account for the ease with which these amines form charge-transfer complexes with halogens.

Complexes of the 'bridge-head' amine Tröger's base (XXXVII) with iodine were also subjected to a more limited study.



XXXVII

In addition it is worth noting that triethylamine, tribenzylamine, piperidine, N-ethylmorpholine and N-(2'hydroxyethyl) morpholine gave tars on treatment with iodine even in the cold. However, in some of these cases, transient coloured precipitates - presumably the corresponding charge-transfer complexes, are observed immediately upon mixing the reactants in dilute, cooled solution.

The choice of acceptors was somewhat simpler. It was decided to compare the iodine complexes with those of bromine, chlorine and iodine monochloride. N-Bromosuccinimide was included as an acceptor following the observation by Henbest[64] that triethylenediamine is resistant to oxidation by this reagent. The TED-NBS adduct obtained by Henbest was considered by the present author to be worthy of further investigation on the grounds that it might prove to be a charge-transfer complex.

All the complexes were prepared by mixing solutions of the donor and the acceptor in a suitable solvent. Usually, immediate precipitation of the product occurred, but in some cases, for example triethylenediamine:NBS, 1:2, complexes formed only after standing for some hours or overnight. The products could not be purified by recrystallisation as this process may lead either to decomposition of the complex, or, as in the case of multifunctional donors, to the formation of a complex with a different stochiometry. For example, during the attempted recrystallisation of the hexamine:iodine, 1:3 complex, a new complex namely hexamine:iodine, 1:2 precipitated from the solvent. For these reasons, the complexes were simply washed quickly at the pump with a small volume of chilled solvent and dried in vacuo at room temperature.

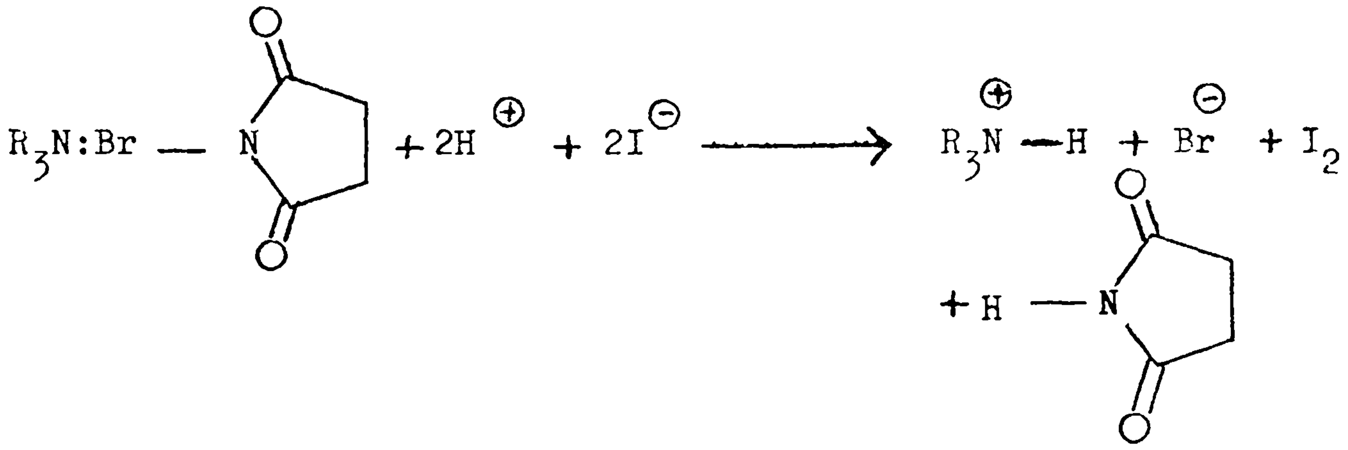
2. Analysis of the complexes

The complexes were analysed using both titrimetric determination of the molecular acceptor and elemental analysis. For those products which were subsequently characterised as molecular complexes all the halogen in the molecule was present as molecular halogen. In those cases where this was not so, for example, the tribenzylamine-iodine product, it was concluded that the solids were not analogous to the charge-transfer complexes which were investigated for this thesis.

The analysis of complexes was complicated by their low solubility. Furthermore, the solid hexamine- and triethylenediamine-iodine complexes reacted only slowly with aqueous sodium thiosulphate and dilute mineral acids. Molecular iodine in these complexes was determined both by direct titration with thiosulphate, and by the addition of excess of the reagent followed by back-titration with a standard solution of iodine. The bromine complexes could not be analysed by titration of the iodine released on the addition of potassium iodide to an aqueous suspension of the complex because, even in the presence of dilute mineral acid, the liberated iodine combined with the amine. However, molecular bromine in the complexes was estimated conveniently by using it to effect oxidation of ferrous to ferric ions and titrating the latter with ascorbic acid.

The proportion of molecular acceptor both in the iodine monochloride and the NBS complexes was determined by treating the complex in each case with mineral acid and potassium iodide followed by titration of the liberated iodine with thiosulphate.

$$R_3N : I\text{-}Cl + H^{\oplus} + I^{\ominus} \longrightarrow R_3N\text{-}H^{\oplus} + Cl^{\ominus} + I_2$$



Analysis of products obtained using the multi-functional donors triethylenediamine, hexamine and Tröger's base showed that the donor acceptor ratio in the product does not always correspond to the molar ratio of reactants used in their preparation (Table 11). For example, the 1:1 complexes of iodine or NBS with triethylenediamine are not formed even when a tenfold excess of the amine is used. The corresponding 1:2 complex is the sole product in each case. However, bromine and iodine monochloride each give both 1:1 and 1:2 complexes with triethylenediamine. Furthermore, where as the strong acceptor iodine monochloride gives the complete range of solid complexes with hexamine, bromine forms only hexamine:bromine, 1:1 and 1:2, and iodine, hexamine:iodine 1:1, 1:2 and 1:3 complexes. With the latter donor, NBS gives the hexamine:NBS, 1:2 complex irrespective of themolar ratio of

TABLE 11 STOICHIOMETRY OF COMPLEXES OBTAINED FROM MULTI-FUNCTIONAL DONORS

DONOR (D)	RATIO OF D:A USED	RATIO OF DONOR TO ACCEPTOR FOUND USING			
		Iodine	Bromine	Iodine monochloride	NBS
TED	1:1	1:2	1:1	1:1	1:2
	1:2	1:2	1:2	1:2	1:2
Hexamine	1:1	1:1	1:1	1:1	1:2
	1:2	mixture(a)	1:2	1:2	1:2
	1:3	1:2	1:2	1:3	1:2
	1:4	1:3	n-s(b)	1:4	n-s(b)
Tröger's base	1:1	1:1	-	-	-
	1:2	1:1	-	-	-

(a) mixture of crystals of 1:1 and 1:2 complexes

(b) non-stoichiometric; product does not correspond to any simple ratio of D:A reactants used. These results cannot be explained with any degree of certainty but it does appear, at least in a number of cases, that the range of complexes given by a multifunctional donor with halogen increases with the acceptor strength of the latter.

3. The electronic spectra of the charge-transfer complexes

In general, the ultraviolet-visible spectrum of a complex formed between an electron donor and an electron acceptor still retains the absorptions of the components, modified to a greater or lesser extent, together with one or more absorption bands characteristic of the complex as a whole. Thus, the electronic spectra of the solutions containing iodine and a considerable excess of aliphatic amine which were studied by Nagakura[119] showed a new absorption band in addition to that due to shifted iodine. This enabled him to identify the amine-halogen interaction as being of the charge-transfer type.

Most of the complexes prepared by the author were not sufficiently soluble for their ultraviolet-visible spectra to be determined in solution. For this reason, reflectance measurements on the powdered solids were also carried out. However, the iodine complexes which are somewhat soluble were studied in chloroform or methylene chloride solution. Each spectrum consists of an absorption band ($\lambda_{max}(CHCl_3)$, 510 nm; $\lambda_{max}(CH_2Cl_2)$ 500 nm) due to uncomplexed iodine (see p.25), a 'complexed' iodine band and a charge-transfer band. Thus, these iodine adducts are charge-transfer complexes. The positions of the latter two bands vary with the nature of the donor. In the three hexamine-iodine complexes the position of the charge-transfer band is also found to vary with the stoichiometry of the complex.

For a series of iodine complexes (Table 12) the wavelength for maximum absorption of the charge-transfer band (λ_{C-T}) varies according to the relative strength of the donor.

In addition to λ_{C-T} and the corresponding ν_{C-T} values for the complexes, Table 12 lists the energy of the charge-transfer transition (E_{C-T}) which is calculated from the equation $E_{C-T} = h\nu_{C-T}$. The formation constant (K_{C-T}) for some of the complexes, and the pKa values and ionisation potentials (I.P.) of the corresponding amines are also included in the same table. The latter two parameters provide a measure of the relative strength of the amine as a base, and as an electron donor, respectively.

Nagakura and his coworkers observed that for simple tertiary amines there is a correlation between the energy of the charge-transfer transition (E_{C-T}) and the ionisation potential (I.P.) of the amine (Figure 5). The present author's data for quinuclidine fit on the same curve, but those for triethylenediamine do not. The 'anomalous' behaviour of triethylenediamine in this respect, is attributed to the existence of a repulsive interaction[119] between the lone pairs of the two nitrogen atoms in the donor molecule.

One would also expect to find (a) a correlation between the formation constant and the energy of the charge-transfer transition for the complexes such that the former decreases as the latter increases; and (b) a similar reciprocal relationship between the formation constant for the complex and the ionisation potential of the donor. However the data in Table 12 suggest that the opposite is true for the simple aliphatic amine donors.

TABLE 12: SPECTROSCOPIC PROPERTIES OF IODINE COMPLEXES

Donor(D)	molar ratio D:A	λ_{C-T} (nm)	E_{C-T} (eV)	K_{C-T} ($l\ mol^{-1}$)	pK_{C-T}	pKa^{c} ($l mol^{-1}$)	I.P.^{c} (eV)
Trimethylamine	1:1	270	4.59	8,000	3.9	9.7	7.82
Triethylamine[a]	1:1	278	4.46	5,000	3.7	10.7	7.50
Tripropylamine[b]	1:1	281	4.41	1,000	3.0	10.7	7.23
Quinuclidine	1:1	272	4.55	330,000	5.5	11.1	7.72
TED	1:2	300	4.13	50,000	4.7	11.0	7.2
Hexamine	1:1	273	4.54	2,500	3.4	5.3	-
	1:2	270					
	1.3	265					

(a) Yada, Tanaka and Nagakura [119]
(b) Halpern and Weiss[144]
(c) of the amine

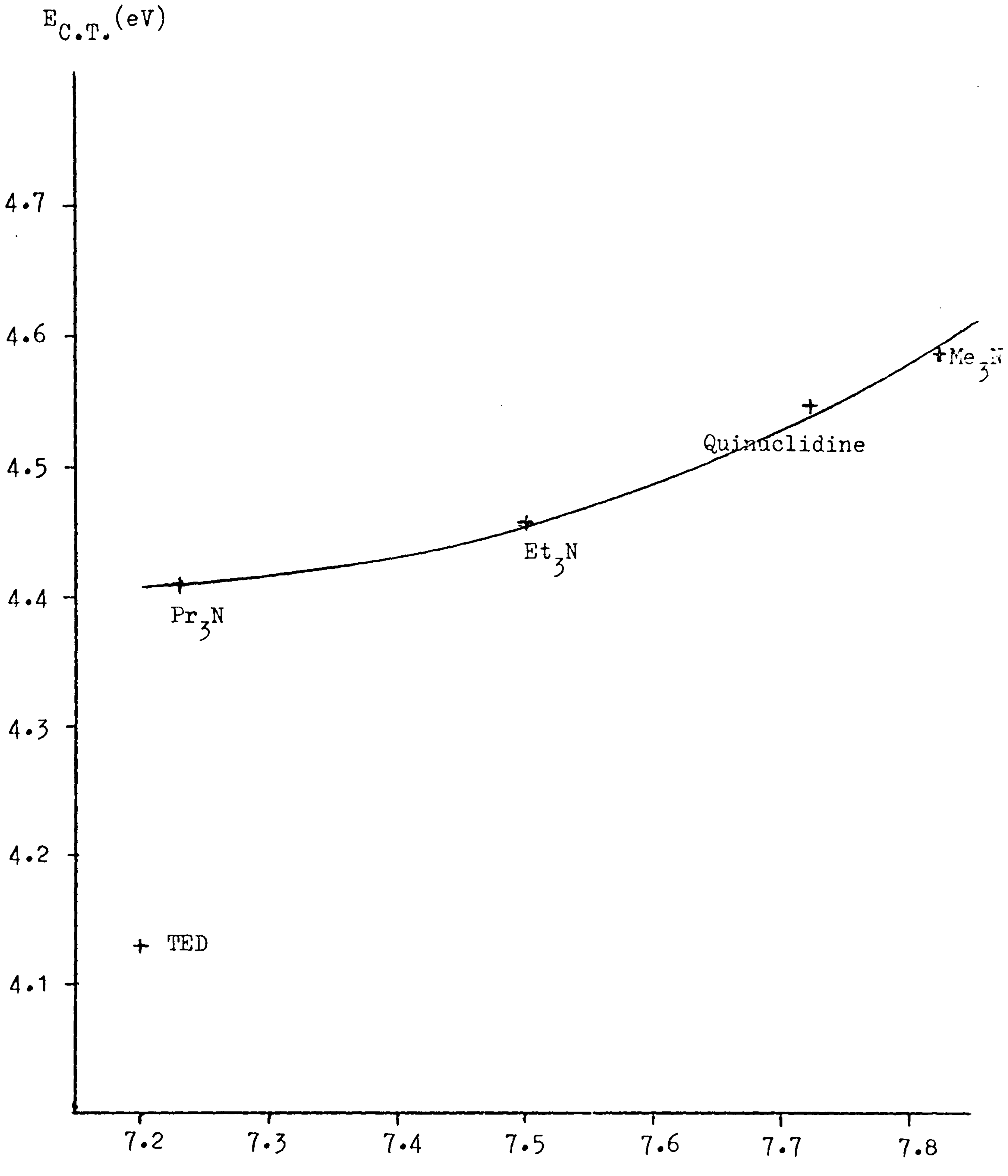


FIGURE 5 VARIATION OF (E_{C-T}) WITH IONISATION POTENTIAL FOR TERTIARY AMINE - IODINE COMPLEXES .

The deviation observed from the expected mode of behaviour in this case is due to steric hindrance. It is well known that steric hindrance can have a profound effect on complex formation. For example, in comparison with hexamethylbenzene, hexaethylbenzene forms complexes of low stability even though the intermolecular charge-transfer band in the hexaethylbenzene complexes is of lower energy. It has already been pointed out in the discussion of the choice of electron donors that the lone pair in triethylamine is sterically hindered. Thus, the decrease in the value of the formation constant observed on ascending the series trimethylamine, triethylamine, tri-n-propylamine, can be related to the increasing bulk of the substituent groups on the nitrogen.

Because of structural and constitutional similarities, triethylenediamine would be expected to be at least as good a donor as quinuclidine, but once again the association constant for this donor is found to be anomalously small. Halpern and Weiss[144] regard this also as being the result of interaction between the lone-pairs of the two nitrogen atoms in the molecule.

The bromine and iodine monochloride complexes are not sufficiently soluble in non-donor solvents for electronic spectra to be determined in solution.

The products of the chlorine-amine interactions are ionic and their spectra, determined in water and in methanol, did not show absorptions which could be assigned to an intermolecular charge-transfer transition. Such absorptions as are present are also present in the spectra of the corresponding hydrochlorides. Consequently, these solids were not investigated further.

The hexamine:NBS, 1:2 complex absorbs at 283 nm and this band is assigned to charge-transfer interaction. By contrast, the triethylenediamine:NBS, 1:2 complex is transparent in this region.

The diffuse reflectance spectra of all the products which were shown by analysis to be molecular complexes contain very intense absorptions in the ultraviolet - visible region. However, the nature of the spectra obtained in most cases makes it extremely difficult to determine the wavelength of maximum absorption for these bands. The diffuse reflectance spectra of the iodine complexes contain a broad absorption band at about 400 nm, whilst the corresponding maxima for bromine and iodine-monochloride complexes are at approximately 325 and 290 nm, respectively. These absorptions are assigned as modified acceptor bands - the acceptors themselves absorb at 520, 410 and 460 nm., respectively[147], in carbon tetrachloride. The greater shift of the bands due to iodine monochloride on complex formation is in keeping with the greater strength of this interhalogen as an acceptor.

4. The vibrational spectra of the complexes

The study of the vibrational spectra of the charge-transfer complexes is conveniently divided into two parts. This division is useful both from the point of view of technique and instrumentation, and of interpretation of results.

In the infrared region (from 4000 to 400 cm^{-1}), the complexes were examined as potassium bromide discs using conventional instrumentation. With the exception of the NBS comples, all vibrations in this region are assigned to the electron donor. The changes in the spectra of the donors on complexation may be correlated with changes in bond order and symmetry.

In the far-infrared region, the complexes were examined as nujol mulls using a Fourier Transform Interferometer. In this spectral region (from 400 to 30 cm^{-1}) the bands which occur can be assigned to the acceptor, and to intermolecular vibrations.

(a) Infrared spectra

When there is only weak interaction between the components of a charge-transfer complex, the infrared spectrum often differs little from the sum of the spectra of the two components. Of the differences which are observed in the solid state spectra, some result from crystal packing effects. Nevertheless, changes in intensity and energy of the vibrational bands of either donor or acceptor, or of both, have been observed by other workers and are generally found to be large in the spectra of complexes involving σ-donors and σ-acceptors, such as amines and halogens.

Haque and Wood[148] in their study of the infrared spectra of pyridine-halogen complexes correlated the degree of charge-transfer, and, hence, the positive charge aquired by the nitrogen, with changes induced in the σ-bonding framework and the π-orbitals of the ring.

The elegant work of Marzocchi and Ferroni[149,150] who examined the solid state infrared spectra of the 1:1 and 1:2 complexes of hexamine with iodine, bromine, iodine monobromide and iodine monochloride is of particular relevance to the present investigation. They were able to account for the differences between the spectrum of hexamine and those of the complex in terms of changes in symmetry which occur when this donor is complexed with halogens.

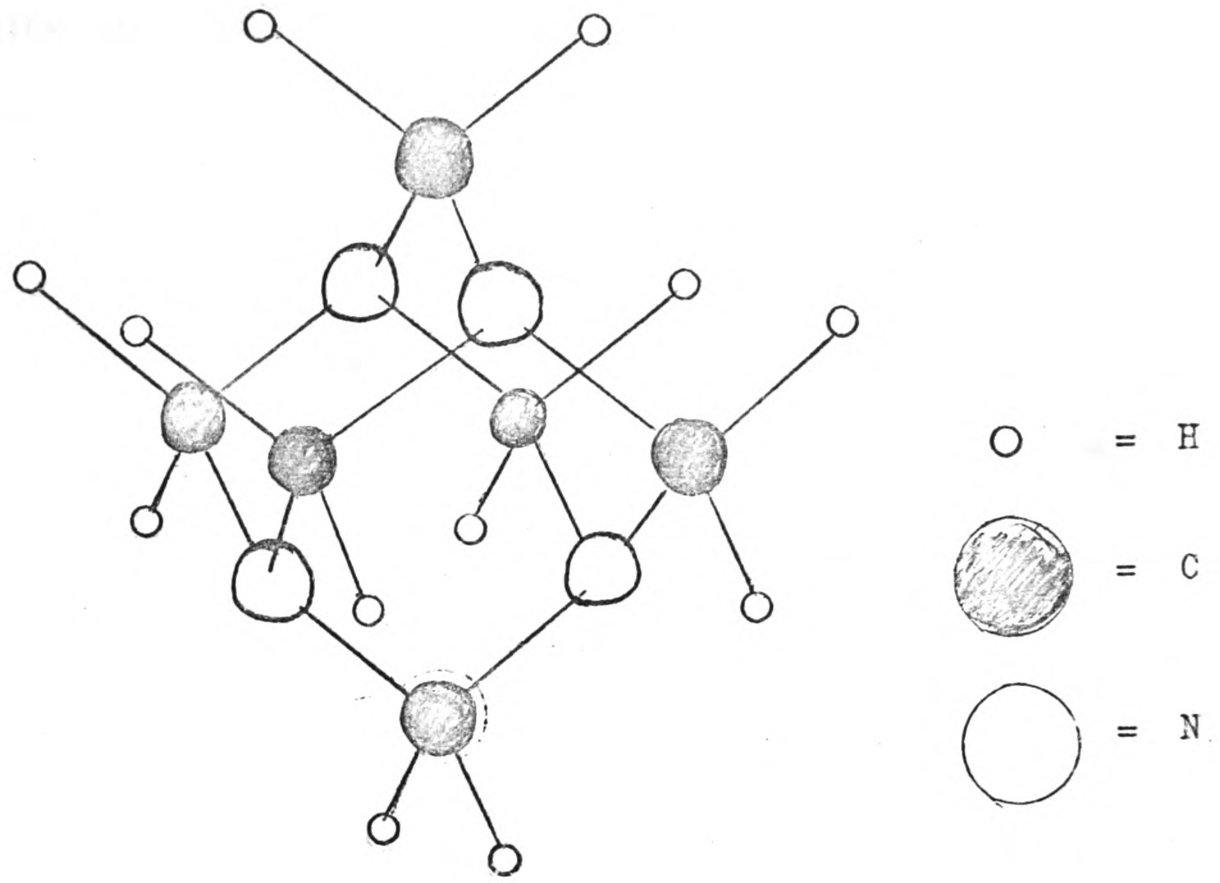


FIGURE 6 STRUCTURAL DIAGRAM OF HEXAMINE

Because of the Td symmetry of the hexamine molecule (see Figure 6) all the nitrogen atoms are equivalent. For the same reason; all the methylene groups are equivalent. If a linear N-X-Y conformation is assumed to be present in the complexes, then, the 1:1 complexes (Figure 7) have C_{3v} symmetry and the 1:2 complexes (Figure 8), C_{2v} symmetry.

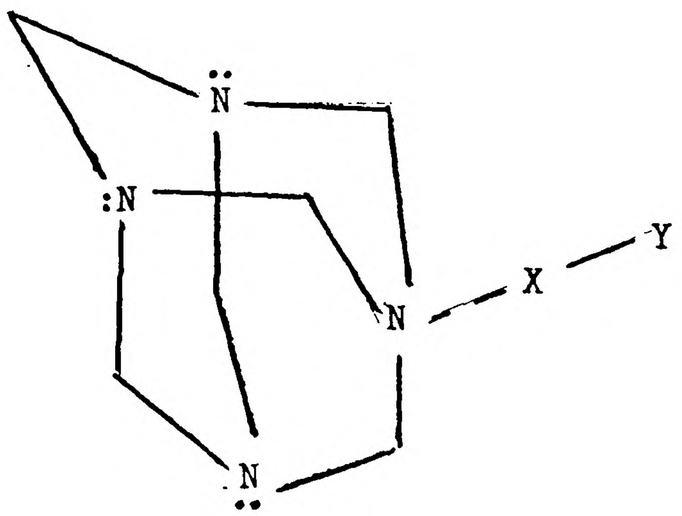


FIGURE 7 HEXAMINE:XY, 1:1

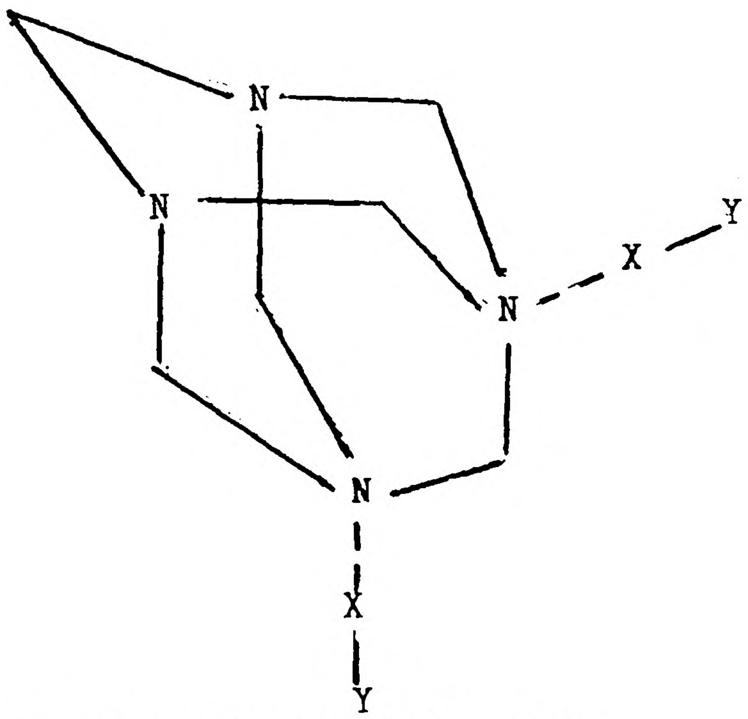


FIGURE 8 HEXAMINE:XY, 1:2

Hexamine has four infrared active skeletal vibrations, whereas the 1:1 and 1:2 complexes have 14 and 20 vibrations, respectively (Table 14). The assignment of the observed bands of the 1:1 and 1:2 complexes is given in Tables 15, 16 & 17 following Marzocchi and Ferroni. The frequencies given are those obtained in the present study and these are in good agreement with values quoted by Marzocchi. However, in the present work the spectral range has been extended below 600 cm^{-1} to 30 cm^{-1}.

TABLE 14. THE INFRARED ACTIVE AND INACTIVE BANDS OF HEXAMINE AND ITS 1:1 AND 1:2 COMPLEXES WITH HALOGENS

Hexamine	1:1 Complexes	1:2 Complexes
$4T_2$ (IR active)	$4A_1+4E$ (both active)	$4A_1+4B_1+4B_2$ (all active)
$2A_1$ (IR inactive)	$2A_1$ (active)	$2A_1$ (active)
$2T_1$ (IR inactive)	$2A_2$(inactive) + 2E (active)	$2A_2$ (inactive)+$2B_1+2B_2$ (all active)
2E (IR inactive)	2E (active)	$2A_2$ (inactive)+$2A_1$ (active)
4 IR active vibrations	14 IR active vibrations	20 IR active vibrations

As a result of this it is now possible to assign several other vibrations. Thus the fourth T_2 band, which in the 1:1 complexes becomes a doublet and in the 1:2 complexes a triplet, is assigned to the absorption at 514 cm^{-1}. Examination of the spectra below 500 cm^{-1} confirms that the second of the E bands is the absorption at 460 cm^{-1}; this is a singlet both in the 1:1 and the 2:1 complexes. The absorption at ca. 375 cm^{-1} in the 1:1 complexes which becomes a doublet in the 1:2 complexes, is assigned to a T_1 vibration.

TABLE 15. THE INFRARED SPECTRUM OF HEXAMINE

cm^{-1}		Species	Assignment
2932,	vs	T_2	$\nu(CH_2)as$
2882,	vs	T_2	$\nu(CH_2)sym$
1465,	s	T_1 T_2	$\delta(CH_2)$ scis
1450,	m	T_2	
1380,	vs	T_2	$\delta(CH_2)$ wag
1240,	vs	T_2	ν_{10}
1049,	m	T_1 T_2	ν_9 ν
1010,	vs	T_2	ν_9
836,	m	T_1 T_2	ν_7 ν_6
813,	s	T_2	(CH_2) rock
675,	m	T_2	ν_8
514,	s	T_2	Ring def

TABLE 16. THE INFRARED SPECTRA OF THE 1:1 COMPLEXES OF HEXAMINE WITH IODINE, BROMINE AND IODINE MONOCHLORIDE

Hex.: I_2, 1:1		Hex.: Br_2, 1:1		Hex. ICl, 1:1		All Complexes	
cm^{-1}		cm^{-1}		cm^{-1}		Species	Assignment
2938,	vw	2942,	vw	2942,	m	A_1,E	$\nu(CH_2)$a
2888,	vw	2880,	vw	2880,	m	A_1,E	$\nu(CH_2)$s
1450,	m	1455,	m	1465,	s	A_1,E	$\delta(CH_2)$scis
1398,	m	1382,	m	1398,	s	A_1,E	$\delta(CH_2)$wag
1340,	vw	1320,	vw	1335,	vw	E	ν_5
1321,	vw	1307,	vw	1325,	w		
1252,	m	1248,	s	1245,	vs	A_1	ν'_{10}
1236,	s	1230,	s	1222,	vs	E	ν''_{10}
1053,	w	1058,	vw	1054,	m		
		1043,	w	1043,	s	A_1	ν_2
1020,	s	1016,	vs	1017,	vs	A_1	ν'_4
997,	vs	993,	s	995,	vs	E	ν''_4
907,	w	900,	vw	900,	m		comb
		893,	vw	892,	m		
822,	m	816,	s	820,	vs	E	$\delta(CH_2)$rock
801,	vw	798,	vw	799,	w	A_1	
				776,	vw		comb
739,	m	748,	m	750)	vs		comb
735,	m	739,	s	)		E	ν''_8
713,	w	709,	m	710,	s	A_1	ν_1
663,	w	657, 651	w	662, 657	m	A_1	ν'_8
527,	vw	524,	vw	528,	m)	A_2E	
507,	vw	504,	vw	507,	w)		
		495,	vw	500,	w)		

TABLE 17. THE INFRARED SPECTRA OF THE 1:2 COMPLEXES OF HEXAMINE WITH IODINE, BROMINE AND IODINE MONOCHLORIDE

Hexamine:I$_2$1:2	Hexamine:Br$_2$,1:2	Hexamine:ICl,1:2	All Complexes	
cm^{-1}	cm^{-1}	cm^{-1}	Species	Assignment
2960, vw	2950, vw	2994, 2967, w	$A_1B_1B_2$	ν(CH$_2$)a
2890, vw	2890, vw	2880, vw	$A_1B_1B_2$	ν(CH$_2$)s
1465, w	1458, m	1470, m	$A_1B_1B_2$	δ(CH$_2$) scis
1398, m	1375, m	1400, m	$A_1B_1B_2$	δ(CH$_2$) wag
1390, m				
		1325,	B_1	ν'_5
		1315,	B_2	ν''_5
1246, m	1246, m	1242, s	A_1	ν'_{10}
1237, m	1234, s	1229, s	B_1	ν''_{10}
1227, m	1225(sh), m	1216, m	B_2	ν'''_{10}
				comb
		1064, w		
1050, w	1044, w	1044, m	A_1	ν_2
1024, s	1021, s	1020, vs	A_1	ν'_9
999, vs	996, vs	993, vs	B_1	ν''_9
992, s	988(sh), s	984, vs	B_2	ν'''_9
923, vw	916,	926, w		comb
		911, m		
832, vw	827, m	832, m	B_1B_2)	δ(CH$_2$)
812, vw	809, vw	811, m	A_1)	rock
786, s	777, s	777, vs	A_1	ν_1 *
783, s	766, s	766, vs	A_1	ν_1 *
	737, m	752, m		comb
708, w	712, s	716, s	B_2	ν'''_8
680, w	678, m	682, m	B_2	ν''_8
657, w	655, vw	650, m		ν'_8
		670, vw		comb
525 vw	525, w	528, m	$A_1B_1B_2$	ν'
512, vw	508, vw	512, m	$A_1B_1B_2$	ν''
503, vw	497, vw	500, w	$A_1B_1B_2$	ν'''

* Doubling due to mechanical coupling of ν_1, and XY stretches (A_1B_1)

TABLE 18. THE INFRARED SPECTRA OF THE 1:3 COMPLEXES OF HEXAMINE WITH IODINE AND IODINE MONOCHLORIDE

Hexamine: I_2, 1:3		Hexamine: ICl, 1:3		Both Complexes	
cm^{-1}		cm^{-1}		Species	Assignment
		2989,	vw	A_1,E	ν (CH_2)s
2955,	vw	2949,	vw	A_1,E	ν (CH_2)a
1462,	s	1469,	s	A_1,E	δ (CH_2)scis
1378,	s	1384,	s	A_1,E	δ (CH_2)wag
1243,	s	1234,	s)		)
1238,	m	1230,	m)	T_2*	) ν_{10}
1225,	m	1216,	m)		)
1060,	w	1061,	w		
1050,	vw	1045,	w	A_1	ν_2
1023,	s	1020,	s	A_1	ν_9
1010,	vs	1008,	vs)	E	ν_9
1000,	s	995,	m)		
990,	s	985,	m)	E	ν_9
983,	s	971,	s)		
921,	m	914,	m		combination
837,	m	842,	m)	E	) $\delta(CH_2)$ rock
830,	w	831,	m)		)
812,	vw	811,	w	A_1	)
788,	vs	784,	vs	E	ν_1
772,	s	769,	s	A_1	ν_2
738,	m	754,	w		combination
730,	m	734,	vw		
707,	m	714,	m	A_1	
695,	m	692,	s		
680,	m	682,	m		
670,	w	669,	vw		)
662,	m	659,	m		) ν_8
655,	m	650,	vw		)
622,	w				
617,	w				
520,	m	525,	m)		) Ring
513,	w	511,	w)	T_2*	) def.
502,	w	500,	w)		)

*T_2 vibration split by both C_{3v} symmetry requirements and by mechanical coupling.

TABLE 19. THE INFRARED SPECTRUM OF HEXAMINE: ICl, 1:4

HEXAMINE: ICl, 1:4

cm^{-1}		Species	Assignment
2950,	vw	T_2	$\nu(CH_2)$
1475,	m	T_2	$\delta(CH_2)$scis
1390,	m	T_2	$\delta(CH_2)$wag
1255,	vw		
1237,	s	T_2	ν_{10}
1216,	m		
1061,	m	T_1T_2	$\nu_9+\nu$
1021,	s	T_2	ν_9
1008,	vs		
984,	vw		
972,	s		-
915,	m		comb
841,	m	T_1T_2	$\nu_7+\nu_6$
829,	vw	T_2	$\delta(CH_2)$rock
785,	vs		ν_1 *
769,	m		
702,	s		-
659,	m	T_2	ν_8
523,	m	T_2	Ring def.
510,	vw		
500,	vw		

* Splitting due to mechanical coupling of ν_1, with acceptor stretching vibration

Marzocchi and Ferroni placed the halogens and interhalogens used in their study in order of relative acceptor strength by comparing the splitting of T_2 bands in the spectra of the complexes. As a measure of acceptor strength, they used the quantity:

$$\frac{\nu' - \nu''}{\nu}$$, where ν' and ν'' are the frequencies (cm^{-1}) of the components of the doublet and ν the frequency of the corresponding absorption in hexamine.

The observed order of acceptor strengths is $I_2 > Br > IBr > ICl$, this is at variance with the accepted sequence $Br_2 > I_2 > IBr > ICl$ (which is based on chemical and physical properties of halogen complexes) and the authors attributed this seeming anomaly to mechanical coupling of vibrations in the component molecules. Thus, since bromine has a smaller reduced mass than iodine, the Br-Br stretching frequency is higher than that of iodine. The vibrations of hexamine are influenced therefore more by bromine than by iodine.

Such differences as do exist between the spectra of 1:1 and 1:2 complexes obtained in the present work and those of Marzocchi and Ferroni are due to the fact that in the present study potassium bromide discs were used whilst the previous workers used nujol and hexachlorobutadiene mulls. The major difference observed is that the potassium bromide discs show the C-H stretching frequency in the complexes to be greatly diminished in intensity. This may be accounted for by the far greater polarity of potassium bromide relative to the organic mulling agents.

Since in the present work the 1:3 hexamine:iodine complex and the hexamine:iodine monochloride 1:3 and 1:4 complexes have also been prepared and characterised, an attempt was made to interpret their infrared spectra in a similar manner (Tables 18 & 19) to that used for the spectra of the corresponding 1:1 and 1:2 complexes. Assuming that the N-X-Y system is linear, the 1:3 complexes would have the same symmetry as the 1:1 complexes, i.e. C_{3v}, and similarly, the 1:4 complex, like hexamine itself, would belong to the Td symmetry group. Hence they would be expected to give similar infrared spectra to the 1:1 complexes and free hexamine, respectively. However, an inspection of the spectra (IR No.'s 1, 2, 3, 5 and 6) shows that in fact, this is not the case. However, the spectra may be interpreted in terms of symmetry correlations and mechanical coupling. In the spectra of the 1:2 complexes both the peaks at 777 and 766 cm^{-1} are considered to be due to the A_1 vibration ν_1. The splitting into a doublet is caused by mechanical coupling between donor and acceptor and, as there are here two halogen molecules these may vibrate in and out of phase. In the spectra of the two 1:3 complexes splitting due to mechanical coupling is also observed. This splitting is greater for the iodine monochloride complex than for the iodine complex as would be expected from the respective values for the fundamental stretching frequency of the acceptor.

The skeletal T_2 vibrations in hexamine at 1240, 1010, 675 and 514 cm^{-1} are split into doublets in the 1:1 complexes and are affected as follows in the 1:3 complexes. The bands at 1240 and 514 cm^{-1} become poorly defined triplets. This splitting may be attributed to mechanical coupling between A_1 and E stretching vibrations of the three acceptor molecules with the T_2 vibrations of hexamine. Similarly the band at 675 cm^{-1} splits into three components.

The band at 1010 cm^{-1} is complex. The E components are both split into doublets as in the 1:2 complexes and are split again by mechanical coupling giving a total of five bands.

As in the 1:2 complexes, the vibration becomes a doublet, but now the higher frequency vibration is the more intense (relative intensities 1:2 instead of 1:1 for the 1:2 complex). In the 1:3 complexes, there is a greater possibility that the three halogen-halogen vibrations will be out of phase (E components) than that they will be in phase (A_1 component).

The E component of the CH_2 rocking mode at 813 cm^{-1} is split into two, so that a triplet is obtained instead of the expected doublet. This splitting occurs in both complexes and is greater in the case of the iodine monochloride complex.

The spectrum of the hexamine:iodine monochloride, 1:4 complex has more bands than would be expected if the complex had Td symmetry, but this may be explained by the coupling of the T_2 skeletal stretching modes (the only IR active vibrations in Td symmetry) with the halogen-halogen vibrations. In addition the spectrum has additional bands at 972 and 702 cm^{-1}. Again the ν_1 mode is split into a doublet and, in keeping with the explanation given in the case of the 1:3 complexes, the intensities of the two components are in the ratio 1:3 (see Table 19).

Triethylenediamine also has a symmetrical structure and an attempt has been made to correlate the changes in the infrared spectra of complexes with changes in symmetry. The free base has D_{3h} symmetry which is lowered to C_{3v} in the 1:1 complex. A 1:2

complex on the other hand has D_{3h} symmetry. It is assumed that in both types of complex the N-halogen-halogen groups are linear.

In triethylenediamine itself and the 1:2 complexes the species A_2'' and E' are infrared active whilst the A' and E'' bands are only Raman active. In the 1:1 complexes the A_1' and A_2'' become A_1 and are therefore both Raman and infrared active, whilst the E' and E'' species become E and thus are both Raman and infrared active. An assignment of the infrared bands of triethylenediamine (based on those given in the literature[151]) together with the spectra of the base and its complexes is given in Tables 20, 21 and 22.

An A_2'' vibration in the spectrum of triethylenediamine appears as a doublet at 770 and 750 cm^{-1} this splitting may be due to Fermi resonance of the A_2'' fundamental with a combination band. The shoulder at 1300 cm^{-1}, although very weak is a fundamental (E$'$).

In the 1:2 complexes there is the possibility of mechanical coupling between the halogen-halogen stretching vibration and some vibrations of the donor. But this does not seem to be the case for these triethylenediamine complexes. It can be seen from IR Nos. 7, 8, 9 and 10, and from Tables 20 and 22 that the infrared spectrum of triethylenediamine is but little altered by formation of the 1:2 complexes. Thus, it is confirmed that the 1:2 complexes have the same symmetry as the uncomplexed donor. However, the 1:1 complexes, which from symmetry considerations would be expected to have considerably more absorption bands than triethylenediamine itself, do not in fact have them. Two bands which are Raman active only in triethylenediamine (the A_1 skeletal modes at 965 and 600 cm.$^{-1}$) are observed for these complexes, but

TABLE 20. THE INFRARED SPECTRUM OF TRIETHYLENEDIAMINE

TRIETHYLENEDIAMINE

cm^{-1}		Species	Assignment*
2960,	vs	A_2''	$\nu(CH_2)a$
2880,	vs	E_1'	$\nu(CH_2)s$
1470,	s	E'	$\delta(CH_2)scis$
1350,	vw	A_2''	$\delta(CH_2)wag$
1320,	s	E'	$\delta(CH_2)wag$
1300,	w	E'	$\delta(CH_2)wag$
1062,	vs	E'	skeletal
995,	s	A_2''	
892,	w	E'	skeletal
831,	w	E'	$\delta(CH_2)rock$
775,	s	accidental	degen. A_2''
754,	m		Fermi

* After Marzocchi[151]

TABLE 21. THE INFRARED SPECTRA OF TRIETHYLENEDIAMINE 1:1 COMPLEXES WITH BROMINE AND IODINE MONOCHLORIDE

TED: Br$_2$, 1:1		TED: ICl, 1:1		Both Complexes	
cm^{-1}		cm^{-1}		Species*	Assignment
2940,	w	2950,	m	A_2''	$\nu(CH_2)a$
2880,	w	2880,	m	E_1'	$\nu(CH_2)s$
1460,	m	1470,	m	E_1'	$\delta(CH_2)scis$
1360,	m	1320,	m		
1320,	m	1310,	m	E_1	$\delta(CH_2)wag$
		1300,	w		
1180,	vw	1176,	w		
		1090,	vw		
1048,	m	1048,	s	E'	skeletal
1004,	w	1011,	vw		
968,	vw	972,	m	A_1'	New band †
		908,	vw		
845,	m	832,	s	E'	$\delta(CH_2)rock$
837,	m				
		797,	m		
780,	vs	789,	vs	acc.degen.	A_2'' & Fermi
		756,	vw		
614,	w			A_1' (Raman active)	Skeletal †

* assignments are for D_{3h} symmetry

† band present in Raman spectrum of triethylenediamine

TABLE 22. THE INFRARED SPECTRA OF THE 1:2 COMPLEXES OF TRIETHYLENEDIAMINE WITH IODINE, BROMINE AND IODINE MONOCHLORIDE

TED: I_2, 1:2	TED: Br_2, 1:2	TED:ICl, 1:2	All Complexes	
cm^{-1}	cm^{-1}	cm^{-1}	Species	Assignment
2960, w	2960, vw	2960, vw	A_2''	ν(CH$_2$)a
2890, vw	2880, vw	2880, vw	E_1'	ν(CH$_2$)s
1470, m	1460, m	1470, s	E_1'	δ(CH$_2$)scis
1370, s	1360, m	1380, s	A_2''	δ(CH$_2$)wag
1330, m	1330, w	1340, m	E'	δ(CH$_2$)wag
1180, vw	1180, vw	1185, vw	E'	δ(CH$_2$)wag
1052, m	1045, m	1046, m	E'	skeletal
1015, vw				
986, vw				
922, vw		925, vw	E'	skeletal
837, m	840, m	838, m	E'	δ(CH$_2$)rock
781, vs	782, vs	787, vs	acc. degen.	A_2''
740, m	760(sh), m	765, w		Fermi
		732, w		
682, vw				
665, vw				
	622, vw			

their spectra, with few other exceptions, are very similar to those of the 1:2 complexes (see IR Nos. 11 and 12, and Table 21).

In quinuclidine the C_{3v} symmetry of the free base would be expected to be retained on charge-transfer complex formation (assuming that the N-X-Y group is linear), and thus the spectra of quinuclidine and its complexes should be very similar. Examination of Table 23 shows that this is so. However, some bands are shifted and some intensities are changed. The A_1 mode at 604 cm^{-1} is shifted to 634 and 640 cm^{-1} on complexation. The Raman active band at 1009 cm^{-1} also becomes infrared active on complexation.

(b) Far-infrared spectra

The stretching vibrations of the free halogens are Raman active only, but become infrared active in the complexes where they occur at lower wavenumbers than the corresponding bands of the 'free' halogens. A similar shift in frequency on complexation is shown by asymmetric acceptors such as iodine monochloride. In addition, the spectra contain bands which cannot be assigned to either the donor or the acceptor and have therefore been assigned to intermolecular stretching vibrations. For amine-halogen complexes both of these absorptions occur in the far-infrared region. Nagakura and his coworkers[123] were the first to study an amine-halogen system in this spectral region and observed bands at 184 and 145 cm^{-1} in the spectrum of the solid trimethylamine-iodine complex. They assigned the higher energy band to the I-I stretching vibration in the complex, and the band at 145 cm^{-1} to the I-N stretching vibration. The energies calculated on the assumption of a linear I-I-N unit are in good agreement with experimental values.

TABLE 23. THE INFRARED SPECTRA OF QUINUCLIDINE AND ITS COMPLEXES WITH IODINE AND BROMINE

QUINUCLIDINE				Q: I_2		Q: Br2	
cm^{-1}*		Species*	Assignment	cm^{-1}		cm^{-1}	
2937,	s	E	$\nu(CH_2)_2$	2935,	m	2935,	s
2916,	m	$E.A_2$		2910,	m	2915,	m
2888,	w(sh)	A_1A_2				2885,	w(sh)
2865,	m	A_1A_2		2860,	w	2865,	m
				1490,	w	1490,	m
1452,	s	E	$\delta(CH_2)$scis	1470,	w	1465,	m
						1370)	w
1348,	m	E	$\delta(CH_2)$ wag	1370,	w	1360}	
1317,	s	E		1330,	w	1325,	w
1266,	m	E		1270,	vw	1270,	w
1200,	s	E		1198,	w	1200,	w
1114,	w	E		1114,	vw	1114,	vw
1082,	w	ν_{36}					
1053,	s	A'		1038,	w	1032,	w
1009,	RAMAN			1008,	vw	1011,	vw
991,	s	A_1		982,	m	982,	m
966,	s	E					
875,	w	E		(895)		(900)	
823,	m	E		828,	m	828,	m
800,	m	A_1				800,	vw
776,	s	A_1		776,	vs	776,	vs
604,	s	A_1		634,	m	640,	m
541,	s	E					

( ) denotes not assigned

* From P. Bruesch and H.H. Gunthard[152].

Relevant studies by other workers have concentrated on pyridine-halogen interactions both in the solid state and in solution, although systems with trimethylamine as a donor have also been further investigated. Some typical values for the intermolecular and halogen-halogen stretching frequencies found by other workers are given in Table 24. In addition, some workers have assigned a band to an N-X-Y deformation.

TABLE 24. LITERATURE VALUES OF FAR-INFRARED ASSIGNMENTS

Complex	ν(N-X) (cm^{-1})	ν(X-Y) (cm^{-1})	Phase	Reference
Me_3N-I-I	145	184	solid	123
Me_3N-I-I	146	172	solid	153
Me_3N-I-Cl	196	249	solid	153
py-I-I	120	167	py solution	126
py-I-Cl	160	277	py solution	126
py-Br-Br	128	229	C_6H_6 solution	154

The results obtained in the present study are given in Table 25 below and some representative spectra are depicted in the Experimental (page 239). The assignments are based on comparisons with literature values and cross references between spectra with common acceptors or donors.

In general, for complexes with a given acceptor the strength of interaction increases as ν N-X increases and ν X-Y decreases. Relative acceptor strengths may be assessed by comparison of the relative shifts (calculated using Equation 2) in the halogen-halogen stretching frequency (Table 26)

$$\frac{\nu \text{ uncomplexed} - \nu \text{ complexed}}{\nu \text{ uncomplexed}} = \frac{\Delta}{\nu} \qquad \text{Equation 2}$$

The values for the uncomplexed halogen-halogen stretching frequency (ν) used in the calculation were those given by Marzocchi,[149] viz. 213, 321 and 381 cm^{-1} for iodine, bromine and iodine monochloride, respectively. Comparison of the data in Table 26 for complexes of a given stoichiometry shows the relative acceptor strengths to be in the order $Br_2 > ICl > I_2$. This order is different to that accepted for the halogens, i.e. $ICl > I_2 > Br_2$, but is the same as the order deduced from the near-infrared data.

Comparison of the data for all the 1:1 complexes of each acceptor in turn affords information regarding the relative strengths of the donors; these are as follows:

iodine complexes: hexamine > quinuclidine > trimethylamine

bromine complexes: triethylenediamine > hexamine > trimethylamine

iodine monochloride complexes: trimethylamine > hexamine > triethylenediamine.

The latter deductions are neither consistent, nor do they place the acceptors in the expected order.

For a series of complexes between an acceptor and a given donor it is found that, without exception, the value of Δ/ν decreases as the molar ratio of halogen:amine in the complex increases. This trend in Δ/ν values probably reflects a gradual decrease in donor-acceptor interaction as the number of complexed nitrogen atoms in the multifunctional donor increases and is indicative of interaction between different donor sites. However, on the data available it cannot be established whether this interaction is greater in triethylenediamine than in hexamine.

TABLE 25. FAR-INFRARED ASSIGNMENTS

(i) Iodine complexes

Donor	D:A ratio	ν(N-I) (cm^{-1})	ν(I-I) (cm^{-1})
Hexamine	1:1	138	159
	1:2	103	165
	1:3	103	172
Triethylenediamine	1:2	125	158
Quinuclidine	1:1	106	168
Trimethylamine	1:1	146	187

(ii) Bromine complexes

Donor	D:A ratio	ν(N-Br) (cm^{-1})	ν(Br-Br) (cm^{-1})
Hexamine	1:1	180	198
	1:2	130	200
Triethylenediamine	1:1	168	190
	1:2	167	209
Quinuclidine	1:1	162	212

(iii) Iodine monochloride complexes

Donor	D:A ratio	ν(N-I) (cm^{-1})	ν(I-Cl) (cm^{-1})
Hexamine	1:1	155	238
	1:2	138	270
	1:3	144	280
	1:4	146	282
Triethylenediamine	1:1	172	258
	1:2	149	266
Trimethylamine	1:1	207	247

(iv) NBS complexes

Donor	D:A ratio	ν(N-Br)	ν(Br-suc)
Hexamine	1:2	90	220
Triethylenediamine	1:2	140	208

TABLE 26. RELATIVE SHIFTS IN HALOGEN-HALOGEN STRETCHING FREQUENCY ON COMPLEXATION

Donor	D:A ratio	Δ (cm^{-1})	Δ/ν
(i) Iodine complexes			
Hexamine	1:1	54	0.266
	1:2	48	0.236
	1:3	41	0.202
Triethylenediamine	1:2	55	0.271
Quinuclidine	1:1	45	0.222
Trimethylamine	1:1	26	0.128
(ii) Bromine complexes			
Hexamine	1:1	123	0.383
	1:2	121	0.377
Triethylenediamine	1:1	131	0.397
	1:2	112	0.360
Quinuclidine	1:1	109	0.340
(iii) Iodine monochloride complexes			
Hexamine	1:1	133	0.349
	1:2	111	0.292
	1:3	101	0.265
	1:4	99	0.261
Triethylenediamine	1:1	125	0.323
	1:2	115	0.302
Trimethylamine	1:1	134	0.362

5. The proton magnetic resonance spectra of the complexes

Although proton magnetic resonance spectroscopy has been used extensively in order to study interactions between molecules in solution, including the determination of association constants for charge-transfer complexes from chemical shift measurements, only a few reports deal with the effects of charge-transfer complex formation between amines and halogen molecules on the spectrum of the donor.

It will be recalled that Fratiello[130] studied the changes in chemical shift of the donor caused by iodine. This author used a variety of amines as donors and regarded the large downfield displacements (75-175 H_z) of the absorptions due to the amino protons as indicative of a charge withdrawal from the nitrogen. Similarly, Yarwood[131] found that the methyl resonances of complexes of iodine and iodine monochloride with methyl-substituted pyridines showed a shift to low field compared with the values given by the free bases. The amount of this shift is greater for iodine monochloride complexes than for the corresponding iodine complexes. Yarwood concluded that, when methylpyridines interact with strong electron acceptors, the changes in chemical shift are largely a measure of the redistribution of electronic charge due to charge-transfer from the nitrogen lone-pair to the acceptor. This lowers the shielding constant of the methyl protons.

The majority of the bromine and iodine complexes used in the present investigation are not sufficiently soluble in non-polar solvents such as carbon tetrachloride or petrol, and nence, acetone had to be used. Although acetone undergoes donor-acceptor interactions with halogens, the author considers that these are considerably weaker than those between the halogens and the nitrogen donors. For iodine monochloride complexes, dimethylsulphoxide had to be used, whilst amine salts were studied in water. In every case, the spectrum of the free donor was measured in the appropriate solvent.

The appearance of the magnetic resonance spectrum of a nucleus which can exist in more than one chemical environment is dependent on the relative lifetimes in the different environments. In the case of a nucleus which can exist in two environments, in either of which alone it appears as a singlet, if the lifetimes in the two states are long compared with $1/\Delta$ (where Δ is the frequency difference in H_3 between the two absorptions) then two lines are observed. If the lifetimes are short compared with $1/\Delta$ then only a single time-averaged line is observed[155]. In the latter case, the position of the line is dependent on the relative populations in the two environments. These observations also apply to a nucleus which is rapidly exchanging between a number of different environments. With charge-transfer complexes, the different environments could be provided by a free donor molecule and one in the complexed state. For nearly all charge-transfer complexes, the rates of exchange between different environments at normal experimental temperatures fall within the category of very fast reactions. As had been pointed out by Foster[155], the possibility must be considered that for systems in which the binding approaches that of a normal covalent bond, the rate of chemical exchange may only be of the same order as, or even less than, the rate of exchange between the magnetic states of the nucleus, in which case line-broadening, or two separate lines will be observed.

This possibility was investigated using the trimethylamine: iodine system. This amine was chosen as it is a readily available, strong, mono-functional donor and the complex is far more soluble than most of the other complexes studied. The p.m.r. spectrum of a solution of trimethylamine in methanol is a singlet at 134 Hz; whilst that of a solution of the trimethylamine:iodine complex (of the same molar strength) is a singlet at 170 Hz (Δ = 36 Hz). A mixture of equal volumes of these solutions would be expected to give a p.m.r. spectrum consisting of a singlet at 152 Hz, if rapid exchange of the iodine between all the available donor sites occurred. In fact, a singlet at 150 Hz was observed. There was no significant change in the spectrum even when it was measured at -80°C. It is concluded that very rapid exchange of the acceptor between donor sites occurs even at this temperature.

The p.m.r. spectrum of hexamine is a singlet since all six methylene groups are equivalent. Here, as in the case of trimethylamine, there is rapid exchange in donor-acceptor interactions and hence the spectrum of a hexamine-halogen complex consists of a singlet which is shifted downfield with respect to the uncomplexed amine. Thus for the hexamine:iodine, 1:1 complex Δ = 11 Hz. The change in chemical shift on complexation is much less for hexamine than for trimethylamine, because in the former case there is exchange between four donor sites in each amine molecule, as well as intermolecular exchange. The measured absorption is due to the methylene groups α to the nitrogen and not to the donor site itself. If one considers the four possible (all equivalent) 1:1 complexes, each methylene group is α to a complexed nitrogen in two of the four complexes. Thus the total shift per molecule (if complexation occurred at one nitrogen only) is 2 x 11 = 22 Hz, indicating that hexamine is a weaker donor than trimethylamine.

It should be noted, however, that the observed shift is not only a function of the amount of deshielding (i.e. the degree of charge-transfer), but also of the time the nitrogen is complexed compared with the time it is not. This is demonstrated by reference to trimethylamine and its derivatives - trimethylamine hydrochloride which absorbs at 176 H_z(Δ = 42 H_z) in methanol, and tetramethylammonium iodide in which resonance occurs at 191 H_z (Δ = 57 H_z) in the same solvent. The charge on the nitrogen is the same in both compounds so that the difference in Δ must be due to the difference in the "residence time" of the charge. In the quaternary ammonium salt the charge is on the nitrogen all the time but in the hydrochloride salt solvation of the cation ensures that the proton is 'shared' by the nitrogen and the solvent, methanol. Therefore, in the latter case, the observed signal results both from the amine lone-pair/acceptor interaction and the acceptor-solvent interaction. This means that one cannot make a quantitative correlation of the shifts observed in different solvents. Unfortunately, in the present study a universal solvent could not be found. Thus, only as a first approximation can it be said that when the difference in chemical shift between the free amine and the charge-transfer complex (in acetone), and that between the free amine and the salt (in water) are the same, the same amount of deshielding has occurred as a result of a similar degree of electronic charge redistribution on complex formation and on protonation, respectively. Strictly speaking, caution must be exercised when the strength of donor-acceptor interaction on charge-transfer complex formation is compared with the donor-acceptor interaction on protonation. In fact two different systems are being compared.

Similar considerations apply to the comparison of the shifts in the p.m.r. spectra of charge-transfer complexes which are measured in solution in different solvents.

The above notwithstanding we can make some qualitative correlations (see Table 27)

TABLE 27. CHANGE IN CHEMICAL SHIFT OF α-PROTONS ON FORMATION OF AMINE-HALOGEN COMPLEXES

Complex		Δ (H_3)
Iodine Complexes		
Hexamine: I_2	1:1	11
	1:2	17
	1:3	18
TED: I_2	1:2	42
Quinuclidine: I_2	1:1	42
Trimethylamine: I_2	1:1	36
Bromine Complexes		
Hexamine: Br_2	1:1	13
	1:2	26
TED: Br_2	1:1	30
	1:2	62
Quinuclidine:Br_2	1:1	52
Iodine Monochloride Complexes		
Hexamine: ICl	1:1	24
	1:2	25
	1:3	26
	1:4	27
TED: ICl	1:1	44
	1:2	46

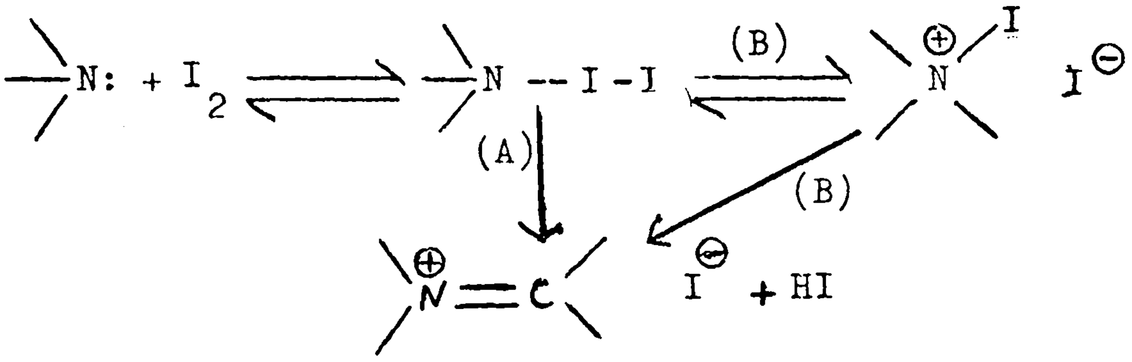
As expected the Δ values for complexes of iodine and bromine with multifunctional amines increase with the molar proportion of halogen in the complex. In contrast, the Δ values in each of the corresponding iodine monochloride series is independent of the proportion of iodine monochloride in the complex. The latter observation indicates that, although a range of solid complexes of iodine monochloride with a given amine can be isolated, only one such combination can exist in solution in the donor solvent, dimethylsulphoxide. Similarly, the value of Δ observed for hexamine:iodine, 1:3 in acetone, is almost identical to that for the corresponding 1:2 complex in the same solvent. The result is in agreement with the reported formation of the 1:2 complex (p. 121) on dissolving hexamine: I_2, 1:3 in a suitable solvent.

The Δ values in Table 27 are the observed changes in chemical shifts of the protons α to the nitrogen. As explained above it is necessary to double the value of Δ for the hexamine 1:1 complexes in order to obtain a value equivalent to all the complexation occurring at one nitrogen. Clearly the same also applies to the corresponding triethylenediamine complexes. The 'corrected' values and the Δ values for the 1:2 complexes may be compared with the results of the quinuclidine and trimethylamine complexes. This comparison shows that hexamine is the weakest of the donors used, with trimethylamine next whilst quinuclidine and triethylenediamine are the strongest donors.

6. The role of charge-transfer complexes during the oxidisation of amines by halogens

The overall conclusion drawn from the spectroscopic study of solid amine-halogen adducts is that, at room temperature these are charge-transfer complexes containing a linear N-X-Y grouping.

This conclusion also applies to the initial interaction between any tertiary amine and iodine. Thus, the brown colour of a solution obtained by mixing iodine with an amine is a clear indication that complexation occurs. Furthermore, the measured ultraviolet absorption of systems such as trimethylamine-iodine and *N*-dodecyldiethanolamine-iodine confirms this view. It is probable, therefore, that oxidation of such amines by iodine proceeds via a charge-transfer complex. As it has been established that the oxidation reaction involves an immonium salt intermediate, the question that arises is whether this is derived in 'one step' from the charge-transfer complex (*route A*), or whether its immediate precursor is an *N*-haloammonium halide, which is itself formed by the ionisation of the complex (*route B*)



In an attempt to differentiate between these two possibilities, the solid complexes were subjected to conductance measurements in solution, and to thermogravimetric analysis (T.G.A.) and differential thermal analysis (D.T.A.)

Previous workers[85, 136] in this field have attributed the conductance of solutions of charge-transfer complexes to the existence of ionic species such as

$$\left[R_3N - X\right]^{\oplus} Y^{\ominus} \qquad \text{and} \qquad \left[R_3N - X - NR_3\right]^{\oplus} Y^{\ominus}$$

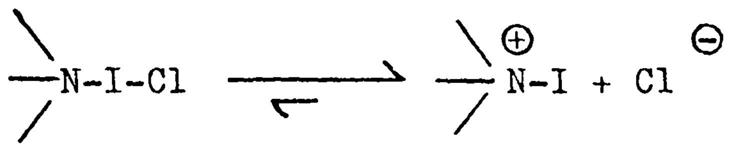
Whilst it is accepted that such ions are formed when the donor is pyridine or a substituted pyridine, such evidence is lacking for aliphatic amines. Nagakura[118] has suggested that the precipitate obtained from triethylamine and iodine in heptane using amine concentrations greater than 10^{-2} molar is $[(C_2H_5)_3N]_2\overset{\oplus}{I}\cdot\overset{\ominus}{I}$.

However, when Schmulbach and Hart[143] attempted to isolate this product, they obtained crystals of triethylammonium iodide. For this reason, in order to exclude the possibility that any observed conductance of solutions of an amine-halogen complex is due to ionic species formed by chemical reaction, the present author employed only triethylenediamine and hexamine as donors.

The extent of ionisation of pyridine-iodine complexes increases with the polarity of the solvent[157]. Accordingly methanol was used as solvent in the present work. The conductances of solutions of the iodine complexes are very low but indicate that the degree of ionisation of these complexes, though small, is measurable. The values obtained from the iodine monochloride complexes were comparable to those of the corresponding amine hydrochlorides and methiodides. Bromine complexes reacted with the solvent but the NBS complexes gave conductances intermediate between the values obtained for the iodine and the iodine monochloride complexes. The observed conductances vary in the manner expected on the assumption that ionisation of the complex depends largely on the nature of the acceptor. This assumption is based on the fact that the amines used here are very strong donors and hence their contribution to the strength of the charge-transfer interaction would be almost the same in each case. Accordingly, the expected order of polarity of the X-Y bond and, hence, the degree of dissociation of the complex is iodine $<$ NBS $<$ iodine monochloride and is the same as that deduced from the conductance measurements. For example, the conductances of the 1:2 complexes of trimethylenediamine are as follows

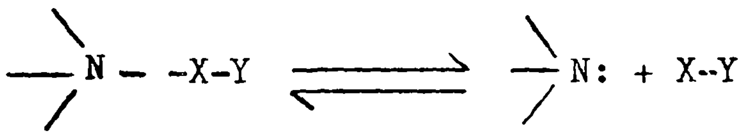
iodine	20	ohm^{-1} cm^2 $mole^{-1}$
NBS	50	"
iodine monochloride	200	"
(hydrogen chloride)	240	"

The greater conductance of solutions of theiodine monochloride complexes compared to that of the corresponding iodine complexes has also been noted by other workers[148] who used pyridines as the donor moiety. The values for the iodine monochloride complexes obtained in this work are sufficiently high to imply either almost complete ionisation as

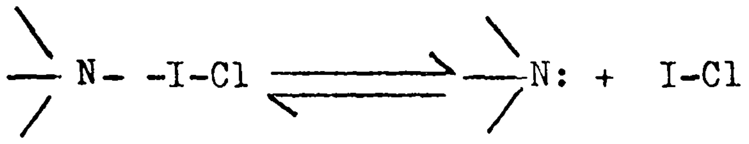


(i)

or formation of ionic species by (i) and by other interactions involving this reactive interhalogen. It will be recalled that in solutions of charge-transfer complexes, there exists the equilibrium

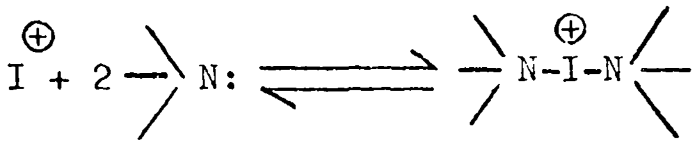


Thus, even a solution of the stable complex triethylenediamine: iodine, 1:2 in chloroform shows absorptions at 510 nm due to free iodine, as well as absorptions due to the complexed species. Similar observations have been made[158] using triethylenediamine: iodine monochloride, 1:2 in methylene chloride. On this basis, the following equilibria may be envisaged in the case of solutions of iodine monochloride, for it is known that this interhalogen is ionised in solution in a variety of organic solvents according to equation (iii)[159]



(ii)

$$2\,I{-}Cl \rightleftharpoons \overset{\oplus}{I} + \overset{\ominus}{I\,Cl_2} \qquad \text{(iii)}$$



(iv)

It was considered that the same charge-transfer complexes might be made to undergo chemical reaction in the solid state. To this end, the complexes were subjected to D.T.A. and T.G.A. Using the former technique, the complex is heated progressively in an inert atmosphere and any endo-or exothermic changes which occur relative to an inert reference are recorded. Thus, both chemical and physical changes can be detected. As T.G.A. records any weight change which occurs on heating, it was hoped that the application of both techniques to the same substance would provide evidence for reactions of the type

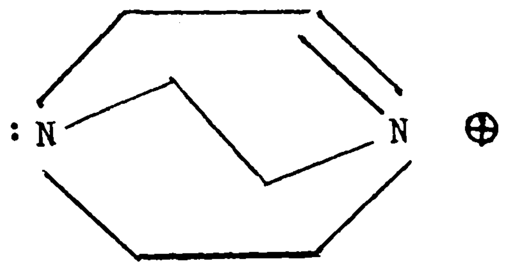
$$R_3N{-}X{-}Y \longrightarrow R_3\overset{\oplus}{N}{-}X + \overset{\ominus}{Y}$$

since D.T.A. would detect the heat of reaction, whilst T.G.A. would show no weight loss at that temperature. It was found that with the exception of the trimethylamine-iodine monochloride complex, no exothermic or endothermic change occurred without a corresponding weight loss. In the majority of cases, D.T.A. showed a very sharp exothermic peak. The temperature at which this occurred correlated reasonably well with a weight loss on the T.G.A. trace. Often this weight loss was almost instantaneous, as is shown below (Figure 9)- the T.G.A. and D.T.A. traces for the thermal decomposition of the triethylenediamine:bromine, 1:1 complex.

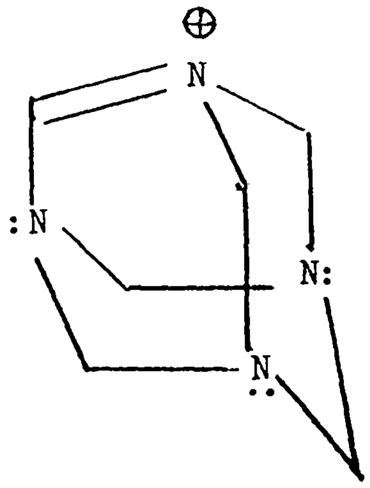
The weight losses observed do not reflect a sudden dissociation of the complex to its component molecules, but correspond to the loss of hydrogen halide. This fact was confirmed by qualitative analysis. It should be noted that decomposition of iodine monochloride complexes is accompanied by the liberation of the more stable hydrogen chloride rather than hydrogen iodide.

The results are summarised in Table 28. For the complexes marked (*) in this table, a gradual weight loss was observed and no conclusions can be drawn from these results.

Whilst it is clear that hydrogen halide is lost during these decompositions, the problem remains as to the nature of the residue. So far in this work it has been assumed that Bredt's Rule would forbid formation of species such as



and



However, Grob and his coworker[160], during investigations on 'fragmentation' reactions, have examined quinuclidine derivatives and concluded the 2-quinuclidinyl cation (XXXVIII)

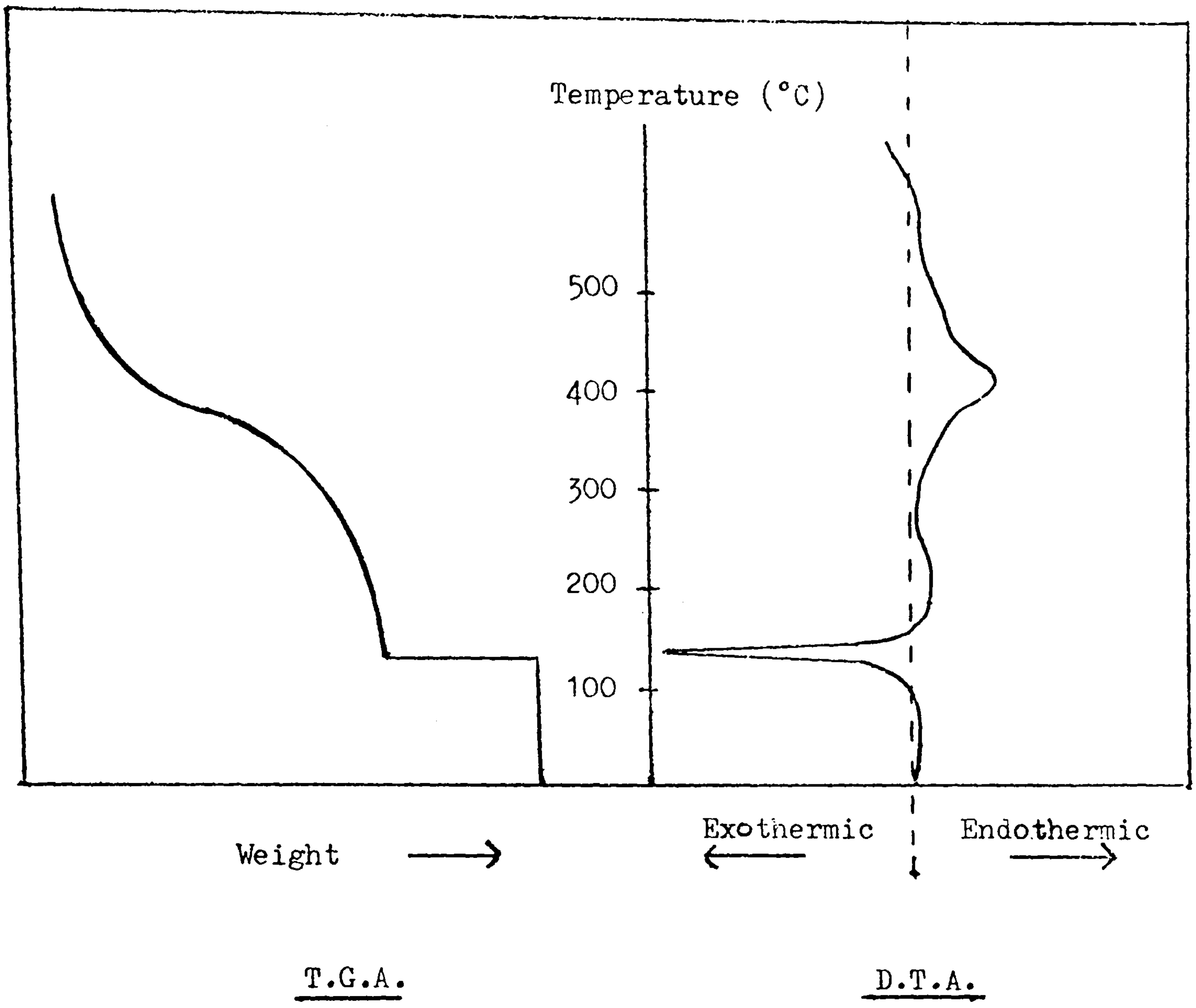


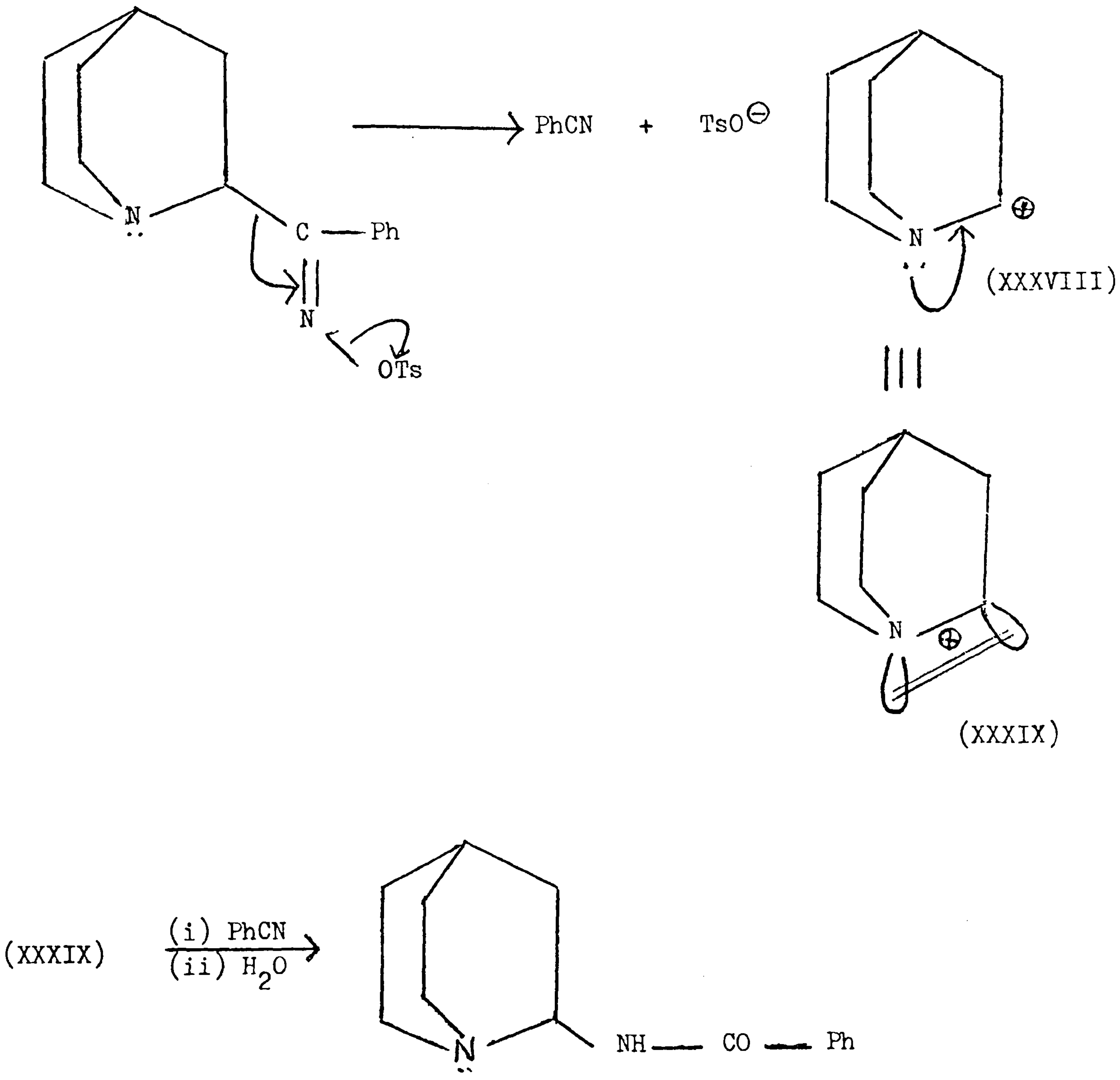
FIGURE 9 T.G.A. and D.T.A. TRACES FOR THE THERMAL DECOMPOSITION OF TRIETHYLENEDIAMINE:BROMINE, 1:1

TABLE 28. WEIGHT LOSSES OCCURRING DURING THE THERMAL DECOMPOSITION OF CHARGE-TRANSFER COMPLEXES

COMPLEX		WT. LOSS (%)	COMPONENT LOST	THEORETICAL WT. LOSS (%)	FOR nHX
Hexamine:Iodine,	1:1*	12	-	33	HI
	1:2*	8	-	40	2 HI
	1:3	38	3 HI	42	3 HI
Hexamine:Bromine,	1:1*	11	-	27	HBr
	1:2	34	2 HBr	35	2 HBr
Hexamine:Iodine	1:1	11	HCl	12	HCl
monochloride,	1:2	16	2 HCl	16	2 HCl
	1:3	18	3 HCl	18	3 HCl
	1:4	16	3 HCl	19	4 HCl
TED:Iodine,	1:2	44	2 HI	41	2 HI
TED:Bromine,	1:1	30	HI	30	HBr
	1:2	42	2 HI	38	2 HBr
TED:Iodine	1:1	14	HCl	13	HCl
monochloride,	1:2*		-	17	2 HCl
Quinuclidine:Bromine	1:1*	22	-	30	HBr

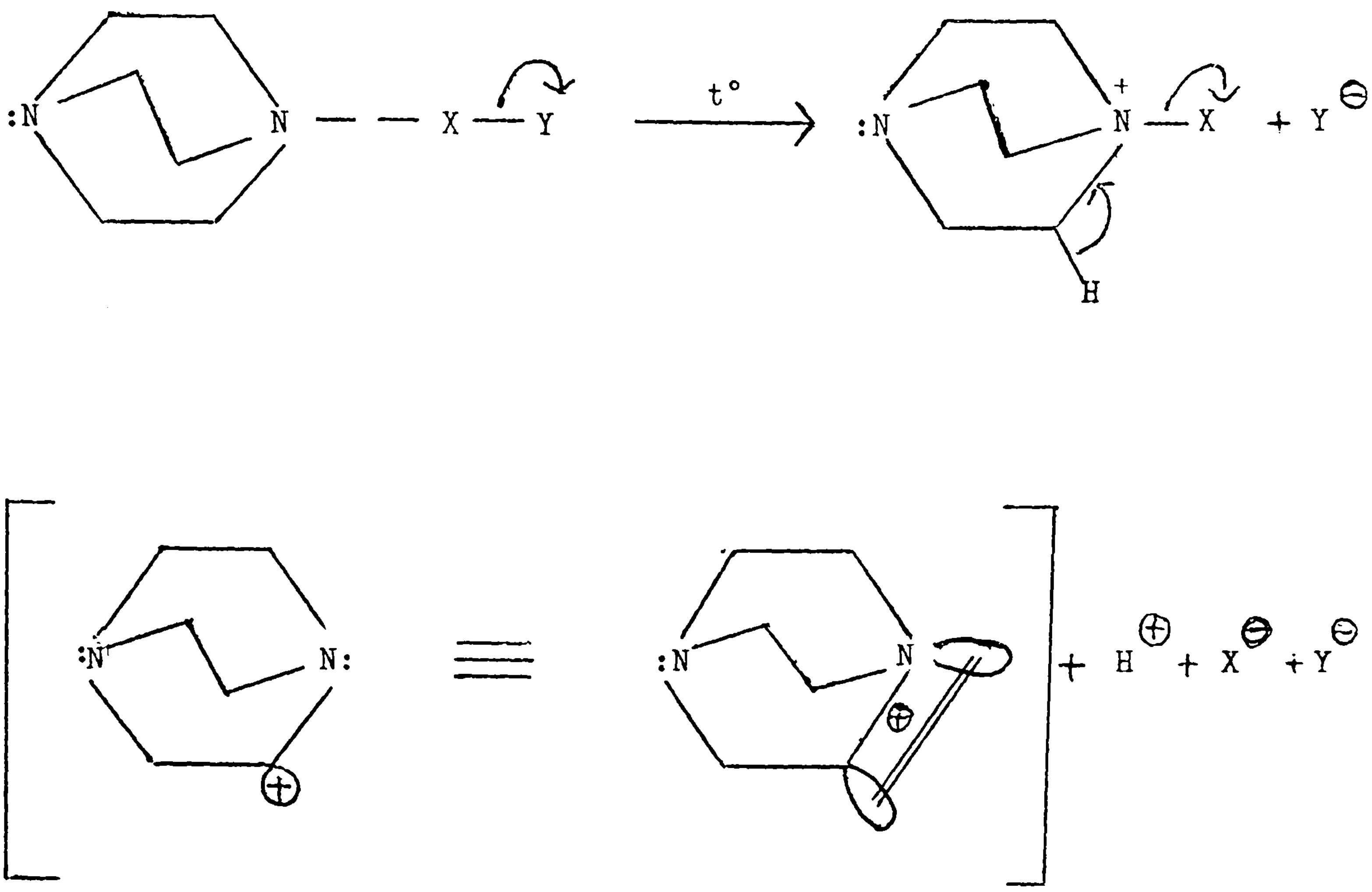
* no sudden weight loss

has a transient existence. As this is a canonical form of the mesomeric 'immonium ion' XXXIX derived from quinuclidine, one is led to the conclusion that Bredt's Rule does not apply to unstable reaction intermediates. Thus XXXIX is regarded as an aliphatic analogue of arynes.



Scheme 15

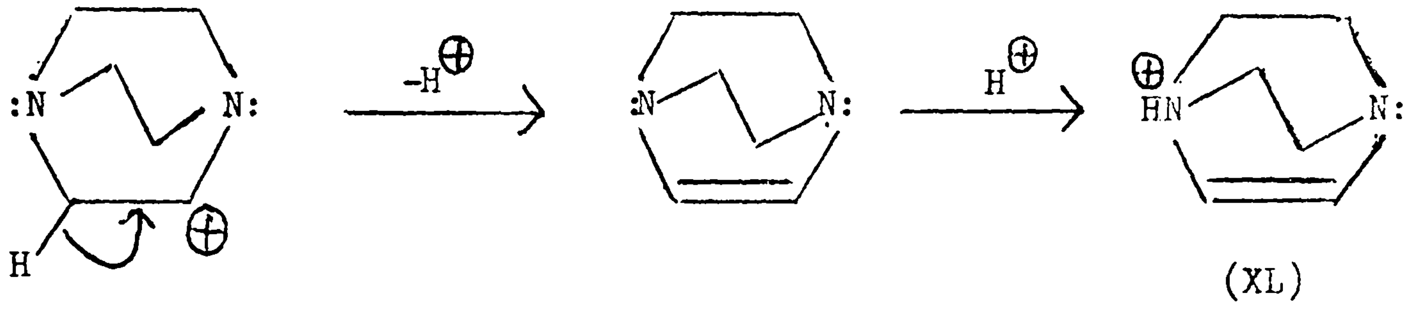
Thus, it is conceivable that under the extreme conditions employed, pyrolysis of the charge-transfer complexes may proceed as shown below for a 1:1 triethylene-diamine-halogen complex (Scheme 16)



Scheme 16

The thermograms show continuous change almost immediately above the temperature at which hydrogen halide is lost. Hence it may be assumed that the resulting intermediate undergoes further changes but it has not proved possible to elucidate their complex nature. However, it is of interest to note in this connection that the product obtained by the loss of hydrogen bromide from triethylenediamine:bromide, 1:1 contains bromide ions. Its infrared spectrum has intense absorptions at 2900 and 1600 cm^{-1}

for ($>\overset{+}{N}\text{-H}$) and ($>C=C<$), respectively. These observations are compatible with the formation of a species like the proposed protonated enamine (XL)


(XL)

Thus the changes observed when these complexes are pyrolysed in an inert atmosphere can be rationalised in terms of an intermediate N-haloammonium halide.

7. Conclusions

Amines form charge-transfer complexes with halogens. Some of these may be isolated, whereas others exist only in solution. The stability of complexes depends both on the nature of the amine and of the halogen.

Conductance measurements using solutions of stable amine-halogen complexes indicate the existence of an equilibrium.

$$>N\text{-}X\text{-}Y \rightleftharpoons >\overset{\oplus}{N}\text{-}X \quad \overset{\ominus}{Y}$$

Thus as far as the oxidation of amines by iodine is concerned, the charge-transfer complex is seen to produce the corresponding N-iodoammonium iodide. The latter intermediate is then converted by loss of hydrogen iodide to the immonium salt (see Chapter Two: B. Discussion) and thence to oxidation products, the nature of which depends on the conditions used in the reaction.

CHAPTER FOUR

EXPERIMENTAL

A. TECHNIQUES AND ANALYTICAL PROCEDURES

I Instrumental Techniques

1. Ultra-violet and visible spectra were measured in solution using a Pye-Unicam SP 800 spectrophotometer. The solvents used were purified by standard techniques[161]. Diffuse reflectance measurements were made using an SP 700 spectrophotometer with magnesium oxide as reference. Attempts were also made to obtain the spectra of solid compounds with the SP 800, using mulls in dry paraffin held between polythene sheet, and by pressing a mixture of the compound and polythene powder to a disc. Both methods were unsuccessful.

2. Infrared spectra were determined using the Perkin-Elmer PE 257 and PE 337 spectrophotometers. Liquid samples were run as thin-films between salt plates and solids as potassium bromide discs.

3. Far-infrared spectra were determined using a Beckman R.I.I.C. FS-720 Fourier Transform spectrophotometer with an FS 300 power supply and Addo tape punch. The samples were run as mulls in sodium-dried liquid paraffin, held between polythene plates.

4. Mass spectra were determined using an AEI 9 C2 spectrometer and in some cases at the Physico-Chemical Methods Unit, Harwell, using an MS 9 instrument.

5. Nuclear magnetic resonance spectra were obtained using a Varian Associates A 60-A spectrometer, with tetramethylsilane as the internal standard.

6. Thermal data were obtained using a Stanton Instruments Thermobalance for thermogravimetric analysis, and a Stanton Instruments Standata 6-25 for differential thermal analysis. All measurements were carried out in duplicate. The samples were heated in platinum vessels under an atmosphere of dried nitrogen.

7. Conductance measurements were made at 25° using a Pye-Unican Conductivity Bridge. The solvents used (methanol and water) were purified by standard techniques.

II Separative Techniques

1. Gas-liquid chromatography for analytical and preparative purposes, was carried out using Pye 104 instruments fitted with flame ionisation detectors. For analytical work 5' x 3/16" I.D. glass columns were used. For preparative work 7' x 1/4" I.D. columns, with Chromosorb as the support material and nitrogen as the carrier gas were employed. The liquid phase and the oven temperature used in each case are given in the text (see later).

2. Thin layer chromatography was carried out using Merck Silica Gel F_{254} as the stationary phase in most cases. However, for some separations, alumina (Merck HF_{254} Basica) proved more effective.

3. Dry column chromatography was carried out using the technique of Loev and Snader[20] with silica gel (Merck; Brockmann activity II-III) as the stationary phase. The technique used involved packing about 60 g. of the adsorbent into a 1" diameter nylon tube sealed at its lower end, to give a column approximately 45 cm. long. The adsorbent was covered with a 2 cm. layer of sand and the material to be chromatographed (ca. 1 g.) placed on it in the form of a concentrated solution in some suitable solvent. After piercing air-holes at the bottom of the tube, the mixture was eluted into the silica gel until it formed a compact band at the top of the column. The chromatogram was then developed with the appropriate eluant which was chosen by preliminary t.l.c. studies. When the solvent front reached the bottom of the column, the latter was cut into convenient fractions and each of these was eluted with methanol. The extracts were monitored by t.l.c. and g.l.c. The fractions containing the required components were bulked and subjected to

further chromatography until the desired material was obtained in sufficient quantity and purity for spectroscopic examination.

III Titrimetric Techniques

1. Determination of amines

(a) N-Alkyldiethanolamines were assayed by dissolving ca. 0.002 mol. in glacial acetic acid (20 ml.) and titrating with 0.1 M perchloric acid in glacial acetic acid using a glass/calomel electrode system. A modification of this method in which an 'Agla' micrometer syringe was used as a burette was applied to 5 mg. portions of the product isolated from the oxidation of C2DEA by iodine in isopropanol solution.

(b) N-Alkyldiethanolamines were also assayed by dissolving ca. 0.002 mol. in glycerol:isopropanol (20 ml; 1:1) previously neutralised to phenolphthalein; the solution was titrated with 0.1 M hydrochloric acid prepared by diluting concentrated hydrochloric acid (8.9 ml; 0.1 mol.) to 1 litre with the same solvent mixture. The end-point was detected potentiometrically using glass/calomel electrodes.

2. Determination of halides

(a) Iodide was determined by titrating a solution of the salt, buffered to pH 4 with sodium acetate/acetic acid buffer, with 0.1 M aqueous silver nitrate. The end-point was detected potentiometrically using silver/calomel (potassium nitrate salt bridge) electrodes.

(b) Chloride was determined by the addition of silver nitrate (0.1 M) to a solution of the salt and back-titration of the excess silver ions with standard aqueous ammonium thiocyanate using ferric ammonium sulphate as indicator. The precipitated silver chloride was masked with nitrobenzene.

3. Determination of the molecular acceptor in the complexes

(a) Iodine (i) direct titration - ca. 0.1 g. of the finely powdered complex was accurately weighed into a conical flask and to this potassium iodide (1 g.), 2.5 M sulphuric acid (5 ml.) and methanol (15 ml.) were added. After grinding for 5 minutes to dissolve the complex, water was added to give a clear solution and the iodine was determined by titration with 0.1 M sodium thiosulphate.

(ii) back titration - ca. 0.1 g. of the finely powdered complex was accurately weighed into a conical flask and to this potassium iodide (1 g.) and 0.1 M sodium thiosulphate (25.0 ml.) was added. After grinding the complex to dissolve it, excess thiosulphate was determined by titration with 0.1 M iodine solution using starch as indicator.

(b) Bromine was determined by weighing ca. 0.1 g. of the complex into a conical flask and adding 0.1 M ammonium ferrous sulphate (25 ml.) and 2.5 M sulphuric acid (5 ml.). The complex was ground until it dissolved, throughout this stage the solution was heated almost to boiling and then cold water was added to it to give a final volume of ca. 100 ml. and a temperature of 60°C. 1 ml. of potassium thiocyanate (0.5 M) was added and the ferric ions produced by the oxidation of the ferrous ammonium sulphate were determined by titration with 0.1 N ascorbic acid.

(c) Iodine monochloride - as for iodine (method (i))

(d) N-Bromosuccinimide - as for iodine (method (i))

IV Miscellaneous

1. Microanalyses were carried out by the National Physical Laboratory, Teddington and by Alfred Bernhardt, 5251 Elbach Über Engelskirehen, West Germany.

2. Melting points were determined using a Gallenkamp electrical apparatus and are uncorrected.

3. Solvents were purified using standard techniques[161], stored over molecular sieves and, where appropriate, redistilled just before use.

B. PREPARATION OF COMPOUNDS

I Amines

1. N-Alkyldiethanolamines

N-Methyldiethanolamine was prepared by the methylation of diethanolamine using the Clark-Eschweiler procedure, in which the secondary amine is treated with a mixture of formaldehyde and formic acid[162]. The N-formylated amine first produced is reduced by formic acid with the evolution of carbon dioxide.

The other N-alkyldiethanolamines were prepared by the reaction of diethanolamine with the corresponding alkyl bromide (except for the ethyl homologue for which ethyl iodide was used) in the presence of potassium carbonate[162] to neutralize the hydrogen halide produced in the alkylation process. The purity of each compound was established by chromatography (g.l.c. on a silicone oil column for up to C10DEA; t.l.c. using silica gel - methylated spirit for C12 to C18DEA) and by potentiometric titration. When required, further purification was effected by redistillation or, in some cases, recrystallisation. All the amines used in the structure - activity studies were at least 98% pure. Each member of the series was identified by infrared and p.m.r. spectroscopy.

(a) N-Methyldiethanolamine

Formic acid (25.6 g. of a 90% w/v solution, 0.5 mol) was added to an ice-cooled solution of diethanolamine (52.5 g. 0.5 mol) in formalin (440 g. of a 34% w/v solution, 0.5 mol. HCHO) at such a rate that the evolution of carbon dioxide was not too vigorous. The reaction mixture was allowed to attain room temperature and was then heated on a boiling water-bath for 4 hours. The crude product yielded on distillation N-methyldiethanolamine (36.1 g., 60%) as a colourless oil, b.p. 108-112°/1 torr (Lit. b.p.[162] 123-125°/4 torr).

$\nu_{max.}$ (thin film) 3350 (OH), 2900 (CH), 1460 (CH_2), 1365 (CH_3), 1075 (C-N), 1035 (C-O) cm^{-1};

δ($CDCl_3$) 2.33 (3H,s, $C\underline{H}_3$), 2.6 (4H,t,$C\underline{H}_2$-N), 3.65 (4H,t, $C\underline{H}_2$-O), 3.98 (2H, s, O$\underline{H}$, exchanged with D_2O) p.p.m.

(b) N-Ethyldiethanolamine

Anhydrous potassium carbonate (69 g., 0.5 mol) was mixed with diethanolamine (52.5 g., 0.5 mol) to a paste and ethyl iodide (78 g., 0.5 mol) was added to this vigorously stirred mixture. The suspension was stirred at room temperature for 1 hour and then heated on a boiling water-bath for 4 hours. After cooling the reaction mixture was diluted with acetone (200 ml.), shaken well and allowed to stand over-night. After further shaking, the suspension was filtered and the residue washed well with acetone. The filtrate and the washings were combined, the acetone was removed and the residue was distilled under reduced pressure to give N-ethyldiethanolamine (34 g., 35%) as a colourless oil, b.p. 116°/1 torr (Lit. b.p.[162] 117-118/3 torr)

$\nu_{max.}$ (thin film) 3350 (OH), 2900 (CH), 1460 (CH_2), 1370 (CH_3), 1070 (C-N), 1040 (C-O) cm^{-1};

δ($CDCl_3$) 1.03 (3H, t, CH_2-$C\underline{H}_3$), 2.6 (4H, m, $C\underline{H}_2$-N), 3.43 (2H,s,O$\underline{H}$, exchanged by D_2O), 3.7 (4H, t, $C\underline{H}_2$-O) p.p.m.

(c) N-Propyldiethanolamine

This was prepared by the propylation of diethanolamine using the method described for N-ethyldiethanolamine. The following quantities of reagents were used: n-propylbromide (61.5 g., 0.5 mol) diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). N-Propyldiethanolamine (56 g., 77%) was obtained as a colourless oil, b.p. 108°/1.0 torr [Lit. b.p.[162] 122-123°/ 3.5 torr].

$\nu_{max.}$ (thin film) 3370 (OH) 2900 (CH), 1460 (CH_2), 1370 (CH_3), 1045 (C-O) cm^{-1};

δ($CDCl_3$) 0.90 (3H,t,-$C\underline{H}_3$), 2.42 (2H,m,-CH_2-$C\underline{H}_2$-CH_3), 2.6 (6H,m,$C\underline{H}_2$-N), 3.35 (2H, s, $O\underline{H}$, exchanged by D_2O), 3.6 (4H, t, $C\underline{H}_2$-O) p.p.m.

(d) N-Butyldiethanolamine

The reagents employed in this preparation were: n-butyl bromide (68.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-butyldiethanolamine (61 g., 75%) as a colourless oil, b.p. 108°/0.5 torr

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1465 (CH_2), 1370 (CH_3), 1040 (C-O) cm^{-1};

δ($CDCl_3$) 0.90 (3H, m,-$C\underline{H}_3$), 1.40 (4H, m, CH_2 ($C\underline{H}_2$)$_2$$CH_3$), 2.6 (6H,m, $C\underline{H}_2$-N), 3.25 (2H,s, $O\underline{H}$, exchanged by D_2O), 3.64 (4H, t, $\underline{CH}_2$-O) p.p.m.

(e) N-Pentyldiethanolamine

The reagents used were: n-pentylbromide (75.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g. 0.5 mol). The crude product yielded on distillation N-pentyldiethanolamine (61 g., 60%) as a colourless oil, b.p. 122°/ 0.35 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1047 (C-O), 720 ($(CH_2)_4$) cm^{-1};

δ ($CDCl_3$) 0.9 (3H, m,-$\underline{CH}_3$), 1.3 (6H, m,-NCH_2($\underline{CH}_2$)$_3$-CH_3), 2.6 (6H, m, $\underline{CH}_2$-N), 3.36 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.6 (4H, t, $\underline{CH}_2$-O) p.p.m.

(f) N-Hexyldiethanolamine

The reagents used were: n-hexyl bromide (82.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-hexyldiethanolamine (66 g., 70%) as a colourless oil, b.p. 130°/ 0.4 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2) 1380 (CH_3), 1047 (C-O), 720($(CH_2)_4$) cm^{-1};

δ($CDCl_3$) 0.88 (3H, m,-$\underline{CH_3}$), 1.37 (8H, s,-$CH_2(\underline{CH_2})_4CH_3$), 2.60 (6H,m, $\underline{CH_2}$-N), 3.5 (2H,s, $\underline{OH}$, exchanged by D_2O), 3.59 (4H,t, $\underline{CH_2}$-O) p.p.m.

(g) N-Heptyldiethanolamine

The reagents used were: n-heptylbromide (89.5 g., 0.5 mol), diethanolamine (68.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-heptyldiethanolamine (46 g., 45%) as a colourless oil, b.p. 151°/0.4 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1045 (C-O), 720 ($(CH_2)_4$) cm^{-1};

δ($CDCl_3$) 0.88 (3H, m,-$\underline{CH_3}$), 1.28 (10H, s, $CH_2(\underline{CH_2})_5$-CH_3), 2.6 (6H, m, $\underline{CH_2}$-N), 3.26 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.59 (4H, t, $\underline{CH_2}$-O) p.p.m.

(h) N-Octyldiethanolamine

The reagents used were: n-octylbromide (96.5 g., 0.5 mol), diethanolamine (68.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-octyldiethanolamine (28 g., 26%) as a colourless oil b.p. 143°/ 0.4 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1045 (C-O), 720 ($(CH_2)_4$) cm^{-1};
δ($CDCl_3$) 0.90 (3H, m,-$\underline{CH_3}$), 1.30 (12H, s, $CH_2(\underline{CH_2})_6$-CH_3), 2.6 (6H, m, $\underline{CH_2}$-N), 3.20 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.60 (4H, t, $\underline{CH_2}$-O) p.p.m.

(i) N-Nonyldiethanolamine

The reagents used were: n-nonyl bromide (103.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate 69 g., 0.5 mol). The crude product yielded on distillation N-octyldiethanolamine (58 g., 50%) as a colourless oil b.p. 155°/ 0.3 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (C-H), 1470 (CH_2), 1380 (CH_3), 1044 (C-O), 718 ($(CH_2)_4$) cm^{-1};
δ($CDCl_3$) 0.87 (3H, m,-$\underline{CH_3}$), 1.26 (14H, s,-$CH_2(\underline{CH_2})_7$-CH_3), 2.6 (6H, m, $\underline{CH_2}$-N), 3.32 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.59 (4H, t, $\underline{CH_2}$-O) p.p.m.

(j) N-Decyldiethanolamine

The reagents used were: n-decylbromide (110.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-decyldiethanolamine (74 g., 60%) as a colourless oil b.p. 161°/ 0.2 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1045 (C-O), 717 ($(CH_2)_4$) cm^{-1};
δ($CDCl_3$) 0.88 (3H, m,-$\underline{CH_3}$), 1.26 (16H, s,-$CH_2(\underline{CH_2})_8$-CH_3), 2.6 (6H, m, $\underline{CH_2}$-N), 3.12 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.60 (4H, t, $\underline{CH_2}$-O) p.p.m.

(k) N-Dodecyldiethanolamine

The reagents used were: n-dodecylbromide (124.5 g., 0.5 mol), diethanolamine (52.5 g., 0.5 mol) and potassium carbonate (69 g., 0.5 mol). The crude product yielded on distillation N-dodecyldiethanolamine (87 g., 64%) as a very pale yellow oil b.p. 181°/0.6 torr.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1075 (C-N), 1045 (C-O), 717 ($(CH_2)_4$) cm^{-1};

δ (acetone, d-6) 0.88 (3H, m, $-\underline{CH_3}$), 1.33 (20H, s, $CH_2(\underline{CH_2})_{10}CH_3$), 2.55 (6H, m, $\underline{CH_2}$-N), 3.52 (4H, t, $\underline{CH_2}$-O), 3.79 (2H, s, $\underline{OH}$, exchanged by D_2O) p.p.m.

(l) N-Tetradecyldiethanolamine

The reagents used were: n-tetradecylbromide (69.3 g., 0.25 mol), diethanolamine (26.3 g., 0.25 mol) and potassium carbonate (34.5, 0.25 mol). The crude product yield on recrystallisation (acetone) N-tetradecyldiethanolamine (15 g., 20%) as a white waxy solid, m.p. 31°

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1075 (C-N), 1045 (C-O), 717 ($(CH_2)_4$) $cm.^{-1}$

δ ($CDCl_3$) 0.88 (3H, t-$\underline{CH_3}$), 1.26 (24H, s, $-CH_2(\underline{CH_2})_{12}-CH_3$), 2.6 (6H, m, $\underline{CH_2}$-N), 3.20 (2H, s, $\underline{OH}$, exchanged by D_2O) 3.6 (4H, t, $\underline{CH_2}$-O) p.p.m.

(m) N-Hexadecyldiethanolamine

The reagents used were: n-hexadecylbromide (76.3 g., 0.25 mol), diethanolamine (26.3, 0.25 mol) and potassium carbonate (34.5, 0.25 mol). The crude product yielded on recrystallisation (acetone) N-hexadecyldiethanolamine (53 g., 65%) a white waxy solid, m.p.

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1380 (CH_3), 1075 (C-N), 1045 (C-O), 717 ($(CH_2)_4$) cm^{-1};

δ($CDCl_3$) 0.88 (3H, t,-$\underline{CH_3}$), 1.27 (28H, s, $CH_2(\underline{CH_2})_{14}$-$CH_3$), 2.6 (6H, m, $\underline{CH_2}$-N), 3.18 (2H, s, $\underline{OH}$, exchanged by D_2O) 3.60 (4H, t, $\underline{CH_2}$-O) p.p.m.

(n) N-Octadecyldiethanolamine

The reagents used were: n-octadecyl bromide (83.3 g., 0.25 mol), diethanolamine (26.3 g., 0.25 mol) and potassium carbonate (34.5 g., 0.25 mol). The crude product yielded on recrystallisation (acetone) N-octadecyldiethanolamine (36 g., 40%) a white waxy solid m.p. 40°

$\nu_{max.}$ (thin film) 3370 (OH), 2900 (CH), 1470 (CH_2), 1075 (C-N), 1045 (C-O), 717 ($(CH_2)_4$) cm^{-1};

δ($CDCl_3$) 0.88 (3H, t,-$\underline{CH_3}$), 1.28 (32H, s, $CH_2(\underline{CH_2})_{16}CH_3$), 2.6 (6H, m, $\underline{CH_2}$-N), 3.24 (2H, s, $\underline{OH}$, exchanged by D_2O), 3.61 (4H, t, $\underline{CH_2}$-O) p.p.m.

2. N,N-Dimethyldodecylamine

To a mixture of dodecylamine (18.5 g. 0.1 mol) and formalin solution (17.6 g. of 34% w/w formaldehyde, 0.2 mol), formic acid (10.2 g. of a 90% w/w solution, 0.2 mol) was added in small portions with stirring. The mixture was heated on a boiling water-bath for 10 hours, made alkaline with 2.5 M sodium hydroxide solution and extracted with 4 x 50 ml. of diethyl ether. The ethereal extract was dried (magnesium sulphate) and ether was removed using a rotary evaporator. The residue was distilled under reduced pressure to give N,N-dimethyldodecylamine (13.9 g., 70%) b.p. 123-125°/ 2 torr. [Lit. b.p.[163] 121-122°/5 torr].

$\nu_{max.}$ (thin film) 2900 (CH), 1468 (CH_2) 1060 (C-N), 715 ($(CH_2)_4$) cm^{-1};

Base hydrochloride m.p. 191-194° [Lit. (m.p.[163]) 171°].

3. N,N-Diethyldodecylamine

This amine was prepared from dodecyl bromide (60.3 g. 0.25 mol) and diethylamine (18.3 g., 0.25 mol) in the presence of potassium carbonate (34.5 g., 0.25 mol) using the same method as outlined for the N-alkyldiethanolamines, except that the vigorously stirred reaction mixture was heated at 70° for 24 hours. Fractionation of the crude product gave N,N-diethyldodecylamine (32 g., 53%) b.p. 122-124°/2 torr (Lit. b.p.[164] 101-104°/0.25 torr)

$\nu_{max.}$ (thin film) 2900 (CH), 1455 (CH_2), 1370 (CH_3), 1060 (C-N), 710 ($(CH_2)_4$) cm^{-1};

Base hydrochloride m.p. 122° [Lit. (m.p.[164]) 119.5°]

4. Tröger's Base[165]

A mixture of hydrochloric acid (60 ml., 0.66 mol) and formalin (70 ml. of 40% w/v formaldehyde, 0.93 mol) was added to a solution of p-toluidine (20 g., 0.19 mol) in methylated spirit (200 ml.). After standing for 24 hours, excess formaldehyde and the solvent were removed under reduced pressure to give a red-brown oil which on trituration with aqueous ammonia (0.880 s.g.; 100 ml.) gave a sticky yellow solid. This was dried at 100°, dissolved in ether (100 ml.) and the solution filtered. The filtrate was evaporated to dryness under reduced pressure and the yellow residue so obtained was twice recrystallised (petroleum spirit 80-100°) to give Tröger's Base as a pale yellow crystalline solid, m.p. 134° (Lit. m.p.[165] 130°)

$\nu_{max.}$ (KBr) 3000 (CH, aromatic), 2900 (CH, aliphatic), 892 & 826 (1,2,4-trisubst aromatic) cm^{-1};

p.m.r. δ ($CDCl_3$) 2.19 (6H, s,-CH_3), 4.28 (2H, t, N-CH_2-N) 4.4 (4H,dd, Ar-CH_2-N), 7 (6H, m, Ar) p.p.m.

5. 2,4,6-Tris(dimethylaminomethyl)phenol[166]

Formalin (28 ml. of 40% w/v solution, 0.40 mol HCHO) was added over 30 minutes to a stirred, ice-cooled solution of phenol (9.4 g., 0.1 mol) in dimethylamine solution (72 ml.; 26% w/v aqueous solution, 0.40 mol $(CH_3)_2NH$). The reaction mixture was stirred at room-temperature for 1 hour, and on a boiling water-bath for a further 2 hours. Sodium chloride (20 g.) was added and the reaction mixture was heated with stirring for a further 30 minutes. Then the two phases which had formed were allowed to separate. The organic layer was removed, diluted with acetone and dried (magnesium sulphate). After removal of the solvent, the yellow oil so obtained was distilled in vacuo to give *2,4,6-Tris (dimethylaminomethyl)phenol* (14.8 g., 56%) as a yellow oil b.p. 148-152°/0.7 torr (Lit. b.p.[166] 130-135°/1 torr)

$\nu_{max.}$ (thin film) 3000 (OH), ca. 2900 (CH), 1610 (1,2,4,6-tetrasubstituted aromatic), 1460 (CH_2), 1370 (CH_3) cm^{-1}

δ($CDCl_3$) 2.18 (6H, s, p-N($\underline{CH_3}$)$_2$), 2.21 (12H, s, o-N-($\underline{CH_3}$)$_2$), 3.28 (2H, s, p-Ar $\underline{CH_2}$N), 3.5 (4H, s, o-Ar $\underline{CH_2}$N), 6.99 (2H, s, Ar), 10.87 (1H, s, $\underline{OH}$, exchanged by D_2O) p.p.m.

6. Benzylidene-benzylamine

Calcium oxide (11.2 g. 0.2 mol) was added to a solution of benzaldehyde (10.6 g., 0.1 mol) and benzylamine (10.7 g., 0.1 mol) in methylene chloride (50 ml.) and the mixture stirred at room-temperature for 5 h. After removal of the calcium salts by filtration, methylene chloride was distilled off to leave the crude product as a pale-yellow oil (18.3 g., 94%), which was fractionated under reduced pressure to give *benzylidene-benzylamine* (12 g., 60%) b.p. 150°/0.4 torr, as a very pale yellow oil.

$\nu_{max.}$ (thin film) 3050 (CH, aromatic), 2850 (CH, aliphatic), 1640 (C=N), 740,680 (mono-subst. aromatic) cm^{-1}.

7. α-Cyanotribenzylamine[52]

Dibenzylamine (30 g., 0.15 mol) was added dropwise and with stirring to a cooled solution of freshly distilled benzaldehyde (15.9 g., 0.15 mol) in glacial acetic acid (100 ml.), followed by the dropwise addition of a solution of potassium cyanide (10 g., 0.15 mol) in water (20 ml.). A precipitate first appeared half-way through the addition of the cyanide. The crude product was filtered off at the pump and washed well with water to remove any excess cyanide. Recrystallised from methylated spirit gave α-cyanotribenzylamine (21.6 g., 45%) as white crystals, m.p. 102-103° [Literature m.p.[52] 103-104°].

$\nu_{max.}$ (KBr) 3050 (CH, aromatic), 2930, 2810 (CH,aliphatic), 1450 (CH_2), 744, 693 (mono-subst. aromatic) cm^{-1};

δ($CDCl_3$) 3.64 (4H, q, Ar-$\underline{CH_2}$-N), 4.92 (1H, s, Ar-$\underline{CH}$-CN), 7.35 (15H, m, Ar) p.p.m.

II Amine Salts

In the course of this work it has been necessary to prepare the hydroiodide, hydrochloride and methiodide salts of amines; the methods used for this purpose are as follows:-

1. Hydrochlorides

Dry hydrogen chloride, prepared by the action of conc. sulphuric acid on ammonium chloride, was passed into a solution of the base in dried ether. The precipitated salt was filtered off, dried in vacuo at room-temperature and recrystallised from a suitable solvent.

2. Hydroiodides

These were prepared by the addition of constant boiling hydriodic acid to a solution of the amine in ether. The precipitated salt was filtered off, dried and recrystallised as in 1.

3. Methiodides

Quaternization was carried out either by treating the amine with methyl iodide in the absence of solvent or in solution in methanol (heating to reflux, when necessary).

All salts were characterised by means of m.p. and assayed by estimation of the anion by the appropriate method.

For the preparation of the mono and dihydrochlorides of triethylenediamine and the hexamine hydrochlorides it was necessary to prepare a standard solution of hydrogen chloride gas in ether. This was done by absorbing the gas in ice-cooled ether (undried). The resulting solution was diluted to a known volume and its strength determined by titration against standard alkali. The appropriate volume of this acid solution was then added to the amine in order to give the required salt.

The procedure used for the preparation of an authentic specimen of N-dodecyldiethanolamine hydroiodide free from iodine was as follows. Hydrogen sulphide was bubbled through hydriodic acid (20 ml., s.g. 1.57) until the colour of iodine was just discharged. The suspension was boiled for 5 minutes to remove excess hydrogen sulphide and filtered. The filtrate was distilled immediately under nitrogen and the fraction boiling at 125°/760 torr was collected purified hydroiodic acid (3 g., 0.013 mol) was immediately added dropwise to a solution of C12DEA (2.73 g., 0.01 mol)in ether (5 ml.) at -10°. The mixture was kept at this temperature for 16 hours and then filtered. Recrystallisation of the residue from isopropanol yielded the hydroiodide (1.2 g., 30%) as a pale yellow solid (m.p. 57°).

C. THE INDUSTRIAL PROCEDURE

I Reaction of Amines with Iodine

The commercial disinfectant is prepared by the reaction of 'Ethomeen C 12' with iodine in the molar ratio of 2:1, respectively. The amine is preheated to 70°C and solid iodine is added to it at such a rate that the temperature of the vigorously stirred reaction mixture rises to ca. 140°C. Stirring is continued after the addition of iodine until the temperature of the reaction mixture drops to 100°C.

This reaction was carried out in the laboratory using pure amines. In some cases, for example when the lower *N*-alkyldiethanolamines were used, it became necessary to heat the reaction mixture to a higher temperature in order to obtain iodine free products. Some typical reaction products are described below

Amine	Reaction Temperature	Physical Nature of Product
'Ethomeen C 12'	140°C	brown, extremely viscous liquid with a characteristic odour
C12DEA	140°C	brown, slightly sticky solid with very slight odour
C2DEA	160°C	sticky brown oil
C3DEA	210°C	hard brown black solid, very hygroscopic
Triethanolamine	120°C	brown solid

In each case the main product was the corresponding amine hydroiodide, the isolation and characterisation of which is illustrated here for C12DEA.H1 and triethanolamine hydroiodide.

1. C12DEA.HI

The reaction mixture (7 g.) was dissolved in boiling carbon tetrachloride (50 ml.) and the solution cooled to -10°. After standing for 16 hours at this temperature, the precipitated solid

was filtered off, washed with cold carbon tetrachloride and dried in vacuo at room-temperature to constant weight. The product (4.25 g., 69%) was a yellow-brown solid, m.p. 55-57°, identical (m.p., i.r. and p.m.r. spectra) with an authentic specimen of N-dodecyldiethanolamine hydroiodide, C12DEA.Hl (mixed m.p. 57°); $\nu_{max.}$ (KBr) 3360 (OH), 2900 (CH), 2720 ($R_3\overset{\oplus}{N}H$), 1470 (CH_2), 1370 (CH_3), 1070 (C-O), 723 ($(CH_2)_4$) cm^{-1};
$\delta(CDCl_3)$ 0.88 (3H, t,-$\underline{CH_3}$), 1.27 (20H, s, $CH_2(\underline{CH_2})_{10}CH_3$), 3.55 (6H, m, $\underline{CH_2}$-$\overset{+}{N}$), 4.06 (4H, m, $\underline{CH_2}$-O), 5.11 (3H, s, $\underline{O-H}$ and $\overset{+}{N}$-$\underline{H}$ exchanged by D_2O) p.p.m.

2. Triethanolamine hydroiodide

The crude reaction mixture (53.2 g.) was triturated with methanol and filtered the solid was washed with methanol, dried in vacuo at room-temperature, and gave a light brown crystalline solid (31.2 g., 59%), m.p. 164-167°, identical (m.p., analysis, i.r. and p.m.r. spectra) to an authentic specimen of triethanolamine hydroiodide, $N(CH_2CH_2OH)_3$.Hl (mixed m.p. 166°),
$\nu_{max.}$ (KBr) 3360 (OH), 3160 ($\overset{\oplus}{N}H$), 2950-2910 (CH), 1465 (CH_2) cm^{-1};
δ(DMSO,d-6)3.32 (6H, t, $\underline{CH_2}$-$\overset{\oplus}{N}$), 3.76 (6H, t, $\underline{CH_2}$-O), 5.25 (4H, s,- very broad, $\underline{OH}$ and $\underline{\overset{\oplus}{N}H}$) p.p.m.

Found: C, 26,16; H,5.60; N, 5.06; I, 45.85; $C_6H_{15}O_3N$.Hl
required C, 26.10; H, 5.48; N, 5.07, I, 45.96%

II Determination of Biocidal Activity

1. The Kelsey-Sykes method[167]

The Kelsey-Sykes procedure was devised for the evaluation of disinfectants and was intended primarily for use in hospitals, but was considered readily adaptable for other applications in the domestic and industrial field.

The modification used by Glasby Pharmaceuticals of the recommended procedure is as follows: 3 ml. of the test solution is added to 1 ml. of bacterial suspension (10^9 cells of Pseudomonas aeruginosa in 2% yeast suspension) and the mixture shaken gently. After 8 minutes 5 drops are placed on to each of 3 nutrient plates. (First step) 2 minutes later (10 minutes after the first inoculation) a further 1 ml. of bacterial suspension is added to the disinfectant mixture. 8 minutes after mixing it is subcultured as before (Second step) 2 minutes later (20 minutes after the first inoculation) the process is repeated (Third step). After incubation at 37°C for 24 hours, the plates are examined for the presence or absence of growth. If none of the plates exhibit growth then the test solution is said to have gone '3 steps' and is a better disinfectant than a solution for which the plates from the first step show no growth but the remainder exhibit growth. The latter solution is said to have undergone 1 step. Where one or two plates of a particular step do not exhibit growth, then the results of that step are expressed as .3 or .6 steps respectively. The higher the number of steps which do not exhibit growth, the better the disinfectant properties of the test solution.

2. Comparison of the Biocidal Activity of C12DEA.Hl to that of the Oxidation Products of C12DEA

A portion (5 g.) of the product obtained by the action of iodine on C12DEA (p.182) was dissolved in the minimum volume of boiling carbon tetrachloride (30 ml.). After cooling to -10° the suspension was filtered; the residue was washed with cold carbon tetrachloride and dried in vacuo at room temperature to give 3.47 g. of C12DEA.Hl (Product A).

The combined filtrate and washings were evaporated to dryness on a rotary evaporator and then dried to constant weight (1.37 g.) in vacuo. (Product B). Total yield 4.84 g., 97% recovery. The two products (A and B) were tested for biocidal activity on a weight basis (see Table 27) by the Kelsey-Sykes method.

Similarly, another portion (10 g.) of the product was crystallised from isopropanol (20 ml.). The solution was kept at -15° for 5 days and the precipitated solid was filtered off, washed with cold isopropanol and dried to constant weight in vacuo to give 2.45 g. of C12DEA.Hl (Product C). The combined washings and filtrate were made up to a known volume and aliquots of this solution were evaporated to dryness (Product D). The total amount of residue from the mother-liquor was 7.38 g. Total yield =9.83 g., 98% recovery. The two products (C and D) were also compared for biocidal activity on a weight basis (See Table 29) using the Kelsey-Sykes method.

TABLE 29 BIOCIDAL ACTIVITY OF C12DEA.Hl AND PRODUCTS ISOLATED FROM THE REACTION OF C12DEA WITH IODINE

Compound	Biocidal Activity ('Steps' in Kelsey-Sykes Test)	
	0.01 M (4 g./l.)	0.015 M (6 g./l)
Crude C12DEA/12 product	2.6	3
Product A	2.3	3
Product B	1.6	3
Product C	2.3	3
Product D	1.6	2.3
Control	1.6	
Authentic C12DEA.Hl (I_2 free)	2.3	2.6

3. The minimum inhibitory concentration (M.I.C.) method[29]

Solutions of the test compounds were prepared as the acetate salts in water, sterilised by filtration and added aseptically to nutrient broth solutions which had previously been sterilized by autoclaving. The pH of all dosed broths prepared in this way was 6.5 ± 0.1. Inoculation of the broths was made from 16 hour broth cultures of E.coli NCIB 8277 to inoculum levels of 2×10^7 cells ml^{-1}, determined by performing total counts on the freshly inoculate broths with a Neubauer counting chamber. The presence or absence of growth after 24 hours incubation at 37°C was determined by visual assessing the turbidity of the cultures. In those cases (C5-, C6- and C7DEA) where addition of the test compound caused immediate turbidity in the nutrient broth, growth was assessed by performing total counts as above. For each test, a check was made of the visual assessment by streaking a loopful of medium from tubes showing no apparent growth onto nutrient agar plates, and examining for growth after 24 hours incubation at 37°C. The results obtained by this method for the series C1DEA to C18DEA are listed in Table 2 (p. 33).

4. Determination of the Critical Micelle Concentration (C.M.C.) of C12DEA at pH 4.6

(a) The dye titration method[6]

The colour of a dyestuff in a solution of a surface active agent depends on whether or not this solution contains micelles. Thus a dyestuff may be employed for the determination of the C.M.C. of a surfactant like, for example *N*-dodecyldiethanolammonium salts. Harkins[7] suggested several dyes suitable for the determination of the C.M.C. of *N*-dodecylammonium chloride, but none of these proved suitable for use with C12DEA. For this reason, fifteen other anionic dyes were screened for reversible colour change on diluting a micellar solution to a concentration below C.M.C. Since all the dyes tested are pH indicators, all the tests were carried out in acetate buffer (pH 4.6) as the solvent. The C.M.C. of C12DEA in acetate buffer, was determined by titrating buffered micellar solutions of C12DEA containing one of the suitable dyes, with a solution of the same concentration with respect to buffer and dye but not containing C12DEA. This procedure prevented colour changes due to dilution of the dye and thus the concentration of C12DEA at the end point, as indicated by the appropriate colour change, corresponded to the C.M.C.

With bromocresol purple, C.M.C. = 1.4 mM

With dichlorofluoroscein, C.M.C. = 1.6 mM

(b) The capillary rise method

The capillary rise at 25°C of a solution of C12DEA was determined by clamping a 10 µl. 'Microcap' disposable pipette (Drummond) vertically, with the lower end immersed 2 mm. below the surface of the solution. Five minutes were allowed for the system to equilibrate and then the capillary rise was measured using a cathetometer. This procedure was repeated over a range of concentrations of C12DEA in acetate buffer using a new 'Microcap' each time. Typical values for the capillary rise obtained in this manner were 23 ± 0.2 mm. for distilled water and 19 ± 0.2 mm. for a 10 mM solution of C12DEA in acetate buffer at pH 4.6. The capillary rise (in mm.) was plotted against the concentration of the C12DEA solution (in mM). The C.M.C. value, read from the point of intersection of the two linear portions of the graph was 1.6 mM.

D. OXIDATION OF AMINES BY IODINE

I. Oxidation of Amines by Iodine in Aqueous Solution

1. N-Ethyldiethanolamine

A solution of C2DEA (2.66 g., 0.02 mol) in water (50 ml.) was placed in a 250 ml. 3-necked flask fitted with a dropping funnel, nitrogen inlet and a condenser connected to a trap containing a solution of 2,4-dinitro-phenylhydrazine sulphate in methanol. The apparatus was flushed with nitrogen, the amine solution heated to reflux and a solution of iodine (2.54 g., 0.01 mol) in aqueous potassium iodide (3.32 g., 0.02 mol; in 50 ml. water) was then addred dropwise during 30 minutes. The colour of the iodine solution was discharged. A yellow solid precipitated in the reaction flask and an orange precipitate appeared in the 2,4-DNP trap. The yellow solid, on recrystallisation (methylated spirit), yielded iodoform (0.2 g.), m.p. 120° (lit. m.p.[168] 120°). The material from the trap yielded on recrystallisation (ethyl acetate) a crystalline solid (50 mg.) m.p. 146°, undepressed by admixture with an authentic specimen of the 2,4-DNP derivative of acetaldehyde (Lit. m.p.[168] 147°).

2. N,N-Dimethylbenzylamine

A mixture of N,N-dimethylbenzylamine (2.7 g., 0.02 mol), iodine (5.08 g., 0.02 mol), potassium iodide (3.32 g., 0.02 mol) and sodium bicarbonate (16.8 g., 0.2 mol) in 100 ml. of water was heated at reflux for 20 minutes. After acidification by the cautious dropwise addition of concentrated hydrochloric acid, the reaction mixture was steam distilled. The distillate was extracted with chloroform (4 X 25 ml.) and the organic layer dried (magnesium sulphate). Removal of the solvent under reduced pressure yielded an oil (0.55 g., 27%). Comparative g.l.c. (5% SE 30, R_t = 1 min.) proved this to be pure benzaldehyde. This conclusion was substantiated further in infrared spectroscopy

ν_{max} (thin film) 3050 (CH, aromatic), 2810, 2725 (CH, aldehydic), 1690 (C=O), 740, 680 (mono-subst. aromatic) cm^{-1};

and by preparation of a 2,4-DNP derivative, m.p. 235° (Lit. m.p.[168] 237°) undepressed by admixture with an authentic specimen.

3. 2,4,6-Tris(dimethylaminoethyl)phenol

Sodium bicarbonate (10 g., 0.13 mol) was added to a stirred, cooled solution of iodine (7.62 g., 0.03 mol) and potassium iodide (10 g., 0.06 mol) in water (100 ml.). When the salts had dissolved, the phenol (2.65 g., 0.01 mol) was added, and after stirring in the cold for 15 minutes, the reaction mixture was refluxed for 25 minutes. The colour of the iodine was discharged and a dark oil formed. The reaction mixture was allowed to stand at room temperature for one hour and was then acidified with hydrochloric acid (1:1 30 ml.), stirred for a further one hour and extracted with chloroform (3 x 100 ml.). The combined extracts were dried (magnesium sulphate) and the solvent removed to give a black oil (0.2 g.)

ν_{max} (thin film) 3200, broad (OH), 1640 (C=O) cm^{-1}

A solution of the oil in methanol was filtered into an excess of a methanolic solution of 2,4-dinitrophenylhydrazone sulphate. The precipitate was recrystallised (dimethylsulphoxide) to give a red solid, m.p. 271°

ν_{max} (KBr) 3400 (OH), 3290 (NH), 3100 (CH, aromatic), 1580 (C=N) cm^{-1}

4. Tribenzylamine and related amines

General

The reactions described in this section gave as products, mixtures containing some of the following: benzaldehyde, tribenzylamine, dibenzylamine, benzylamine and benzylidene-benzylamine together with some unidentified minor products. In order to avoid unnecessary repetition, the general methods used for the separation and identification of these products in each case are described below.

The reaction mixture or the product after removal of the solvent was treated with an excess of 2.5 M sodium hydroxide solution and the resultant suspension extracted with at least 3 x 25 ml. portions of chloroform. After drying (calcium sulphate) and removal of the solvent under reduced pressure, the residue was made up to a known volume with chloroform and subjected to qualitative and quantitative analysis by g.l.c. using SE30 or SE52 columns. In order to effect complete separation of the components temperature programmed g.l.c. was used. The initial temperature of the column oven was 120° and 3 minutes after injection it was increased at the rate of 48° per minute to 250°. The retention times on an SE30 column were: benzaldehyde 1, benzylamine 1.5 , benzylidene-benzylamine 6 , dibenzylamine 6 and tribenzylamine 9 minutes.

The SE30 and SE52 columns did not effect the separation of dibenzylamine from benzylidene-benzylamine, and, thus for this purpose a sodium hydroxide treated Chromosorb column coated with Ucon oil was used (R_t dibenzylamine = 3 , R_t benzylidene-benzylamine = 3.5 minutes). A complete chromatographic investigation of the products was accomplished using both the SE and the treated Chromosorb columns. This became necessary because dibenzylamine andbenzaldehyde could not be separated on a sodium hydroxide treated Chromosorb column.

A quantitative determination of the relative amounts of the components of the product mixture was made by comparing peak areas with those obtained using standard solutions of authentic samples examined under the same conditions.

The separation and characterisation of the products was accomplished as follows. Benzaldehyde was removed by extraction with ether or by steam-distillation from acid solution. In the latter case, the distillate was extracted with chloroform; and in both cases the organic extract was dried (magnesium sulphate), and the solvent removed to give an oil which was identified by comparison of its infrared spectrum, and melting point of its DNP derivative with those of an authentic sample.

Basification of the aqueous solution, followed by extraction with chloroform as above, gave an oil which on adding absolute ethanol deposited crystals of tribenzylamine. This was identified by comparison of melting-point and infrared spectrum with those of an authentic specimen. Evaporation of the ethanolic solution gave an oil, an ethereal solution of which was treated with gaseous hydrogen chloride and gave an off-white precipitate. After several recrystallisations from methanol this gave a white crystalline solid identified, by means of its melting point and infrared spectrum, as dibenzylamine hydrochloride.

In some cases the products were isolated by preparative g.l.c. using an SE30 column. The products were identified by infrared spectroscopy and the preparation of suitable derivatives.

(a) Tribenzylamine

A suspension of tribenzylamine (5.74 g., 0.02 mol) and iodine (2.5 g., 0.01 mol) was refluxed for 30 minutes, at the end of which time a colourless solution was obtained. On cooling a mass of pale yellow crystals formed. The reaction mixture was basified with 2.5 M aqueous sodium hydroxide (40 ml.,0.1 mol), extracted with chloroform (3 x 100 ml.) and the extract worked-up as described above. This gave an oil (5.6 g.) which was examined by g.l.c. and was shown to be a mixture of benzaldehyde (0.006 mol), dibenzylamine (0.008 mol) and tribenzylamine (0.011 mol). The products were separated and characterised as described above.

In subsequent work it was found that a solution of potassium triiodide (0.5 mol; 12.7 g. iodine and 23 g. potassium iodide in 100 ml. of water) was equally effective as an oxidant.

(b) Dibenzylamine

A mixture of dibenzylamine (3.94 g., 0.02 mol), iodine (2.54 g. 0.01 mol) and potassium iodide (3.32 g., 0.02 mol) in water (100 ml.) was heated to reflux for 30 minutes. Basification and work-up in the usual manner gave an oil, which was shown by g.l.c. to be an almost equimolar mixture of benzylidene-benzylamine (0.009 mol) and dibenzylamine (0.010 mol).

(c) Benzylamine

A mixture of benzylamine (2.14 g., 0.02 mol), iodine (2.54 g., 0.01 mol) and potassium iodide (3.32 g., 0.02 mol) in water (100 ml.) was heated under reflux for 30 minutes. Work up yielded an oil which was shown by g.l.c. to be benzylidene-benzylamine (0.008 mol). This assignment was established by comparison of its infrared spectrum with that of an authentic sample.

(d) Tribenzylamine (in the presence of hexamine)

A vigorously stirred mixture of tribenzylamine (2.87 g., 0.01 mol) iodine (7.62 g., 0.03 mol), potassium iodide (15 g.) and hexamine (14.0 g., 0.1 mol) in water (100 ml.) was refluxed for 1 hour. When cold the reaction mixture was treated with 2.5 M aqueous sodium hydroxide (100 ml., 0.25 mol) and extracted with chloroform (3 x 100 ml.). After drying (magnesium sulphate) and removal of the solvent, a brown oil was obtained (3.1 g.) which was shown by g.l.c. to consist mainly of benzaldehyde. Distillation at atmospheric pressure yielded benzaldehyde (2.7 g. 85%), characterised in infrared spectroscopy and preparation of the 2,4-DNP derivative.

(e) Tribenzylamine (in the presence of calcium carbonate)

The reaction described in (d) above was repeated using calcium carbonate (10 g., 0.1 mol) instead of hexamine. The reaction mixture was vigorously stirred during 1 hour reflux and on work-up yielded benzaldehyde (2.3 g., 72%).

(f) Tribenzylamine (in the presence of sodium bicarbonate)

The reaction was carried out in the presence of sodium bicarbonate (16.8 g., 0.2 mol). The reaction mixture was stirred at room-temperature for 1 hour* and when worked up in the normal manner gave benzaldehyde (1.85 g., 53%) together with recovered tribenzylamine (0.52 g., 0.0018 mol, 18%).

* The reaction mixture was not refluxed in order to ensure that bicarbonate is not converted to carbonate, which is known to cause conversion of iodine to iodate.

5. Oxidation of Tribenzylamine salts with iodine generated by $K1O_3/K1$

(a) Tribenzylamine hydroiodide

A suspension of tribenzylamine hydroiodide (1.245 g., 0.003 mol) in water (50 ml.) was refluxed for 30 minutes during the dropwise addition of a solution of potassium iodate (0.214 g. 0.001 mol) in water (25 ml.). After cooling, and basification with 2.5 M sodium hydroxide solution (25 ml.), the reaction mixture was extracted with chloroform (4 x 25 ml.). The extract was dried (K_2CO_3) and the solvent removed to give an oil (0.62 g.), which was examined both by g.l.c. (SE52 and Ucon Oil on Chromosorb coated with sodium hydroxide) and t.l.c. (silicagel/ benzene:acetone, 90:10). The product was thus shown to be an approximately equimolar mixture of tribenzylamine (0.0012 mol), benzylidene-benzylamine (0.0011 mol), and benzaldehyde (0.0008 mol.)

(b) Tribenzylamine hydrochloride

A suspension of tribenzylamine hydrochloride (1.57 g., 0.005 mol) in a solution of potassium iodide (0.83 g., 0.005 mol) in water (50 ml.) was heated to reflux whilst a solution of potassium iodate (1.07 g., 0.005 mol), in water (50 ml.) was added in small portions over a period of 10 minutes. After a further 25 minutes heating the reaction was worked up as above. Chromatography showed that the product (1.45 g.) is an approximately equimolar mixture of benzylidene-benzylamine (0.005 mol) and benzaldehyde (0.004 mol.). This was confirmed by subjecting the product to preparative g.l.c. and examining the pure components by infrared spectroscopy.

(c) Tribenzylamine hydrochloride (using a small amount of potassium iodide)

Potassium iodide (0.083 g., 0.0005 mol) was added to a suspension of tribenzylamine (2.87 g., 0.01 mol) in 1M hydrochloric acid (10 ml., 0.01 mol) and water (75 ml.). The mixture was refluxed and stirred whilst a solution of potassium iodate (2.14 g. 0.01 mol) in water (75 ml.) was added over a period of two hours. After heating for a further three hours, the reaction was worked up as before to give an oil (2.74 g.) which on chromatographic examination was shown to be an approximately 2:1 mixture of benzylidene-benzylamine (0.011 mol) and benzaldehyde (0.0065 mol).

II. Oxidation of Amines by Iodine in Isopropanol Solution

General

Amines were oxidised by iodine in isopropanol solution according to the same general procedure described in detail below (II. 1) for N-ethyldiethanolamine. All the reactions were carried out using a molar ratio of amine:iodine of 2:1. The general method employed was as follows:-

a solution of 0.1 mole of the amine in isopropanol (50 ml.) was heated to reflux and a solution of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) was added dropwise over a period of six to twenty four hours. After further refluxing, the solvent was distilled off to give a residue which was a mixture of hydroiodide salts. This was treated with sodium hydroxide and the amines so liberated extracted with methylene chloride. The extract was dried and the solvent removed to give a mixture of amines which was examined by t.l.c. and g.l.c., and, where possible, the major oxidation product was isolated by a suitable method (see below). The latter product was characterised by high-resolution mass-spectrometry, p.m.r., and infrared spectroscopy, and, where possible, by the determination of its equivalent weight and preparation of a derivative.

Attempts to improve the yield of oxidation product by carrying out the reaction in the presence of a competing base are also described in this section.

1. N-Ethyldiethanolamine (C2DEA)

(a) To a refluxing solution of C2DEA (13.3 g., 0.1 mol) in isopropanol (50 ml.), a solution of iodine (12.7 g., 0.05 mol) in the same solvent (350 ml.) was added dropwise over a period of 4 hours. Heating was continued for a further 2 hours. The reaction mixture was then evaporated to dryness and the residual solid dissolved in 2.5 M sodium hydroxide solution (50 ml.; 0.125 mol). The aqueous solution was extracted continuously for 168 hours with methylene chloride using a cascade type extractor. The organic phase was dried over potassium carbonate, and the solvent evaporated under reduced pressure to give an oil (10.0 g.), which solidified on cooling.

An alternative procedure used in this preparation consisted of placing the solid iodine in the body of the soxhlet extractor and allowing refluxing isopropanol (200 ml.) to condense and drip onto the iodine. The resulting solution of iodine was allowed to enter the reaction flask at such a rate that all the iodine was added over a period of 5 hours. The reaction was then worked up as before.

In both cases, examination of the product by t.l.c. (silica gel/methylated spirit) showed that it consisted largely of C2DEA with one major and two minor oxidation products. This was confirmed by g.l.c. (5% silicone oil, 170°) which showed the components were present in the following proportions, 76% (C2DEA), 14%, 6% and 4% respectively. The largest component was isolated by preparative g.l.c. and identified as recovered starting material by comparison of infrared spectra. Excessive tailing on the column precluded the isolation of any of the oxidation products by g.l.c. This was accomplished by dry-column chromatography. The amine mixture was chromatographed in 1 g. portions on columns of silica gel (Merck) using industrial methylated spirit as the mobile phase. The column was cut into 4 cm. fractions and each of these was eluted with methanol (4 x 20 ml.). The resulting solutions were monitored by t.l.c. and the required fractions (i.e. those containing the major oxidation product) were bulked and the solvent removed to give an oil. The bulked residue from all the columns was subjected to further dry-column chromatography until the required component was obtained pure. This was then dissolved in chloroform and the solution allowed to stand for 24 hours to allow silica gel which was eluted with the oxidation product to precipitate. After filtration the solvent was removed under reduced pressure to give a yellow-brown oil (500 mg.), identified as 2-isopropoxy-4-(2'-hydroxyethyl)morpholine. The purity of the product was not less than 98% as indicated by t.l.c. and g.l.c. Identification of the product was based on the following evidence. Equivalent weight by titration against standard perchloric acid = 192 (calculated for $C_9H_{19}NO_3$, 189);

ν_{max} (thin film) 3400 (OH), 2900 (CH, aliphatic), 1455 (CH_2), 1380, 1367 ($CH(CH_3)_2$), 1130 (C-O-C), 1095 (C-N), 1055 (C-O) cm^{-1}

δ ($CDCl_3$) 1.18 (6H, dd, $OCH(C\underline{H}_3)_2$), 2.5 (6H, m, $\underline{C}H_2$-N), 3.8 (5H, m, $C\underline{H}$-O), 4.45 (1H, s, $O\underline{H}$, exchanged by D_2O), 4.70 (1H, dd, O-$C\underline{H}$-O) p.p.m.;

$M^{\oplus}$ 189.1372 (calc. for $C_9H_{19}NO_3$; M, 189.1365); $^m/e$ 189 ($M^{\oplus}$), 159 ($M^{\oplus} - CH_2O$), 158 ($M^{\oplus} - CH_2OH$, base peak), 146 ($M^{\oplus}$ - Pr), 130 ($M^{\oplus}$- OPr), 87, 73, 57, 42 and 28.

Treatment of the product (0.200 g.) with benzoylchloride (excess) in chloroform gave a benzoate hydrochloride (0.25 g., 72%) as white crystals (isopropanol), m.p. 167°

δ ($CDCl_3$) 1.18 (6H, t, $OCH(C\underline{H}_3)_2$), 3.1 and 3.5 (7H[1H + 6H]. very broad singlet and m, $\underline{H}\overset{\oplus}{N}$ and $C\underline{H}_2$ -$\overset{\oplus}{N}$), 4.1 (3H, m, $C\underline{H}$-O), 4.85 (2H, t, $C\underline{H}_2$-O-CO), 5.20 (1H,m, O-$C\underline{H}$-O), 7.75 (5H, m, Ar) p.p.m.

(b) N-Ethyldiethanolamine (in the presence of calcium carbonate)

A solution of iodine 12.7 g., 0.05 mol) in isopropanol (350 ml.) was added dropwise over a period of 6 hours to a vigorously stirred suspension of calcium carbonate (10 g., 0.1 mol) in a refluxing solution of C2DEA (3.3 g., 0.025 mol) in isopropanol (100 ml.). After refluxing for a further 2 hours, the reaction mixture was cooled, filtered and the solvent removed on a rotary evaporator. The residual solid was treated with a solution of sodium thiosulphate to remove unreacted iodine, and the resulting solution was made alkaline by the addition of sodium hydroxide pellets. After continuous extraction for 96 hours with methylene chloride, the organic phase was dried (potassium carbonate) and the solvent removed to give an oil (2.3 g.) which on examination by g.l.c. (5% silicone oil) and by t.l.c. (silica gel-methylated spirit)was found to consist of unreacted starting material (70%).

(c) N-Ethyldiethanolamine (in the presence of hexamine)

Hexamine (14 g., 0.1 mol) was added to a solution of C2DEA (3.3 g., 0.025 mol) in isopropanol (50 ml.) Iodine (12.7 g. 0.05 mol) in isopropanol (350 ml.) was added to the stirred reaction mixture over 15 minutes. The reaction mixture was then heated at reflux for 8 hours. Work-up as described in the previous experiment led to the recovery of starting material (2.5g.).

2. 2-(Diethylamino)ethanol

(a) Treatment of 2-(diethylamino)ethanol (11.7 g., 0.1 mol) with a solution of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) over a period of 5 h. followed by 1 h. further reflux gave a mixture of hydroiodide salts (24 g.). After basification with a solution of sodium hydroxide (20 g.) in water (60 ml.) and extraction with methylene chloride (5 x 50 ml.), drying (potassium carbonate) and removal of the solvent, an oil (9.6 g.) was obtained. This was shown by g.l.c. (silicone oil) and t.l.c. (silica gel/methylated spirit) to contain 3 oxidation products, the major of which was isolated by preparative g.l.c.

(silicone oil). This was a colourless liquid (90 mg.) identified as 2-isopropoxy-4-ethylmorpholine on the basis of the following evidence;

ν_{max} (thin film) 2900 (CH), 1475 (CH_2), 1385 (CH_3), 1170-1045 (C-O-C, C-N and C-O) cm^{-1};

δ ($CDCl_3$) 1.2 (9H, m, C$\underline{H}_3$), 2.5* (6H, m, C$\underline{H}_2$-N), 3.9 (3H, m, C$\underline{H}$-O), 4.75 (1H, dd, O-C$\underline{H}$-O) p.p.m.

$M^{\oplus}$, 173·1412 (calculated for $C_9H_{19}NO_2$; m 173·1416), $^m/e$ 173 ($M^{\oplus}$), 158 ($M^{\oplus}-CH_3$), 130 ($M^{\oplus}$-Pr), 114 ($M^{\oplus}$ - OPr), 73, 57 (base peak), 42,28.

* This absorption showed marked downfield shift on addition of trifluoroacetic acid.

(b) 2-(Diethylamino)ethanol (in the presence of hexamine)

A suspension of hexamine (14.0 g., 0.1 mol) in isopropanol (100 ml.) was added to iodine (2.54 g., 0.01 mol) and diethylaminoethanol (1.17 g., 0.01 mol) in isopropanol (75 ml.). The vigorously stirred suspension was refluxed for 2 hours and the resulting clear solution was distilled at reduced pressure. The residue was treated with 2.5 M aqueous sodium hydroxide (20 ml., 0.05 mol), the solution was diluted with water (40 ml.) and was extracted with methylene chloride (3 x 100 ml.). After drying (potassium carbonate) and removal of the solvent, a residue was obtained (2.5 g.) which was shown by g.l.c. (silicone oil) and t.l.c. (silica gel - methylated spirit) to be a mixture of hexamine and diethylaminoethanol.

3. N-Propyldiethanolamine

Treatment of C3DEA (14.7 g., 0.1 mol) with a solution of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) over a period of 6 hours, gave, after a total reaction time of 8 hours, 25 g. of hydroiodide salts. After basification with 2.5 M aqueous sodium hydroxide (50 ml., 0.125 mol), continuous extraction with methylene chloride for 168 hours, drying (potassium carbonate) and removal of the solvent yielded an oil (11 g.). Chromatographic examination of this product (g.l.c. - silicone oil; t.l.c. - silica gel/methylated spirit) shoed the presence of three oxidation products. The major product was isolated by dry-column chromatography (silica gel/industrial methylated spirit) followed by preparative g.l.c. (silicone oil) to give an oil which on trituration with chloroform yielded a pink sticky solid (10 mg.), which was identified as 2-methyl-3-isopropoxy-4-(2'-hydroxyethyl)-morpholine on the basis of the following evidence:

ν_{max} (thin film) 3400 (OH), 2900 (CH), 1460 (CH_2),1380 (CH_3), 1100, very broad (N-C-O, C-N, C-O, C-O-C) cm^{-1}

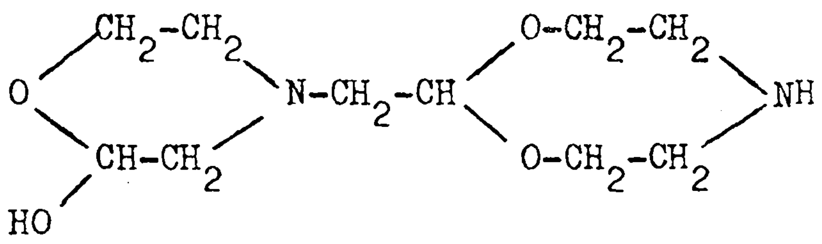
δ ($CDCl_3$) 1.2 (9H, m, $C\underline{H}_3$), 2.5 (5H, m, $C\underline{H}$-N), 3.51 (1H, s, $\underline{OH}$, exchanged by D_2O), ca. 4 (6H, m, $\underline{CH}$-O) p.p.m.

$M^{\oplus}$, 203.1517 (calculated for $C_{10}H_2$,NO_3,m, 203.1521)

m/$_e$ 203 ($M^{\oplus}$), 172 ($M^{\oplus}$- CH_2OH), 160 ($M^{\oplus}$- Pr), 144 ($M^{\oplus}$- OPr), 100, 71, 63, 56 (Base peak), 45, 30, 28

4. Triethanolamine

A solution of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) was added dropwise over a period of 6 hours to a refluxing solution of triethanolamine (14.9 g., 0.1 mol) in isopropanol (50 ml.) After refluxing for a further 1 hour, the reaction mixture was cooled in ice and the yellow crystalline solid which separated was filtered off and dried in vacuo (16.2 g.). This was identical (m.p. and mixed m.p.) with authentic triethanolamine hydroiodide. The filtrate was evaporated to dryness to give a mixture of hydroiodide salts (11 g.). This residue was treated with sodium hydroxide (7 g.) in water (50 ml.) and the resulting solution was extracted continuously for 112 hours with methylene chloride. The extract was dried (potassium carbonate) and after removal of the solvent gave an oil (1.7 g.) which was shown by t.l.c. (silica gel - methylated spirit) to consist of 3 oxidation products, the major of which was isolated by repetitative dry column chromatography. Threatment of the sticky oil so obtained with chloroform gave a buff solid which is tentatively identified as



from its mass spectrum;

$M^{\oplus}$, 232.1417 (Calculated for $C_{10}H_{20}N_2O_4$; M, 232.1423)

$^m/e$; 232 ($M^{\oplus}$), 217, 201, 188, <u>174</u>, 158, 146, 130, 129, <u>118</u> (base peak, $^m/2e$), 114, 113, 101, 100, 98, 86, 74, <u>56</u>, 45, 42, 28.

5. N-Phenyldiethanolamine

A solution of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) was added to a refluxing solution of the amine (18.1 g., 0.1 mol) in isopropanol, over a period of 6 hours. After a further 1 hour at reflux, the solvent was removed under reduced pressure to give a residue (23 g.) which was rendered basic by the addition of a solution of sodium hydroxide (7 g., 0.18 mol) in water (50 ml.). Extraction of this solution with methylene-chloride (3 x 100 ml.) gave, after drying (potassium carbonate) and removal of the solvent, an oil (18.5 g.). Dry-column chromatography (silica gel-- ether) was used to isolate the major of the 5 oxidation products indicated by t.l.c. This was identified as N-(2'hydroxyethyl)-N-iodoaniline from the following evidence:-

ν_{max} (thin film) 3400 (NH), 3040 (CH, aromatic), 2900 (CH, aliphatic), 1920, (1750), 1720, 1660 (mono-subst. aromatic), 750, 690 (mono subs. aromatic) cm^{-1}

δ ($CDCl_3$) 2.6 (1 H, s, broad, $-\underline{OH}$; exchanged by D_2O), 3.25 (2H, m, $-\underline{CH}_2-O$) 3.75 (2H, m, $N-\underline{CH}_2$), 7.0 (5H, m, $\underline{Ar}$) p.p.m.

$M^{\oplus}$, 262.9815 (Calculated for $C_8H_{10}NOl$; M, 262.9809)

m/$_e$; 262 (M^+), 232 (base peak, $M^{\oplus}-CH_2OH$), 148, 137 ($MH^{\oplus}- I$) 106 ($MH^{\oplus}-I-CH_2OH$), 91 ($C_6H_5N^{\oplus}$), 77 ($C_6H_5^{\oplus}$).

6. Triethylamine

Triethylamine (10.1 g., 0.1 mol) in isopropanol (50 ml.) was oxidised by the addition of iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) over a period of 6 hours in the usual manner. After refluxing for a total of 23 hours, the solvent was removed under reduced pressure leaving a black residue (25.1 g.) which on treatment with an aqueous solution of sodium thiosulphate (5 g., 0.02 mol), followed by basification with a solution of sodium hydroxide (7 g., 0.18 mol) gave a black solution. Extraction of this solution with methylene chloride (3 x 100 ml.) gave, after drying (potassium carbonate) and removal of the solvent, a black oil (3 g.). Chromatographic examination (by g.l.c. - silicone oil, and t.l.c. - silica gel/methylated spirit) indicated the presence of 4 oxidation products. The major component was isolated (20 mg.) by a combination of preparative g.l.c. and repetitive dry column chromatography (silica gel-methylated spirit) and was identified as 2-(diethylamino)-acetaldehyde-di-isopropyl acetal from the following evidence:

δ ($CDCl_3$) 1.2 (18H, m, $\underline{CH}_3$), 2.65 (6H, $\underline{m}$, $\underline{CH}_2-N$), 3.9 (2H, m, $O-\underline{CH}\ (CH_3)_2$), 4.70 (1H, t, $O-\underline{CH}-O$) p.p.m.

$M^{\oplus}$, 217.2045 (Calculated for $C_{12}H_{27}NO_2$; M, 217.2042)
$^{m}/e$ 217 ($M^{\oplus}$), 202 ($M^{\oplus}-CH_3$), 159 ($M^{\oplus}$-OPr), 131 ($M^{\oplus}$-2Pr),
86 (Base peak, $Et_2\overset{\oplus}{N} = CH_2$), 43, 28.

7. <u>N,N-Diethylaniline</u>

N,N-Diethylaniline was purified according to the method described by Vogel[169], which entails refluxing the base (50 g.) with half its weight of acetic anhydride for four hours. Distillation of the mixture yielded the pure amine (b.p. 214-217°)

Pure N,N-diethylaniline (14.9 g., 0.1 mol) in isopropanol (50 ml.) was treated with iodine (12.7 g., 0.05 mol) in isopropanol (350 ml.) over a period of 6 hours. After refluxing for a further 16 hours, the solvent was removed under reduced pressure to give a red-brown solid, which was treated with 2.5 M aqueous sodium hydroxide (100 ml, 0.25 mol) and then extracted with methylene chloride (4 x 100 ml.). The extracts were dried (potassium carbonate) and after the removal of the solvent a dark brown oil (15.9 g.) was obtained. The presence of about 10% of an oxidation product was detected by g.l.c. (silicone oil). This product, a colourless liquid (50 mg.) which was identical (p.m.r. and infrared spectra; t.l.c. and g.l.c. characteristics) with an authentic specimen of N-ethylaniline, was isolated using preparative g.l.c. (silicone oil)

δ (CCl_4)1.17 (3H, t, $-\underline{CH_3}$), 3.08 (2H, q, $-\underline{CH_2}$), 3.21 (1H, s, NH, exchanged by D_2O), 6.75 (5H, m, Ar) p.p.m.

8. <u>N,N-Dimethylaniline</u>

Dimethylaniline (12.1 g., 0.075), purified according to the method described by Vogel[169], (boiling range 192-194°) was treated exactly as described for N,N-diethylaniline and yielded a purple oil (8.7 g.). Chromatographic examination of the product by t.l.c.

and g.l.c. showed that the major of the 3 oxidation products was N-methylaniline

t.l.c. (a) silica gel - CCl_4:$CHCl_3$, 3 + 1; R_F 0.6

(b) basic alumina - petrol (40-60°); R_f 0.5

The R_F values were the same for authentic *N*-methylaniline and for the major oxidation product

g.l.c. (a) 10% silicone oil - 140°; R_t 5 minutes

(b) 10% carbowax - 140°; R_t 8 minutes

R_t was the same for authentic *N*-methylaniline and for the major oxidation product.

T.l.c. also showed that the purple colouration of the oil was due to a small amount of an intensely coloured material (R_F 0.05; silica gel - methylene chloride). Accordingly the oil was subjected to dry-column chromatography (silica gel - methylene-chloride) in 1 g. portions. The purple coloured zones were bulked and extracted with methanol. Removal of the solvent gave a small amount of sticky purple oil, identical (u.v. and p.m.r. spectra) with an authentic specimen of crystal violet. Treatment of this oil with 20% aqueous sodium hydroxide caused the precipitation of the corresponding alcohol, identical (m.p. and mixed m.p.) with the authentic material.

9. Tribenzylamine

(a) A solution of iodine (6.35 g., 0.025 mol) in isopropanol (175 ml.) was added dropwise to a solution of tribenzylamine (14.4 g., 0.05 mol) in isopropanol (50 ml.) at reflux, over a period of 2 hours. After refluxing for a further 19 hours the reaction mixture was cooled in ice and diluted with sodium-dried ether (100 ml.). Filtration gave brown crystals (7.2 g.), which after recrystallisation (ethanol) were shown to be identical (m.p. and mixed m.p.) with an authentic sample of tribenzylamine hydroiodide. This was confirmed by treating 1 g. of the solid with 2.5 M aqueous sodium hydroxide (25 ml.) and extracting with chloroform (4 x 25 ml.). The isolated oil (0.64 g.) was shown by g.l.c. to be tribenzylamine.

The filtrate obtained by the removal of the solid hydroiodide from the reaction solution was evaporated to dryness and the resulting residue. was refluxed with 1.24 M hydrochloric acid (100 ml.) for 30 minutes. Steam distillation followed by extraction of the distillate with chloroform (3 x 50 ml.) gave an oil (2.25 g.) identified as benzaldehyde. The residue from the steam distillation was basified by the addition of 2.5 M aqueous sodium hydroxide (100 ml.) and extracted with chloroform (3 x 100 ml.). After drying (magnesium sulphate) and removal of the solvent an oil (7.5 g.) was obtained, shown by g.l.c. to be a mixture of dibenzylamine (63%) and tribenzylamine (37%), these were identified in the usual manner.

(b) Tribenzylamine (in the presence of potassium cyanide)

A solution of iodine (6.4 g., 0.025 mol) in isopropanol (200 ml.) was added over 2 hours to a refluxing solution of tribenzylamine (14.4 g., 0.05 mol) and potassium cyanide (3.4 g., 0.05 mol) in isopropanol (50 ml.) After refluxing for a further one hour, the reaction mixture was allowed to attain room temperature and the pale yellow solid (5.0 g.) which had formed was removed by filtration. This was found to be identical (i.r. spectrum) with an authentic specimen of tribenzylamine hydroiodide.

The filtrate was evaporated to dryness and the resulting residue dissolved in 2.5 M aqueous sodium hydroxide (100 ml., 0.25 mol). This solution was extracted with chloroform

(3 x 100 ml.) and after drying (magnesium sulphate), the solvent was removed under reduced pressure to give an oil (14.20 g.) which solidified readily. Comparative qualitative chromatographic examination (g.l.c. - methyl silicone gum SE30; and t.l.c. - silica gel - ethyl acetate, silica gel - carbon tetrachloride and basic alumina - petrol) indicated the presence of tribenzylamine, α-cyanotribenzylamine and a trace of dibenzylamine.

The crude product was dissolved in ether and treated with excess hydrogen chloride to precipitate the hydrochlorides of tribenzylamine and dibenzylamine. After filtration, the ether was removed from the filtrate, to give an oil (2.6 g.) which on trituration with methanol yielded a white crystalline solid, identical with an authentic specimen of α-cyanotribenzylamine as regards m.p., mixed m.p., t.l.c. (silica gel - petrol and basic alumina - carbon tetrachloride), i.r. and p.m.r.

(c) Tribenzylamine (in the presence of competing bases)

The oxidation of tribenzylamine by iodine in non-aqueous solution was attempted in the presence of a number of other bases. In each case tribenzylamine (0.01 mol) was treated with an equimolar quantity of iodine in the presence of the competing base (0.1 mol). Hexamine, calcium carbonate, and 2-aminobenzimidazole were used in isopropanol solution; sodium acetate was employed in dioxan purified according to the method of Cava et al[100], whilst pyridine was used both as competing base and as solvent. The results from these experiments are summarised in Table 30.

TABLE 30. OXIDATION OF TRIBENZYLAMINE IN NON-AQUEOUS SOLVENTS IN THE PRESENCE OF A COMPETING BASE

Competing Base	Tribenzylamine Recovered		Other Products (g)	
	Weight(g)	%	Benzaldehyde	Dibenzylamine
Hexamine (i)	2.8	97	-	-
Calcium carbonate(i)	1.5	51	0.3	0.9
Sodium acetate (ii)	2.0	70	0.2	0.4
2-Aminobenzimidazole (i)	1.8	63	0.3	0.5
Pyridine (iii)	2.5	87	-	-

(i) carried out in isopropanol, (ii) in dioxan and (iii) pyridine

(d) Tribenzylamine (in the presence of other oxidants)

The oxidation of tribenzylamine by iodine in isopropanol solution was attempted in the presence of other oxidants. In each case tribenzylamine (0.01 mol) was treated with an equimolar quantity of iodine, in the presence of the second oxidant (0.1 mol). The products isolated after work up in the normal manner are given in Table 31

TABLE 31. OXIDATION OF TRIBENZYLAMINE IN ISOPROPANOL SOLUTION IN THE PRESENCE OF A SECOND OXIDANT

Second Oxidant	Tribenzylamine Recovered		Other products (g)	
	Weight (g)	%	Benzaldehyde	Dibenzylamine
Pyridine-N-oxide	1.7	60	0.2	0.5
Benzoquinone	2.1	75	-	-

III. The Oxidation of Amines by Iodine in Other Solvents

1. N-Alkyldiethanolamines

A solution of iodine (1.21 g., 0.0048 mol) in dried methylene chloride (95 ml.) was added slowly and with stirring to a solution of the N-alkyldiethanolamine (C1, C2 and C3DEA: 0.01 mol) in dried methylene chloride (100 ml.). After standing at room-temperature for 16 hours the pale yellow methylene chloride was decanted. The semi-solid brown residue was washed with petrol (40-60°) and dried in vacuo, whereupon the product solidified. Each product was examined by infrared and p.m.r. spectroscopy. These results, together with the determination of the percentage of iodine which was converted to iodide ion (by potentiometric titration with silver nitrate) indicated that the product in each case was the corresponding hydroiodide. The results are given in Table 32

TABLE 32. OXIDATION OF CnDEA IN METHYLENE CHLORIDE SOLUTION

Amine	% Conversion of Iodine to Iodide	Chemical Shift*	Frequency+ (cm^{-1})
C1DEA	91.6	3.4	2680
C2DEA	97.1	3.6	2720
C3DEA	99.8	3.6	2750

* Chemical shift, in p.m.r. spectra of products, for CH_2 groups adjacent to the N

\+ Frequency of absorptions, in infrared spectra of products, assigned to $R_3\overset{+}{N}H$

2. Triethylamine

To a solution of freshly distilled triethylamine (6.0 g., 0.06 mol) in dried tetrachloroethylene (50 ml.) at reflux a solution of iodine (6.6 g., 0.03 mol) in the same solvent (700 ml.)

was added dropwise over 6 hours. After standing for 6 hours, the suspension was filtered and the residue (11.3 g.), a black granular solid, was dried at 110°.

A portion (5 g.) of this crude product was boiled with distilled water (100 ml.) for 10 minutes. The bulk of the material dissolved and the remaining insoluble solid (0.4 g.), a black powder of an intractible nature m.p. 360°, was isolated and analysed, but was not investigated further. Found: C, 43.5, H, 4.3; N, 5.1, I 36.5 and a residue, 1.27%.

The aqueous solution contained iodide ions, (57.1% of the soluble matter by titration; triethylamine hydroiodide requires: $I^{\ominus}$, 55.5%). Accordingly, a further 5 g. of the original reaction product was boiled in methanol, filtered and the filtrate evaporated to dryness. The brown residue, after 2 recrystallisations from isopropanol, gave a pink crystalline powder (2.3 g.), m.p. 176-177°, identical (m.p., mixed m.p. and infrared spectrum) with an authentic specimen of *triethylamine hydroiodide*.

3. *N,N*-Dimethyldodecylamine

A solution of iodine (1.2 g., 0.0048 mol) in dried tetrachloroethylene (150 ml.) was added dropwise over a period of 1.5 hours to a refluxing solution of *N,N*-dimethyldodecylamine (2.13 g., 0.01 mol) in dried tetrachloroethylene (25 ml.). The reaction mixture was refluxed for a further one hour, and when cooled in ice it gave a dark brown solvent layer and a yellow-brown precipitate. The latter was removed by filtration, and after drying and recrystallisation from water yielded a pale-yellow solid (1.5 g.), m.p. 115-116°, identical (m.p., mixed m.p. and infrared spectrum) with an authentic specimen of *N,N-dimethyldodecylamine hydroiodide*.

4. Tribenzylamine

A solution of tribenzylamine (5.75 g., 0.02 mol) in dried tetrachloroethylene (100 ml.) was heated to reflux so as to extract iodine (2.54 g., 0.01 mol) contained in a soxhlet extractor. When the addition of the iodine was complete (6 hours) the reaction mixture was cooled. Filtration yielded a a brown solid (9 g.), a portion of which was suspended in water and refluxed for 24 hours. Basification, extraction and examination by g.l.c. in the usual manner indicated the presence of a trace of benzaldehyde and approximately equimolar amounts of dibenzylamine and tribenzylamine. The solid product was a mixture of the hydroiodide salts of these two bases (infrared and p.m.r. spectra).

E. MOLECULAR COMPLEXES

I Preparation

The complexes were prepared by mixing cold solutions containing the donor and acceptor in the appropriate proportions. In each case, the precipitated complex was filtered, washed and dried in vacuo. All the complexes were subjected to micro-analysis and titrimetric determination of the proportion of the molecular acceptor.

1. Complexes of Iodine

(a) With Hexamine

To 4 aliquots of a solution of hexamine (each containing 1.40 g., 0.01 mol) in methylene chloride (40 ml.) were added 60, 120, 180 and 240 ml., respectively, of a solution of iodine in methylene chloride (2.54 g. 0.01 mol I_2 in 60 ml.). After standing for 16 hours, the precipitates were filtered off, and each washed with methylene chloride and dried in vacuo at room-temperature. Quantitative micro-analysis led to the following stoichiometries for the complexes:

hexamine: I_2, 1:1, chocolate brown crystals (2.53 g., 65%) Found: C, 18.33; H, 3.24; N, 14.03; I, 64.43. $C_6H_{12}N_4.I_2$ requires: C, 18.27; H, 3.07; N, 14.22; I, 64.42 %

hexamine: I_2, 1:2, glistening orange-brown crystals (4.20 g., 65%). Found: C, 11.17; H, 2.07; N. 8.58; I, 77.93. $C_6H_{12}N_4.2I_2$ requires C, 11.11; H, 1.88; N, 8.65; I, 78.35%

hexamine: I_2, 1:3, glistening purple crystals (6.28 g., 78%) obtained using hexamine and iodine in the molar ratio of 1:4, respectively. Found: C, 8.14; H, 1.68; N, 6.06; I, 83.94. $C_6H_{12}N_4.3I_2$ requires: C, 7.99; H, 1.34; N, 6.21; I, 84.47%

A hexamine: I_2, 1:4 complex was not obtained even when a large excess of iodine was used. All such attempts led to the formation of hexamine: I_2, 1:3 complex. Similarly, hexamine and iodine in the ratio of 1:3 gave a mixture of the 1:1 and the 1:2 complexes.

The 1:1 and 1:3 complexes were also prepared from aqueous solutions. Under these conditions the complexes precipitated as orange powders immediately upon mixing the reactants.

(b) with triethylenediamine (TED; 1,4-diazabicyclo [2,2,2] octane)

To 2 aliquots of a solution of triethylenediamine (each containing 1.12 g., 0.01 mol) in methylene chloride (20 ml.) were added 60 and 120 ml., respectively, of a solution of iodine in methylene chloride (2.54 g., 0.01 mol I_2 in 60 ml. solvent). After standing for 16 hours, the precipitates were filtered off, washed with methylene chloride and dried in vacuo at room-temperature. Micro-analysis showed that only the following complex was formed

TED: I_2, 1:2, dull orange powder (3.73 g., 60%). Found: C, 11.82; H, 2.08; N, 4.53; I, 81.65. $C_6H_{12}N_2.2I_2$ requires C, 11.65; H, 1.95: N, 4.52: I. 81.90%

Repeated attempts to prepare the TED:I_2; 1:1 complex by employing the amine in excess during the reaction, failed. In each case the 1:2 complex was isolated instead. Similarly, reaction of triethylenediamine and iodine under (i) aqueous condisions and (ii) in methanol gave the 1:2 complex only, as a brown-red powder. A transient yellow precipitate was noted during an experiment using a 5-fold excess of donor in methanol.

(c) with Tröger's base

To 2 aliquots of a solution of Tröger's base (1.25 g., 0.005 mol) in methylene chloride (10 ml.) was added 30 and 60 ml. respectively, of a solution of iodine in the same solvent (1.27 g., 0.005 mol I_2 in 30 ml.). In neither case did a precipitate form even after prolonged standing. The solvent was removed under reduced pressure, each residue was recrystallised from methylated spirit and dried in vacuo at room-temperature to give red-brown needles (1.68 g., 88%) and orange-brown needles (2.11 g., 56%), respectively. The two solids gave identical infrared spectra and were found by titration to contain the same proportion of available iodine, corresponding to the stoichiometry Troger's base I_2; 1:1 Found: C, 40.46; H, 3.54; N, 5.71. $C_{17}H_{18}N_2.I_2$ requires C, 4 05; H, 3.5; N, 5.6%.

(d) with trimethylamine

A solution of trimethylamine (1.8 g. of a 33% w/w solution in ethanol; 0.6 g. $(CH_3)_3N$, 0.01 mol), diluted with absolute ethanol (5 ml.), was added dropwise to a solution of iodine (2.54 g., 0.01 mol) in absolute ethanol (20 ml.). The resultant complex precipitated immediately and was filtered, washed with ethanol and dried in vacuo at room temperature. The yellow solid (1.5 g., 48%) was shown to be trimethylamine:iodine, 1:1 by estimation of the percentage of available iodine (see later). Found: I_2, 81.1; $C_3H_9NI_2$ required I_2, 81.2%.

(e) with quinuclidine

(i) Aqueous potassium hydroxide (10 ml., 30% w/v) was added to a solution of quinuclidine hydrochloride (7 g., 0.48 mol) in water (5 ml.), and the oil which separated was extracted continuously with methylene chloride for 3 hours. After drying (calcium sulphate), the extract was evaporated leaving an off-white solid (6.8 g., theory 5.3 g.) which was not basic and would not sublime (cf. quinuclidine). Qualitative analysis demonstrated the presence of nitrogen and chlorine; quantitative micro-analysis gave C, 47.67; H, 7.54; N, 7.26; Cl, 36.68. $C_7H_{13}N. CH_2 Cl_2$ requires C, 49.00; H, 7.66; N, 7.15; Cl, 36.20%.

To a solution of this solvate (1.1 g., 0.0075 mol) in methylene chloride (10 ml.) was added a solution of iodine (2.54 g., 0.01 mol) in methylene chloride (60 ml.). No precipitate was formed even after 48 hours. The solvent was then evaporated leaving a black oil which solidified to black crystals on treatment with 10% aqueous potassium iodide (20 ml.). The solid was filtered and dried in vacuo (3.3 g.). Recrystallisation from methylated spirit gave purple-brown needles, identical (infrared spectrum and analysis) with a second crop (1.14 g.) obtained by adding a little water to the filtrate. Found: C, 17.58; H, 1.75; N, 3.14. $(C_7H_{13}N)_2 . CH_2Cl_2 . I_2$ requires C, 32.1; H, 5.0; N, 5.0; I, 45.3; Cl, 12.6%; estimation of available iodine gave 46.5% I_2.

(ii) Aqueous potassium hydroxide (10 ml., 30% w/v) was added to a solution of the solvated amine (1:1 g., 0.0075 mol) in water (2 ml.). The white solid which separated was filtered and washed with a few drops of water. This material was dissolved in water (5 ml.) and 0.25M aqueous potassium tri-iodide (50 ml., 0.0125 mol) was added. The precipitated complex was dried in vacuo at room temperature over phosphorus pentoxide. Estimation of elemental iodine gave 46.5% I_2. $C_7H_{13}N.I_2$ requires I_2, 69.10%.

(iii) Aqueous sodium hydroxide (3.5 ml., 1 M, 0.0035 mol) was added to a solution of quinuclidine hydrochloride (0.5 g., 0.0034 mol) in water (1 ml.) and this was treated with 0.25 M aqueous potassium tri-iodide (20 ml., 0.005 mol). The resultant yellow-brown precipitate was filtered and washed successively with 10% aqueous potassium iodide (3 x 10 ml.) and water (3 x 20 ml.), and dried in vacuo at room temperature to give a brown powder (1.13 g., 91%). Found: C, 19.47; H, 3.22; N, 3.02; I, 69.17. $C_7H_{13}NI_2$ requires C, 23.64; H, 3.53; N, 3.80; I, 69.10% Attempted recrystallisation led to decomposition of the complex.

(f) with tribenzylamine

A solution of iodine (2.54 g., 0.01 mol) in dried ether (15 ml.) was added dropwise to a solution of tribenzylamine (2.87g., 0.01 mol) in the same solvent (15 ml.). After standing for 30 minutes, the resultant black solid was filtered off, washed with dried ether and dried in vacuo (2.62 g.). Found: C, 21.67; H, 1.89; N, 1.62; I, 73.94. Available iodine 65.2; tribenzylammonium heptaiodide, $[(C_6H_5CH_2)_3N.H]^{\oplus} I_7^{\ominus}$ requires C, 21.60; H, 1.87; N, 1.31; I, 75.6%, and contains 64.8% available iodine. Thus the product was the poly-iodide $\underline{[(C_6H_5CH_2)_3N.H]^{\oplus} I_7^{\ominus}}$

2. Complexes of Bromine

(a) with hexamine

(i) A solution of bromine (1.6 g., 0.01 mol) in methylene chloride (16 ml.) was added to a solution of hexamine (2.0 g., 0.014 mol) in the same solvent (60 ml.). The reaction mixture was allowed to stand for 16 hours, the precipitated solid was then filtered off, washed with methylene chloride and dried in vacuo at room-temperature to give a pale yellow solid (2.87 g., 96%). Found: C, 24.19; H, 4.14; N. 18.62; Br, 53.40. $C_6H_{12}N_4.Br_2$ requires C, 24.02; H, 4.03; N, 18.68; Br, 53.27%. Thus the product was identified as the complex hexamine:bromine, 1:1

(ii) To 3 aliquots of a solution of hexamine (each containing 1.40 g., 0.01 mol) in methylene chloride (50 ml.) were added 32, 48 and 75 ml. respectively of a solution of bromine in methylene chloride (1.60 g., 0.01 mol Br_2 in each 16 ml. of solution). The products were isolated as described in 2 (a(i)). Percentage available bromine was determined titrimetrically (Table 33).

TABLE 33 PREPARATION OF COMPLEXES OF HEXAMINE WITH BROMINE

Ratio of Reactants	% Available Bromine		Nature of Product	Yield	
Donor:Acceptor	Found	Required		(g.)	%*
1:2	68.0	69.5 (for 1:2)	Yellow powder	4.03	88
1:3	69.7	77.5 (for 1:3)	Yellow powder	4.26	93
1:4 (excess Br_2)	72.7	82.1 (for 1:4)	Orange powder	4.90	-

* of 1:2 complex

The product obtained from the 1:3 reaction was hexamine:Br_2; 1:2. Found: C, 15.74; H, 2.67; N, 12.07; Br, 69.50. $C_6H_{12}N_4.2Br_2$ requires C, 15.67; H, 2.63; N, 12.18; Br, 69.52

(b) with triethylenediamine

(i) A solution of bromine (1.6 g., 0.01 mol) in methylene chloride (16 ml.) was added to a solution of triethylenediamine (1.5 g., 0.0133 mol) in methylene chloride (50 ml.). After work up in the usual manner, a yellow powder (2.49 g., 92%) was obtained. Found: C, 26.25; H, 4.39; N, 10.40; Br, 58.72. $C_6H_{12}N_2.Br_2$ requires C, 26.49; H, 4.45; N, 10.30; Br, 58.75%. The product was the triethylenediamine:bromine, 1:1 complex

(ii) Triethylenediamine (1.12 g., 0.01 mol) in methylene chloride (40 ml.) and bromine (4.0 g., 0.025 mol) in methylene chloride (40 ml.) gave a pale-yellow powder (4.32 g., 100%). Found: C, 16.86; H, 2.90; N, 6.33; Br, 74.07. $C_6H_{12}N_2.2Br_2$ requires C, 16.69; H, 2.80; N, 6.49; Br, 74.01%. The product was the triethylenediamine:bromine, 1:2 complex

(c) with trimethylamine

A solution of trimethylamine in ethanol (3.8 g. of a 33% w/w solution, 0.02 mol) was added dropwise to a solution of bromine

(3.2 g., 0.02 mol) in cold ethanol (10 ml.). The precipitate was filtered, washed with ethanol and dried in vacuo at room-temperature to give a yellow powder which decomposed overnight to a sticky yellow solid and a brown oil.

The preparation was also attempted by the slow, dropwise addition of a solution of bromine (3.2 g., 0.02 mol) in cold carbon tetrachloride (25 ml.) to a solution of trimethylamine in ethanol (3.6 g. of a 33% w/w solution, 0.02 mol) diluted with cold methylene chloride (20 ml.). The yellow precipitate so obtained decomposed during work up.

(d) with quinuclidine

Aqueous sodium hydroxide (5.0 ml., 1M 0.005 mol) was added to a solution of quinuclidine hydrochloride (0.74 g., 0.005 mol) in water (2.5 ml.), and the resulting solution was added dropwise to a solution of bromine (0.9 g., 0.0056 mol) in 5% aqueous potassium bromide (25 ml.). The precipitate was filtered and washed successively with 5% aqueous potassium bromide (2 x 10 ml.) and water (3 x 10 ml.). Drying in vacuo at room-temperature gave a pale yellow solid (1.25 g., 92%). Found: C, 30.98; H, 4.95; N, 5.02; Br, 59.31. $C_7H_{13}N\ Br_2$ requires C, 31.0; H, 4.8; N, 5.2; Br, 59.0 %. Thus the product was identified as the quinuclidine:Br_2, 1:1, complex

3. Interaction of some amines with chlorine

A standard solution of chlorine was prepared by dissolving dried (conc. sulphuric acid) chlorine gas in ice-cold carbon tetrachloride. The solution was then diluted with cold solvent so that a known weight of chlorine was contained in some convenient volume of the solution.

Preparation of amine:chlorine complexes was attempted by adding the ice-cold solution of chlorine in carbon tetrachloride dropwise to an ice-cold solution of the amine in methylene chloride. The products were washed with cold carbon tetrachloride and dried in vacuo at room-temperature.

(a) <u>with hexamine</u>

(i) Hexamine (7.0 g. 0.05 mol) in methylene chloride (150 ml.) and chlorine (1.42 g., 0.02 mol) in carbon tetrachloride gave a white solid (4.0 g. 95%). Found: C, 37.05; H, 6.74; N, 29.14; Cl, 21.23; Cl_2, NIL: $Cl^{\ominus}$, 17.5. $C_6H_{12}N_4.Cl_2$ requires C, 34.13; H, 5.73; N, 26.54; Cl (and Cl_2) 33.59%, and $C_6H_{12}N_4.HCl$ requires $Cl^{\ominus}$, 20.1 %.

(ii) Hexamine (1.4 g., 0.01 mol) in methylene chloride (50 ml.) and chlorine (3.05 g., 0.043 mol) in carbon tetrachloride (75 ml.) gave a white solid (1.0 g. 57%). Found: C, 32.22; H, 6.81; N, 24.08; Cl, 26.05; Cl_2, NIL; $Cl^{\ominus}$ 24.9. $C_6H_{12}N_4.2Cl_2$ requires C, 25.52; H, 4.26; N, 19.86; Cl (and Cl_2), 50.36% $C_6H_{12}N_4.2HCl$ requires $Cl^{\ominus}$, 33.3 %.

(b) <u>with triethylenediamine</u>

(i) Triethylenediamine (5.7 g., 0.05 mol) in methylene chloride (50 ml.) and chlorine (1.42 g., 0.02 mol) in carbon tetrachloride (71 ml.) gave a white solid (5.82 g.). Found: C, 43.38; H, 8.11; N, 16.55; Cl, 21.94; Cl_2, NIL; $Cl^{\ominus}$, 19.8. $C_6H_{12}N_2.Cl_2$ requires C, 39.35; H, 6.61; N, 15.30; Cl (and Cl_2), 38.73%, and $C_6H_{12}N_2.HCl$ requires $Cl^{\ominus}$, 23.9%.

(ii) Triethylenediamine (1.12 g., 0.01 mol) in methylene chloride (50 ml.) and chlorine (1.9 g., 0.027 mol) in carbon tetrachloride (95 ml.) gave a white solid (1.83 g., 100%).

Found: C, 34.83; H, 7.10; N, 14.4; Cl, 32.38; Cl_2, NIL; Cl^-, 31.5. $C_6H_{12}N_2.2Cl_2$ requires C, 28.37; H, 4.76; N, 11.04; Cl (and Cl_2), 55.83%. $C_6H_{12}N_2.2HCl$ requires $Cl^{\ominus}$, 38.3%.

None of these water soluble products were charge-transfer complexes and they were not investigated further.

4. Complexes of Iodine Monochloride

The iodine monochloride complexes were prepared by the dropwise addition of a solution of the interhalogen in methylene chloride to an ice-cold solution of the amine in the same solvent. After standing for 1 hour the precipitate which had formed was filtered off, washed with methylene chloride and dried in vacuo at room-temperature.

(a) with hexamine

(i) 1:1 complex Hexamine (1.50 g., 0.011 mol) in methylene chloride (30 ml.) and iodine monochloride (1.62 g., 0.01 mol) in methylene chloride (10 ml.) gave a pale yellow solid (3.0 g., 100%). Found: C, 23.66; H, 3.83; N, 18.56. $C_6H_{12}N_4.ICl$ requires C, 23.9; H, 4.0; N, 18.6%.

(ii) 1:2 complex Hexamine (1.40 g., 0.01 mol) in methylene chloride (25 ml.) and iodine monochloride (3.25 g., 0.02 mol) in methylene chloride (20 ml.) gave a pale yellow solid (4.3 g., 93%). Found: C, 15.32; H, 2.59; N, 11.98. $C_6H_{12}N_4.2ICl$ requires C, 15.5; H, 2.6; N, 12.0%.

(iii) 1:3 complex Hexamine (0.70 g., 0.005 mol) in methylene chloride (20 ml.) and iodine monochloride (2.44 g., 0.015 mol) in methylene chloride (15 ml.) gave a yellow solid (2.82 g., 90%). Found: C, 11.63; H, 2.01; N, 8.84. $C_6H_{12}N_4.3ICl$ requires C, 11.5; H, 1.9; N, 8.9%.

(iv) 1:4 complex. Hexamine (0.70 g., 0.005 mol) in methylene chloride (20 ml.) and iodine monochloride (4.05 g., 0.025 mol) in methylene chloride (25 ml.) gave a yellow solid (3.14 g., 80%). Found: C, 10.38; H, 1.72; N, 8.19. $C_6H_{12}N_4.4ICl$ requires C, 9.1; H, 1.5; N, 7.1%.

(b) with triethylenediamine

(i) 1:1 complex. Triethylenediamine (1.50 g., 0.012 mol) in methylene chloride (20 ml.) and iodine monochloride (1.62 g., 0.01 mol) in methylene chloride (10 ml.) gave a bright yellow crystalline solid (1.37 g., 50%). Found: C, 26.72; H, 4.31; N, 10.15. $C_6H_{12}N_2.ICl$ requires C, 26.3; H, 4.4; N, 10.2%.

(ii) 1:2 complex. Triethylenediamine (1.12 g., 0.01 mol) in methylene chloride (20 ml.) and iodine monochloride (4.05 g., 0.025 mol) in methylene chloride (25 ml.) gave a pale-brown solid (5.13 g.). Found: C, 15.08; H, 2.52; N, 5.30. $C_6H_{12}N_2.2ICl$ requires C, 16.5; H, 2.7; N, 6.4%.

(c) with trimethylamine

A solution of trimethylamine in ethanol (3.6 g. of a 33% w/w solution, 0.02 mol) was added dropwise to an ice-cooled solution of iodine monochloride (3.25 g., 0.02 mol) in ethanol (10 ml.). The pale buff precipitate was filtered, washed well with ethanol and dried in vacuo at room temperature to give a pale yellow solid (2.25 g., 53%). This was shown to be the trimethylamine:iodine-monochloride, 1:1 complex by estimation of the available iodine monochloride. Found: ICl, 74.3; C_3H_9NICl requires ICl, 73.5%

5. Complexes of N-Bromosuccinimide (NBS)

(a) with hexamine

A solution of NBS (1.78 g., 0.01 mol) in methylene chloride (50 ml.) was added to each of 4 solutions of hexamine (1.40, 0.70, 0.47 and 0.30 g.; 0.01, 0.005, 0.0033 and 0.0021 mol, respectively) in methylene chloride (50, 25, 17 and 10 ml. respectively). In each case, the precipitate was filtered, washed with methylene chloride and dried in vacuo to give a white solid (1.42, 2.09, 2.41 and 0.63 g., respectively).

Estimation of available NBS showed that the latter product did not possess a simple stoichiometry, whilst the 3 other solids, that is those formed by the interaction of hexamine and NBS in the ratio 1:1, 1:2 and 1:3 respectively, were identified as the hexamine:NBS; 1:2 complex. Furthermore, the solids gave identical infrared spectra. Found: C, 33.95; H, 4.02; N, 16.94. $C_6H_{14}N_4$; $2(C_4H_4NO_2Br_2)$ requires C, 33.9; H, 4.0; N, 16.9%

(b) with triethylenediamine

1:2 complex. A solution of NBS (3.56 g., 0.02 mol) in benzene (170 ml.) was filtered into a solution of triethylenediamine (1.12 g., 0.01 mol) in benzene (50 ml.). After standing for 2 hours the product was filtered, washed with benzene and dried in vacuo at room temperature to give a very pale buff solid (3.19 g., 68%). Found: C, 36.48; H, 4.28; N, 12.08. $C_{14}H_{20}N_4O_2Br_2$ requires C, 35.9; H, 4.25; N, 12.0%.

The same complex was also isolated as the sole product using NBS (1.78 g. 0.01 mol) and TED (1.12 g., 0.01 mol). Thus in both cases the product was identified as the triethylenediamine:NBS, 1:2 complex.

II Determination of the Acceptor in the Complexes

The percentage of molecular acceptor in each product was determined by the methods described on p 169. The results given here (Tables 34, 35, 36 and 37) are the mean values from several determinations. These, together with the values given by micro-analysis, were used to determine the donor to acceptor ratio in the products. Only those solids in which all the acceptor is present as the complexed molecule are regarded as molecular complexes. Those products in which some of the halogen is not present as molecular halogen are regarded as salts, with substituted ammonium cations and poly halide anions.

TABLE 34 PROPORTION OF AVAILABLE IODINE IN THE COMPLEXES

Donor	Molar Ratio	Total Iodine (%) by micro-analysis		Molecular Iodine (% I_2)
	$D:I_2$	Theory	Found	Found
Hexamine	1:1	64.4	64.4	64.7
	1:2	78.4	77.9	79.5
	1:3	84.5	83.9	84.6
TED	1:2	81.9	81.7	82.0
Troger's base	1:1	50.4	50.3*	49.9
Trimethylamine	1:1	81.2	-	81.1
Quinuclidine	1:1	69.1	69.2	64.3
Tribenzylamine	-	-	73.9	65.2

* by difference

TABLE 35 PROPORTION OF AVAILABLE BROMINE IN THE COMPLEXES

Donor	Molar Ratio	Total Bromine (%) by micro-analysis		Molecular Bromine (% Br_2)
	$D:Br_2$	Theory	Found	Found
Hexamine	1:1	53.3	53.4	53.5
	1:2	69.5	69.5	69.7
TED	1:1	58.8	58.7	59.4
	1:2	74.0	74.1	73.7
Quinuclidine	1:1	59.0	59.3	60.7
Tribenzylamine	-	35.8	50.2*	10.7

* by difference

TABLE 36 PROPORTION OF AVAILABLE IODINE MONOCHLORIDE IN THE COMPLEXES

Donor	Molar Ratio	Total ICl (%) by micro-analysis		Molecular ICl (%)
	D:ICl	Theory	Found	Found
Hexamine	1:1	53.5	54.0*	54.1
	1:2	69.9	70.1*	71.6
	1:3	77.7	77.5*	77.7
	1:4	82.3	79.7*	80.8
TED	1:1	59.1	58.8*	60.2
	1:2	74.4	77.1*	71.3

* by difference

TABLE 37 PROPORTION OF N-BROMOSUCCINIMIDE IN THE COMPLEXES

Donor	Molar Ratio	Molecular NBS	
	D:NBS	Theory	Found
Hexamine	1:2	71.7	72.5
TED	1:2	76.1	73.6

III. Spectroscopic, conductance and thermal analysis data

1. Far-infrared spectra

Absorption spectra in the far infrared region were obtained as described on p. 166 . The more important absorption maxima in the region 40 to 350 cm^{-1} are listed below, both for the donors and the complexes (Representative spectra are depicted on p.238 and 239).

(a) Iodine complexes

Donor	D:I_2	ν_{max} (cm^{-1})						
Hexamine	1:1	47,	68,		138,	159,	190,	
	1:2	50,	74,	103,	125,	165,		
	1:3	40,	67,	103,	130,	172,		
TED	1:2	55,			125,	158sh	185,	210
Trimethylamine	1:1			96,	146,		187,	
Quinuclidine	1:1				152,	168		
Quinuclidine solvate				105,	130,	155		
Tröger's base	1:1						180,	195

(b) Bromine complexes

Donor	D:Br_2	ν_{max} (cm^{-1})						
Hexamine	1:1	50,	75,	150sh,		180,	198,	
	1:2	50,	70,	130,	165,		200,	
TED	1:1	50,	85		168,	190,	210,	240,
	1:2	55,		135	167,	185sh	209	
Quinuclidine	1:1	56,			162		212	

(c) Iodine monochloride complexes

Donor	D:ICl	ν_{max} (cm^{-1})							
Hexamine	1:1	54,	72,	90,		155,			238
	1:2	64,		88,		138,		200,	270
	1:3		70,			144,		230,	280
	1:4	54				140,	174,		282
TED	1:1	56,		90,	114,		172,	190,	258
	1:2				102,	149		202,	266
Trimethylamine	1:1			94,				207,	247

(d) N-Bromosuccinimide complexes

Donor	D:NBS	ν_{max} (cm^{-1})			
Hexamine	1:2	90,	140,	200(sh),	220
TED	1:2		140,	208,	240

(e) Donors - uncomplexed

Hexamine	85
TED	85
Quinuclidine - solvated	60 to 190 (very broad and intense)

The far-infrared spectrum of N-bromosuccinimide contained absorptions at 125, 135, 185, 215, 250 cm^{-1}

2. Absorption Maxima (nm) in the Ultraviolet-Visible Spectra of the Complexes

(a) In solution

(i) Iodine complexes

Hexamine : I_2	1:1	273,	385,	500	in CH_2Cl_2
	1:2	270,	385,	512	in $CHCl_3$
	1:3	265		513	in $CHCl_3$

(Hexamine does not absorb above 240 nm)

TED : I_2	1:2	300,	355(sh),	500	in CH_2Cl_2

(TED absorbs at ca. 240 nm. The absorption tailing to 300 nm).

Trimethylamine : I_2	1:1	270,	390,	310	in CH_2Cl_2

(ii) Bromine complexes

No absorption maxima, cut-off at 235 nm.

(iii) NBS complexes

Hexamine :NBS	1:2	cut off	235, 283	in CH_2Cl_2
TED :NBS	1:2	cut off	240	"

(NBS very weak absorption ca. 240 nm).

(iv) Amine-chlorine products and other compounds

Hexamine/ Cl_2	1:1	cut-off at	235	in H_2O
	1:2	" " "	235	" " and CH_3OH
Hexamine: HCl	1:1	" " "	205	" "
	1:2	" " "	205	" " " "
Hexamine: CH_3I	1:1	" " "	240	" CH_3OH
Hexamine		" " "	220	" H_2O
TED/ Cl_2	1:1	" " "	240, 330	in H_2O
	1:2	" " "	210, 350 (sh)	" "
TED: HCl	1:1	" " "	210	" "
	1:2	" " "	210	" " and CH_3OH
TED: CH_3I	1:1	" " "	240	" CH_3OH
TED		" " "	235	" H_2O

(b) Diffuse reflectance spectra

(i) Iodine complexes

Hexamine : I_2	1:1	225,	270,	ca. 40
	1:2	230,		ca. 475
	1:3	230,		ca. 500
Hexamine		cut off 210		
TED : I_2	1:2	220,	270,	ca. 400
TED		230,	270	
Trimethylamine: I_2	1:1			ca. 400
Tröger's base: I_2	1:1	230,		ca. 400
Tröger's base		230,	280,	
Quinuclidine : I_2	1:1	225		ca. 400
Quinuclidine-solvate : I_2				ca. 400
Quinuclidine-solvate		225,	350(sh)	
Tribenzylamine : I_2	1:1	230,	275,	ca. 500
Tribenzylamine			270	

(ii) Bromine complexes

Hexamine : Br_2	1:1	210,		ca. 350
	1:2	220,		ca. 350
TED : Br_2	1:1		270	ca. 320
	1:2	230,		ca. 320
Quinuclidine : Br_2	1:1	230		ca. 300

(iii) Iodine monochloride complexes

Hexamine : ICl	1:1	225,	ca. 290
	1:2	225,	ca. 285
	1:3	220,	ca. 285
	1:4	215,	ca. 280
TED : ICl	1:1	225,	ca. 290
	1:2	230,	ca. 280

(iv) NBS complexes

Hexamine : NBS	1:2	230,	270
TED : NBS	1:2	225,	290
NBS			270

3. Conductance Measurements

Conductance measurements were carried out using solutions of the molecular complexes and amine salts in water and methanol. The values given below are calculated from measurements made using 10^{-3} M solutions, except those indicated by (*) which were made on 10^{-4} M solutions, because the compound under test was not sufficiently soluble.

(a) Conductance measurements in aqueous solution

Compound		Molar Conductance (ohm^{-1} cm^2 $mole^{-1}$)
Hexamine		8
Hexamine / Cl_2	1:1	159
	1:2	369
Hexamine : HCl	1:1	139
	1:2	459
TED		13
TED / Cl_2	1:1	151
	1:2	504
TED : HCl	1:1	115
	1:2	459

(b) Conductance measurements in absolute methanol

Compound		Molar Conductance (ohm^{-1} cm^{2} $mole^{-1}$)
Hexamine		1
Hexamine : Iodine	1:1	12*
	1:2	29*
	1:3	27*
Hexamine : Bromine		374
Hexamine : Iodine monochloride	1:1	105*
	1:2	270*
	1:3	315*
	1:4	367*
Hexamine : NBS	1:2	111
Hexamine / Chlorine	1:2	239
Hexamine : HCl	1:2	269
Hexamine : Methyl Iodide	1:1	165
TED		1
TED : I_2	1:2	18
TED : Br_2	1:2	478
TED : Iodine monochloride	1:1	135
	1:2	203
TED : NBS	1:2	54
TED / Chlorine	1:2	261
TED : HCl	1:2	238
TED : Methyl Iodide	1:2	186
Trimethylamine : Iodine	1:1	22
Trimethylamine : Iodine monochloride	1:1	122
Quinuclidine : Iodine	1:1	14

4. Proton Magnetic Resonance Spectra

The chemical shifts (in p.p.m.) relative to TMS, of the protons on the carbon atoms <u>α</u> to the donor nitrogen atoms are listed here. It should be noted that hexamine, triethylenediamine, trimethylamine and their complexes with iodine, bromine, iodine monochloride and NBS give only a singlet attributable to these <u>α</u>-protons

Compound		Observed shift (p.p.m.) in			
		Acetone	Water	Methanol	DMSO
Hexamine		279	280		275
Hexamine : I_2 ,	1:1	290			
	1:2	296			
	1:3	297			
Hexamine : Br_2,	1:1	292			
	1:2	305			
Hexamine : ICl,	1:1				289
	1:2				290
	1:3				291
	1:4				292
Hexamine : NBS,	1:2	290			
Hexamine / Cl_2,	1:1		294		
	1:2		295		
Hexamine : HCl,	1:1		298		
	1:2		302		
Hexamine : CH_3I	1:1		307		
TED		160	164		155
TED : I_2,	1:2	202			
TED : Br_2,	1:1	190			
	1:2	222			
TED : ICl	1:1				199
	1:2				201
TED : NBS,	1:2	165			
TED / Cl_2,	1:1		192		
	1:2		232		

(Table continued)

Compound		Observed shift (p.p.m.) in			
		Acetone	Water	Methanol	DMSO
TED:: HCl,	1:1		197		
	1:2		230		
TED : MeI	1:1		204		
	1:2		247		
Trimethylamine				134	
Trimethylamine : I_2	1:1			170	
Trimethylamine : Br_2	1:1			178	
Trimethylamine : HCl	1:1			176	
Trimethylamine CH_3I	1:1		191		
Trimethylamine : I_2 + Trimethylamine	1+1			150	
Quinuclidine				148	
Quinuclidine : I_2	1:1			190	
Quinuclidine : Br_2	1:1			200	
Quinuclidine : HCl	1:1			200	
Quinuclidine-solvated				220	
Quinuclidine-solvated + I_2				220	

3. Thermal Analysis

Compound		T.G.A.		D.T.A.	
		% Weight loss	Temp. (°C)	Decomposition Temp. (°C)	+(Endo) -(Exo)
Hexamine : I_2	1:1	12	160	153	-
	1:2	8	70	86	-
	1:3	39	90	89	-
TED : I_2,	1:2	44	190	204	-
Quinuclidine:I_2	1:1	*	179	187	-
Hexamine : Br_2,	1:1	11	150	150	-
	1:2	34	110	118	-
TED : Br_2,	1:1	30	130	133	-
	1:2	42	150	163	-
Quinuclidine:Br_2,	1:1	22	167	191	-
Hexamine : ICl,	1:1	11	163	177	-
	1:2	16	170	183	-
	1:3	18	173	189	-
	1:4	16	177	193	-
TED : ICl,	1:1	14	10		-
	1:2	*			-
Hexamine : NBS,	1:2	41	101	133	-
TED : NBS,	1:2	77	91	111	-

* gradual weight loss

F. SPECTRA

I. Infrared spectra

The following infrared spectra are given:-

I.R. No. 1	Hexamine
I.R. No. 2	Hexamine:Iodine, 1:3
I.R. No. 3	Hexamine:Iodine monochloride, 1:1
I.R. No. 4	Hexamine:Iodine monochloride, 1:2
I.R. No. 5	Hexamine:Iodine monochloride, 1:3
I.R. No. 6	Hexamine:Iodine monochloride, 1:4
I.R. No. 7	Triethylenediamine
I.R. No. 8	Triethylenediamine:Iodine, 1:2
I.R. No. 9	Triethylenediamine:Bromine, 1:2
I.R. No.10	Triethylenediamine:Iodine monochloride, 1:2
I.R. No.11	Triethylenediamine:Bromine, 1:1
I.R. No.12	Triethylenediamine:Iodine monochloride, 1:1

II. Far infrared spectra

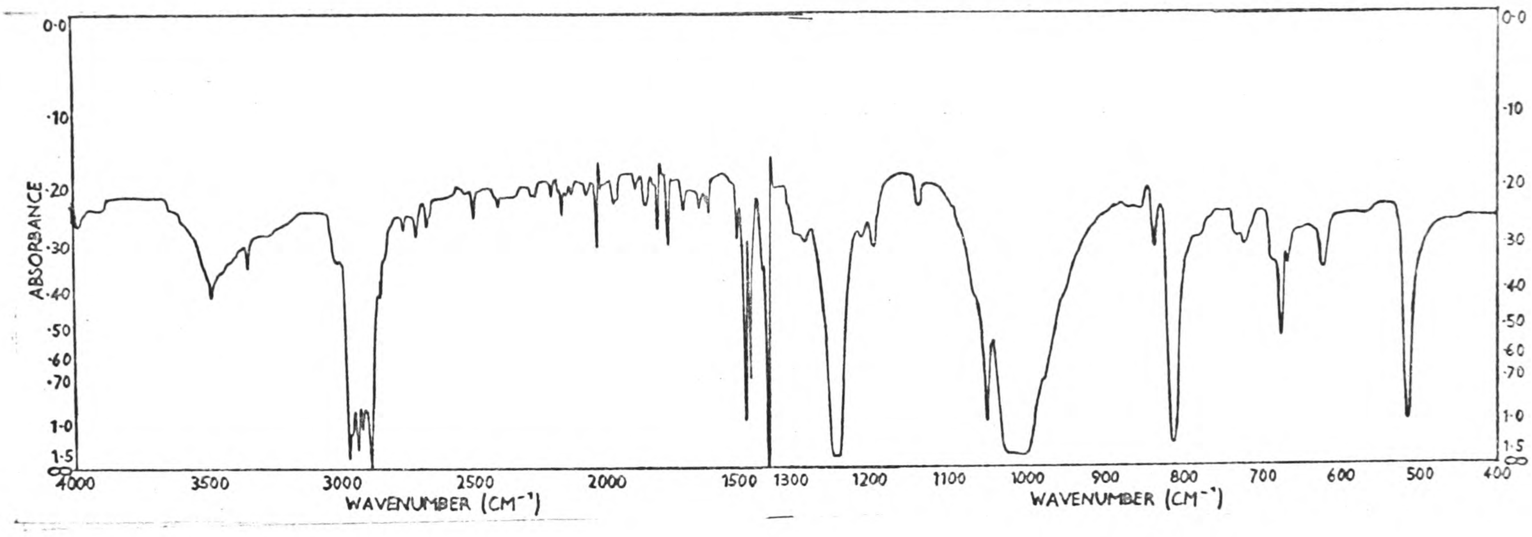
The following far infrared spectra are given

Far I.R. No. 1	Hexamine : Iodine, 1:1
Far I.R. No. 2	Triethylenediamine : Bromine, 1:1
Far I.R. No. 3	Hexamine : Bromine, 1:2
Far I.R. No. 4	Triethylenediamine : Bromine, 1:2

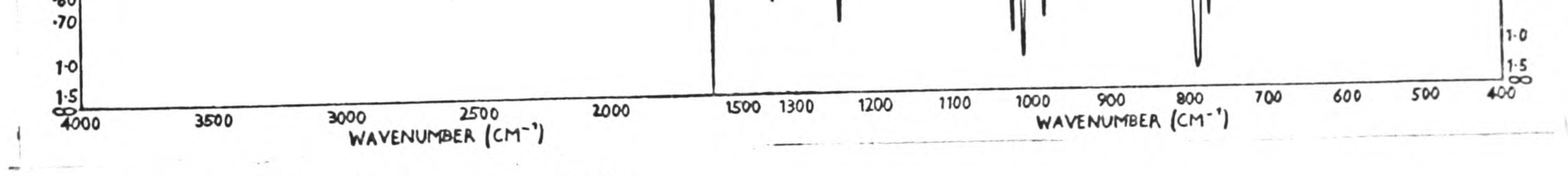
III. Proton magnetic resonance spectra

The following proton magnetic resonance spectra are given

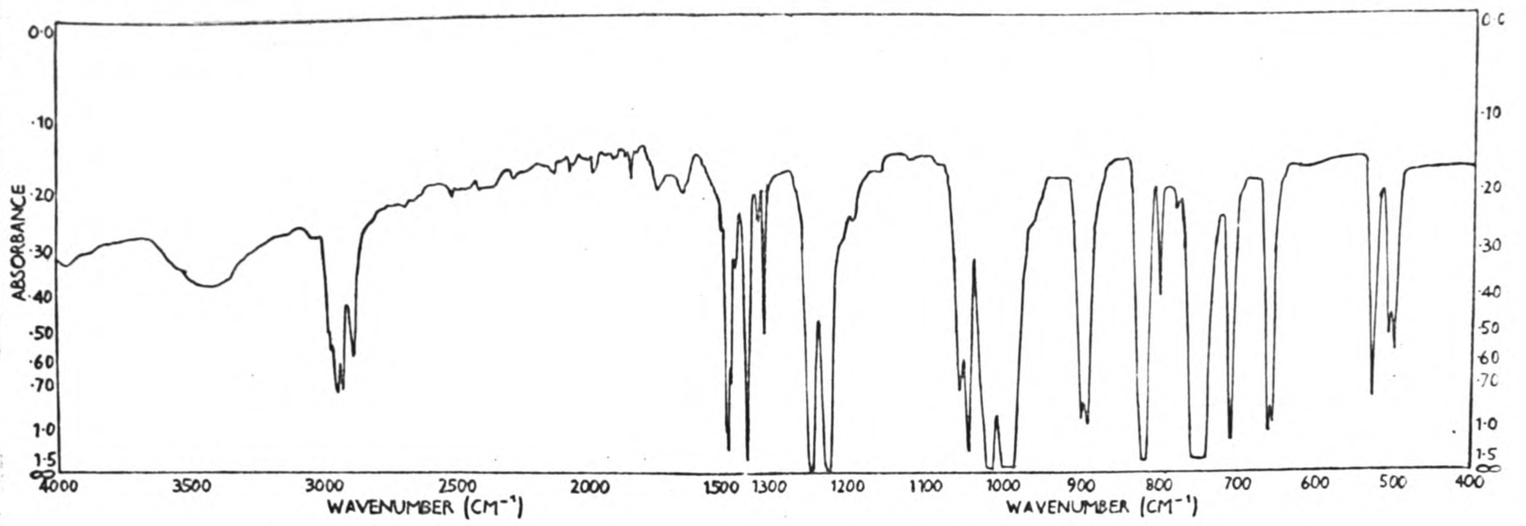
P.M.R. No. 1	Oxidation product of C2DEA (XIX)
P.M.R. No. 2	Oxidation product of diethylaminoethanol (XXI)
P.M.R. No. 3	Oxidation product of C3DEA (XX)
P.M.R. No. 4	Oxidation product of triethylamine (XXII)



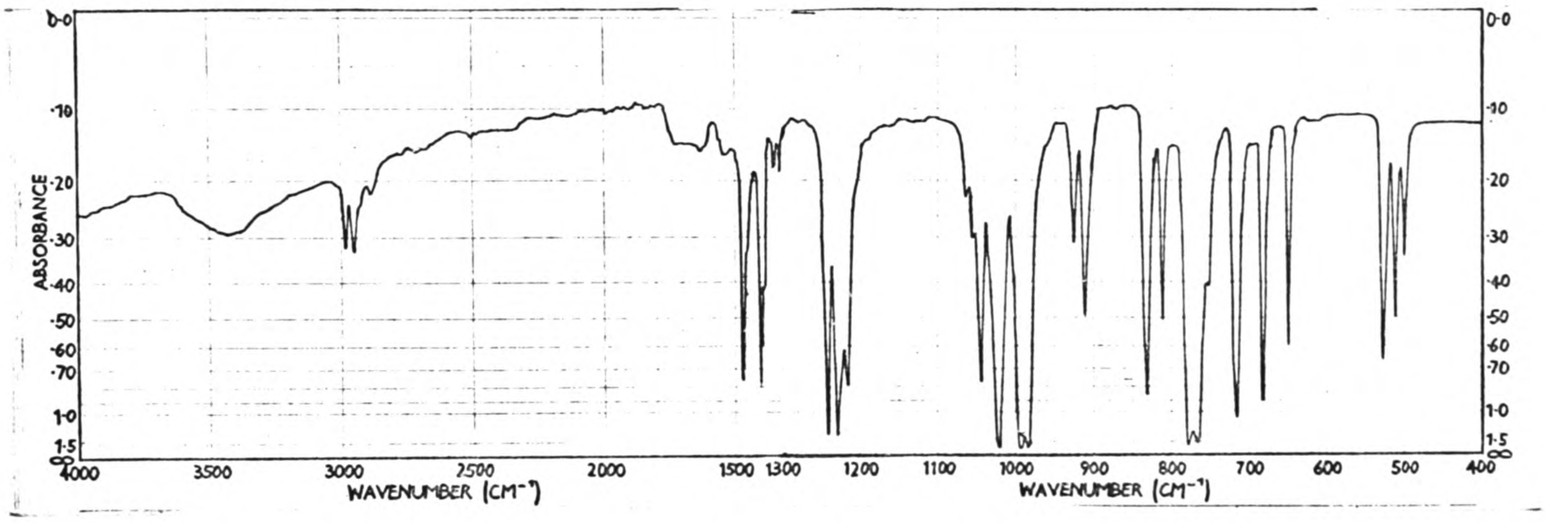
I.R. No. 1 Hexamine



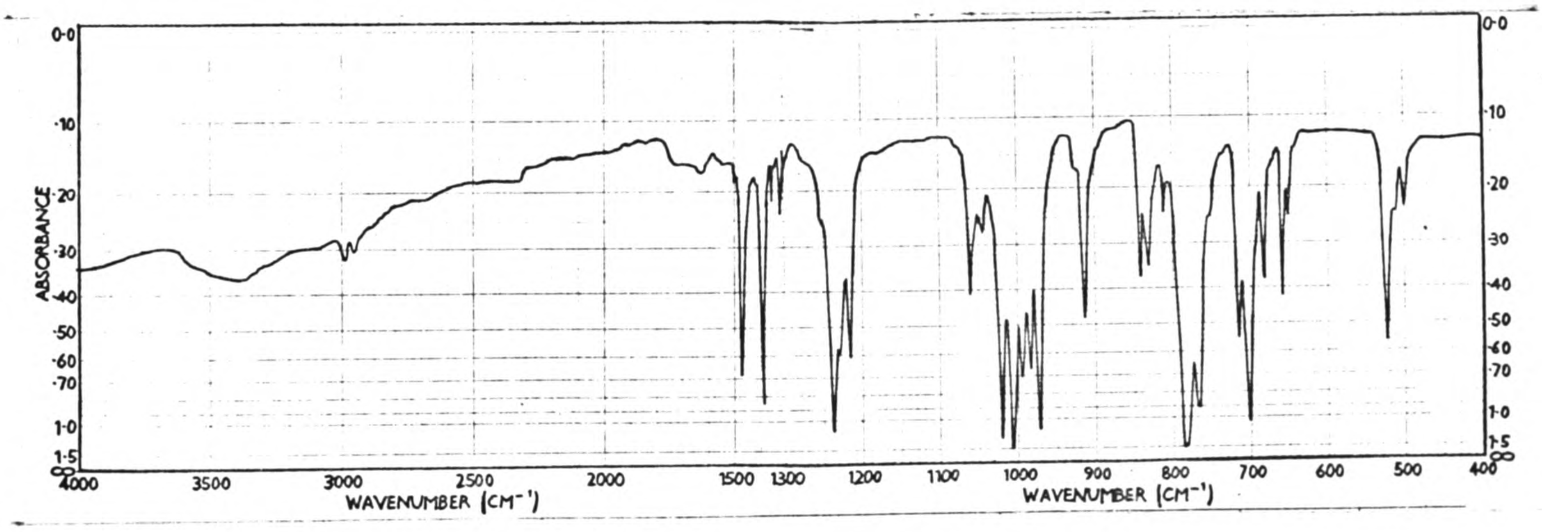
I.R. No. 2 Hex: I_2, 1:3



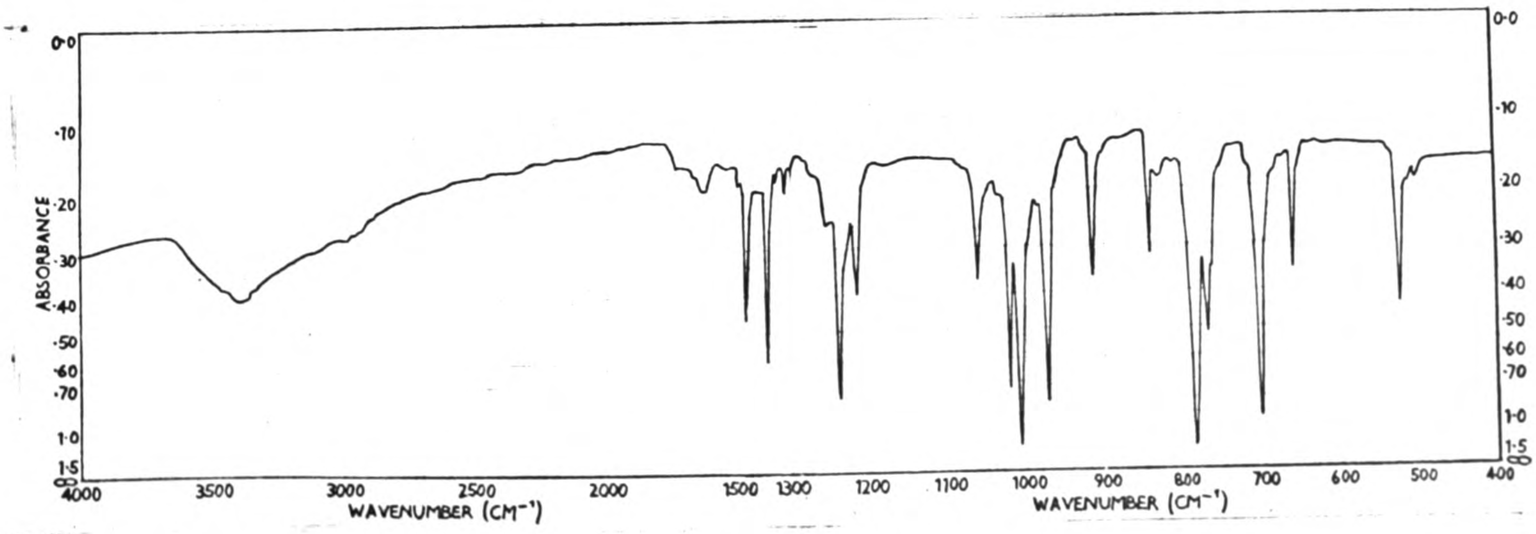
I.R. No. 3. Hex:ICl, 1:1



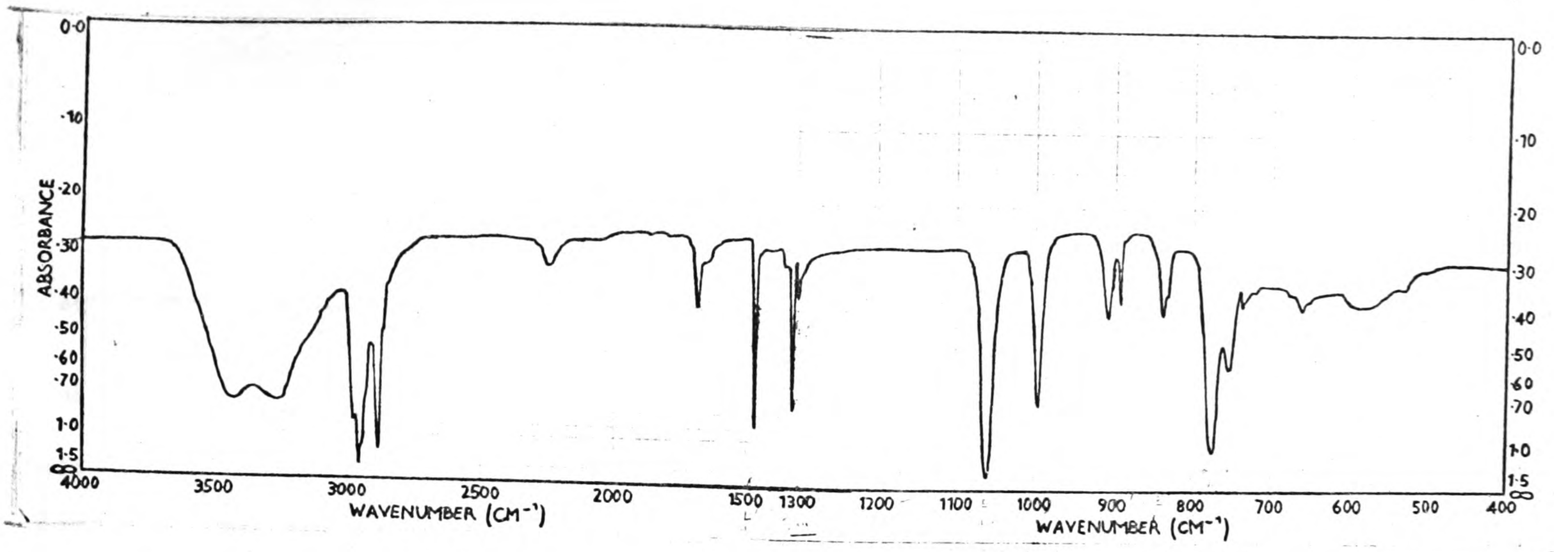
I.R. No. 4. Hex:ICl, 1:2



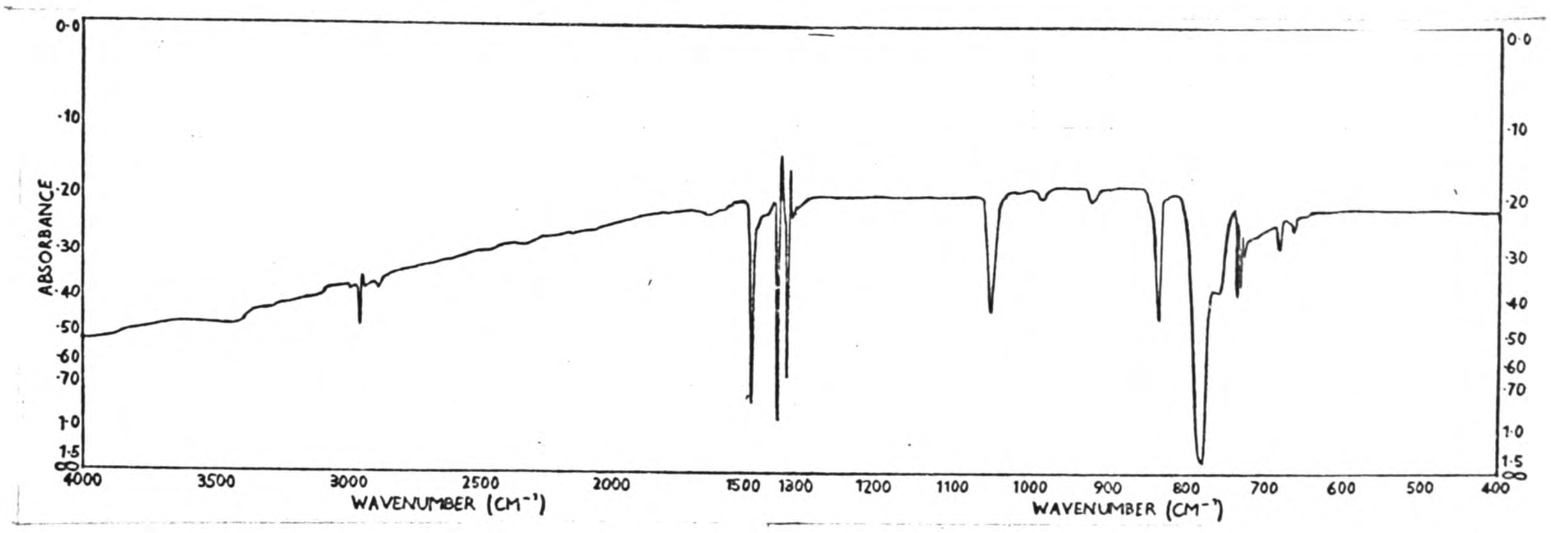
I.R. No. 5. Hex:ICl, 1:3



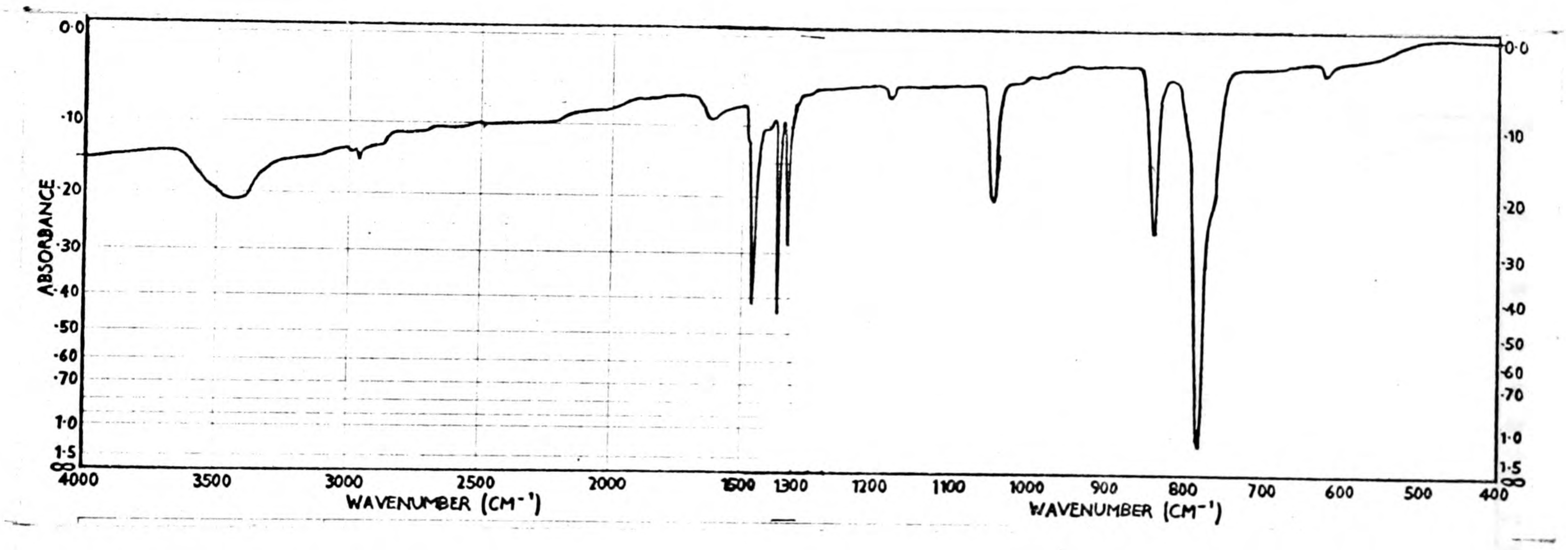
I.R. No. 6. Hex:ICl, 1:4



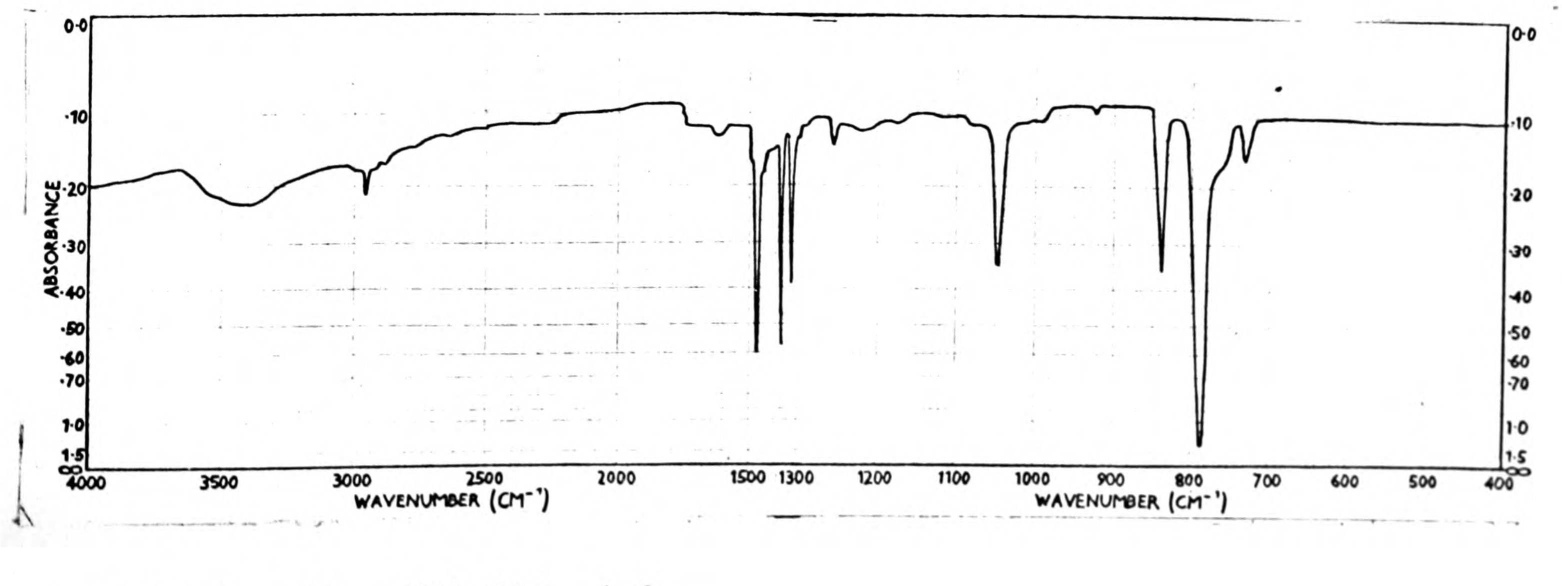
I.R. No. 7 TED



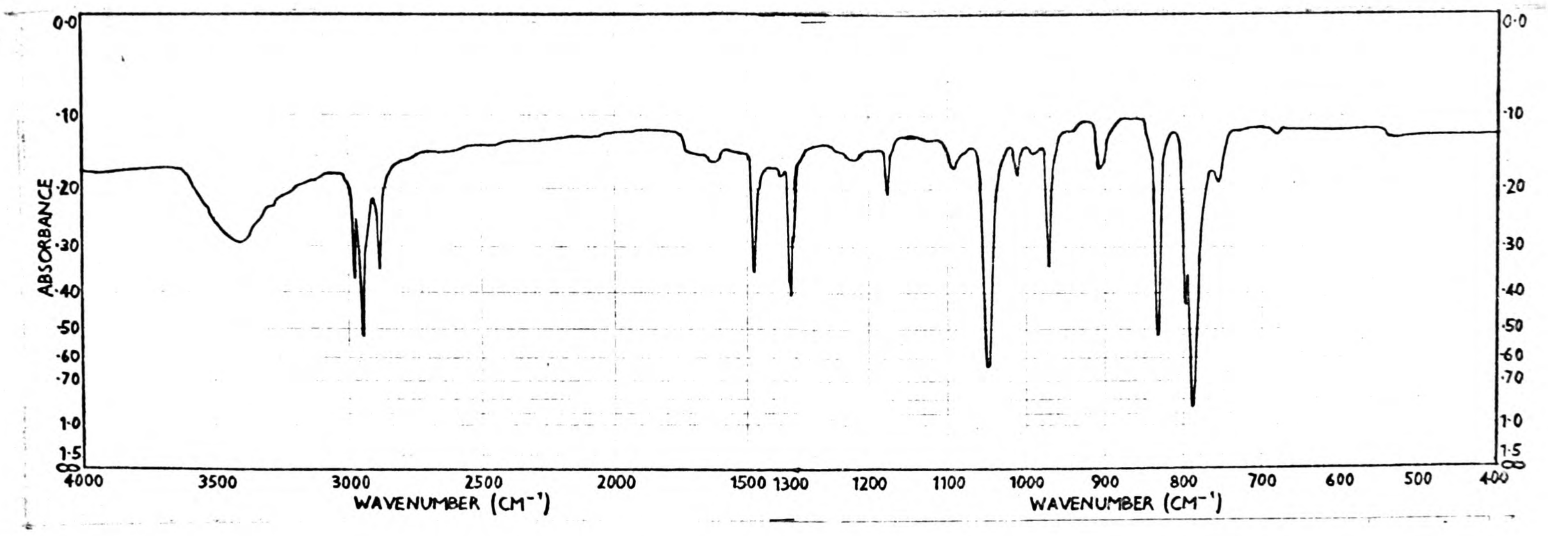
I.R. No. 8. TED:I_2, 1:2



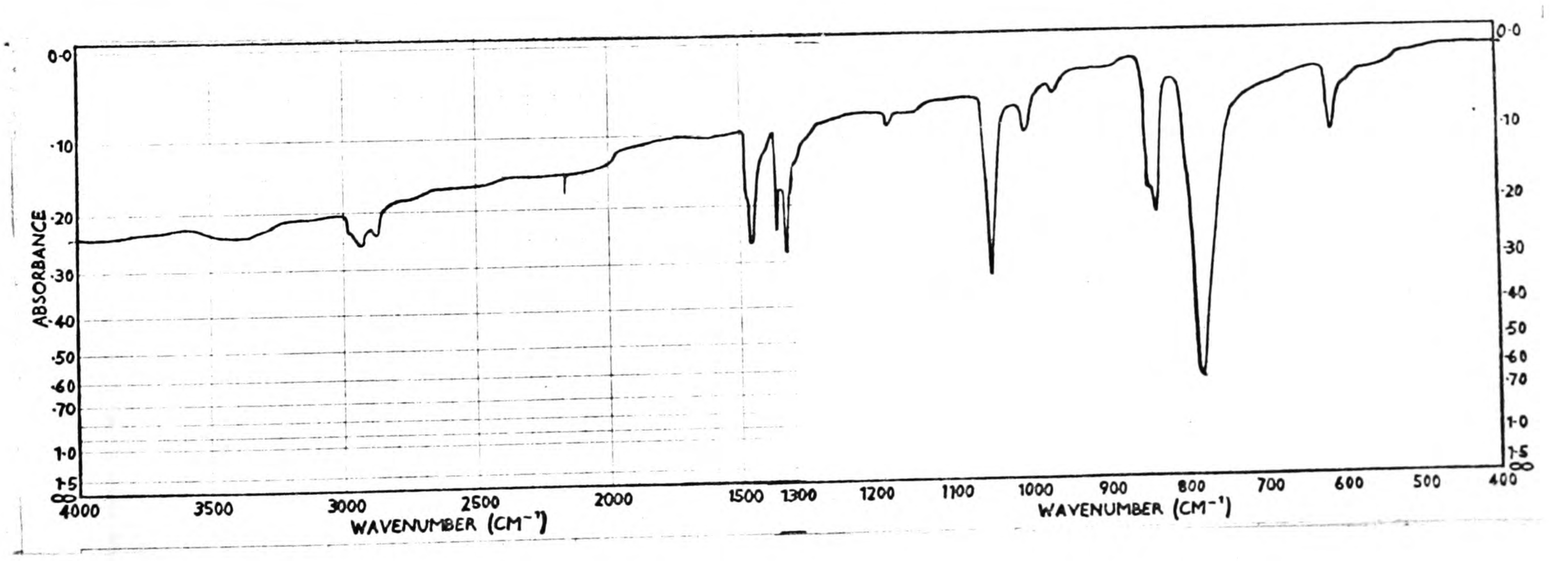
I.R. No. 9. TED:Br_2, 1:2



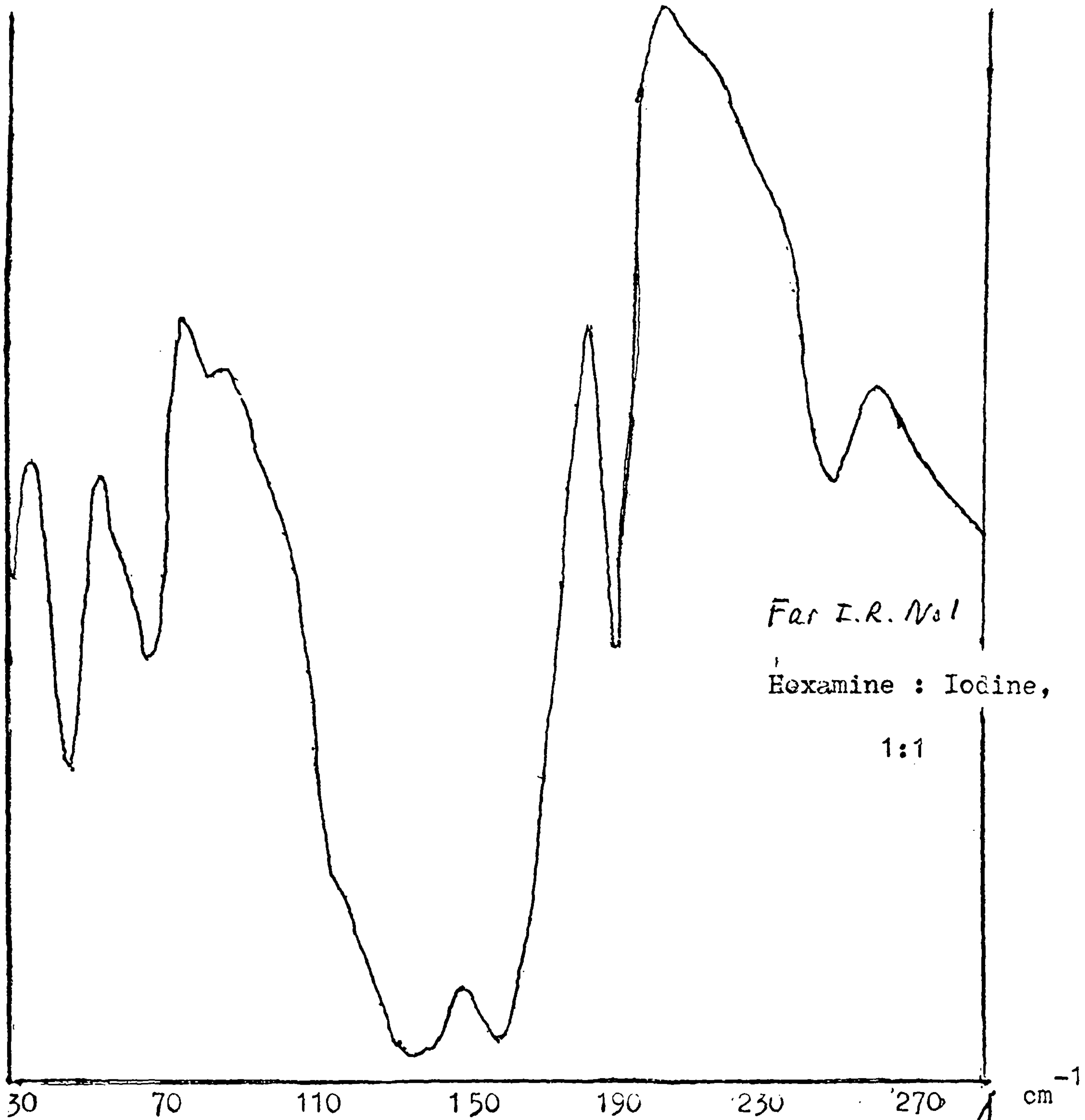
I.R. No. 10. TED:ICl, 1:2



I.R. No. 12. TED:ICl, 1:1



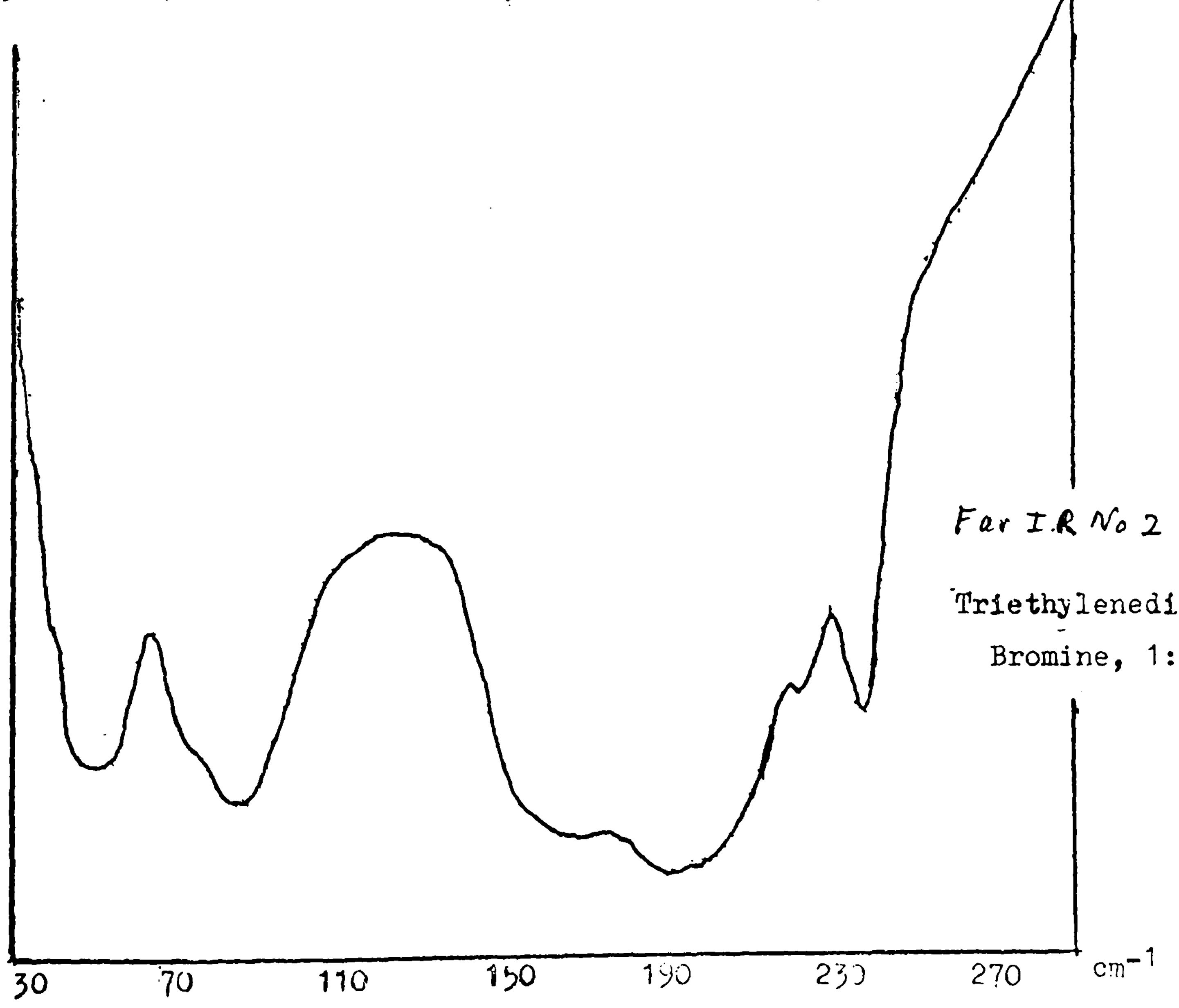
I.R. No. 11. TED :Br_2, 1:1



Far I.R. No 1

Hexamine : Iodine,

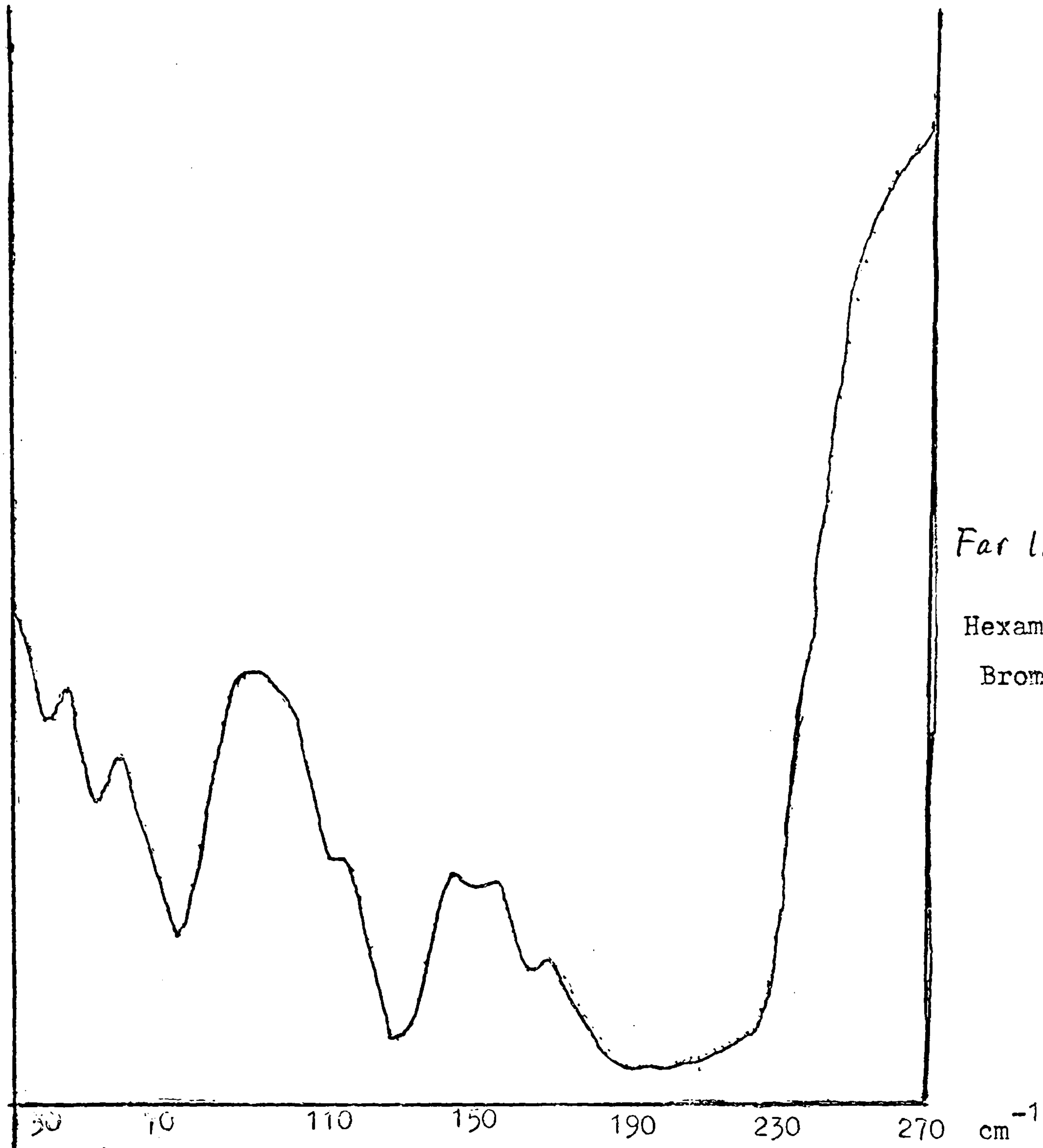
1:1



Far I.R No 2

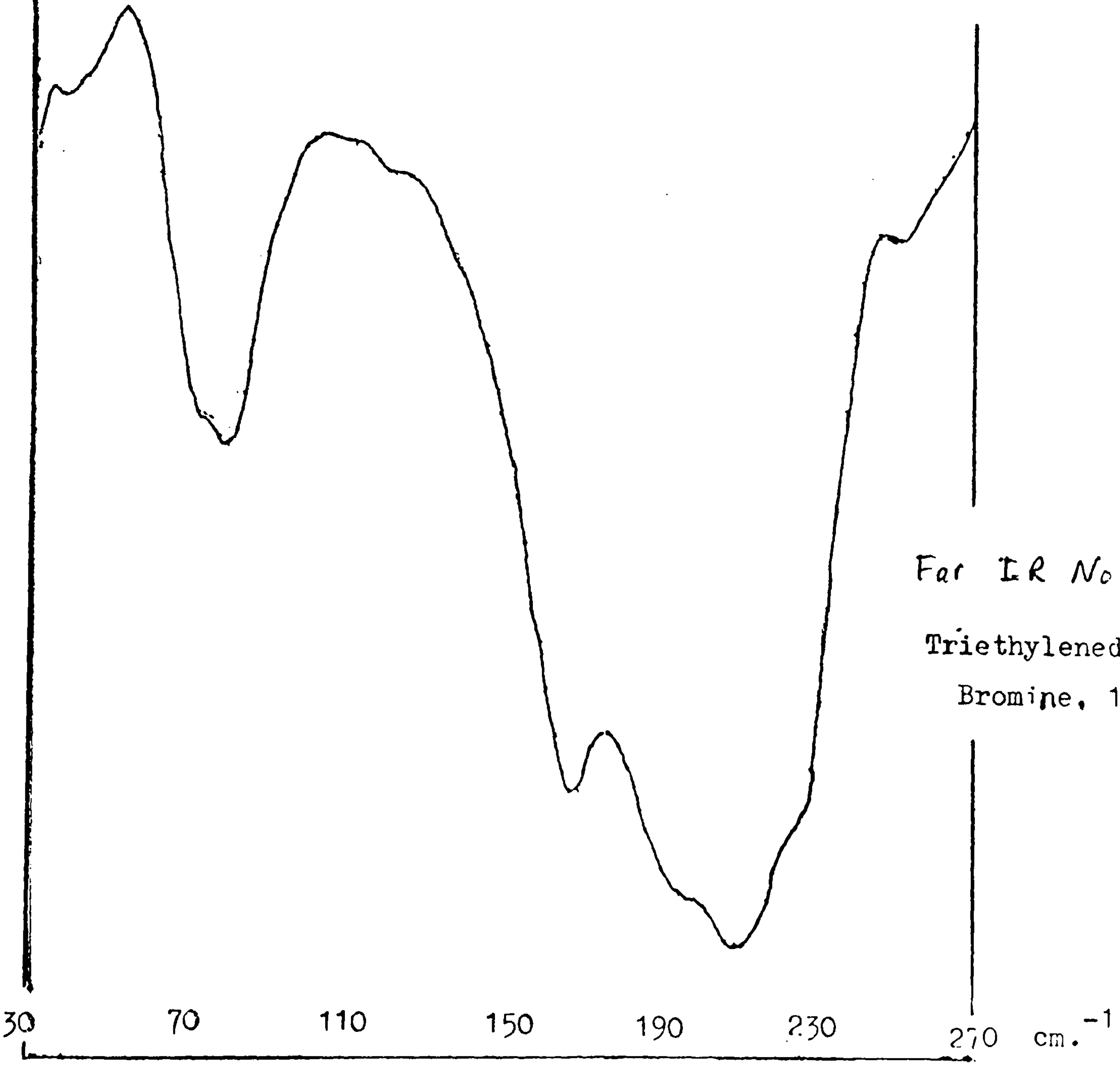
Triethylenediamine:

Bromine, 1:1



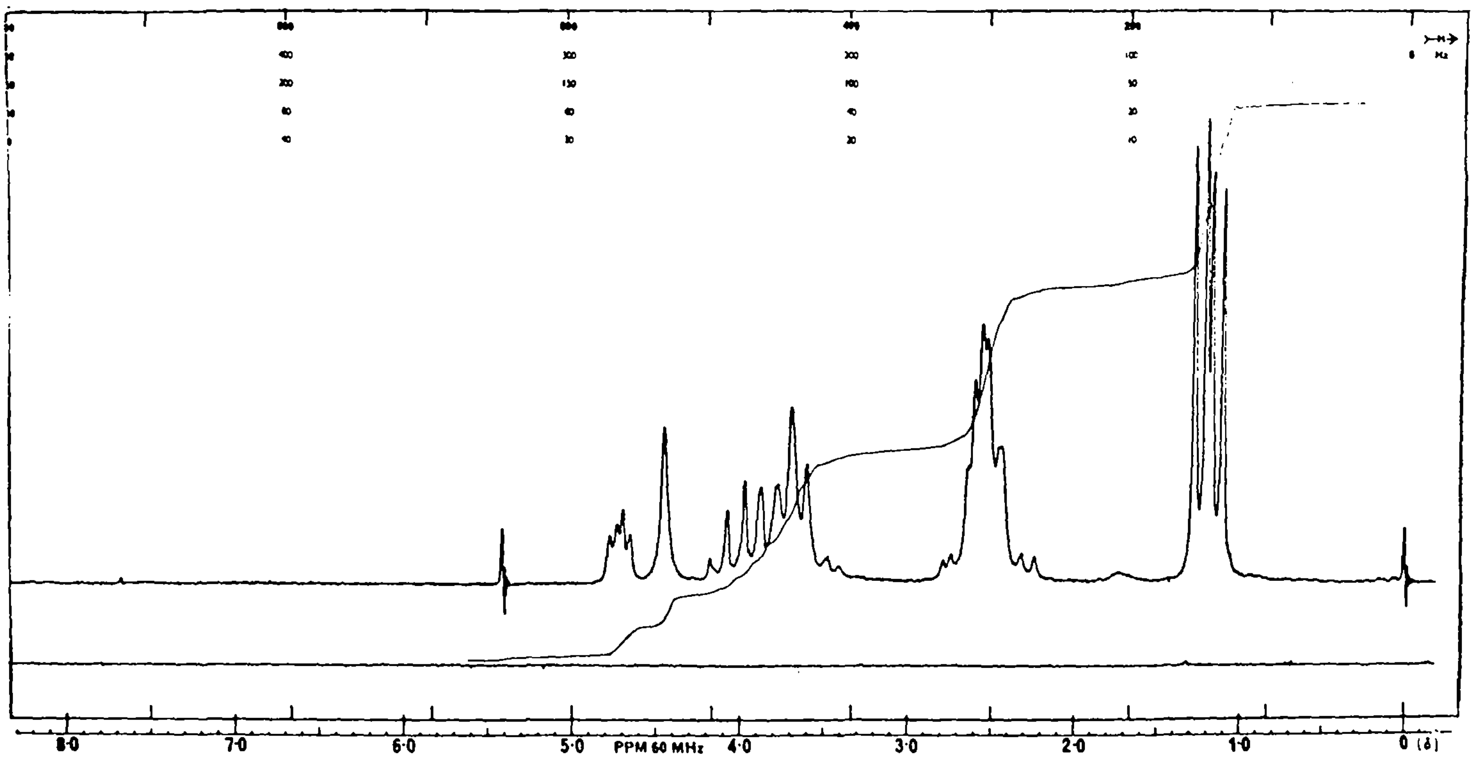
Far IR No. 3

Hexamine:
Bromine, 1:2

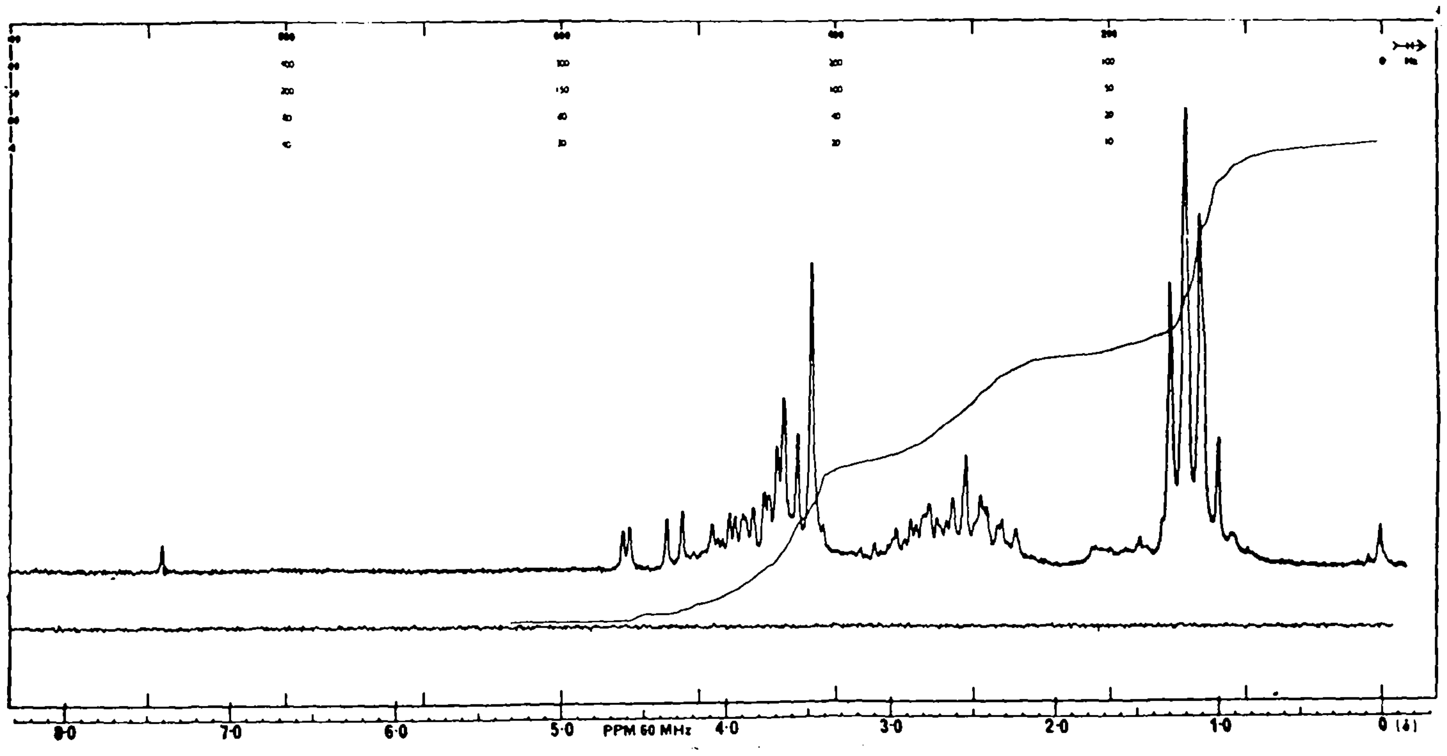


Far IR No 4

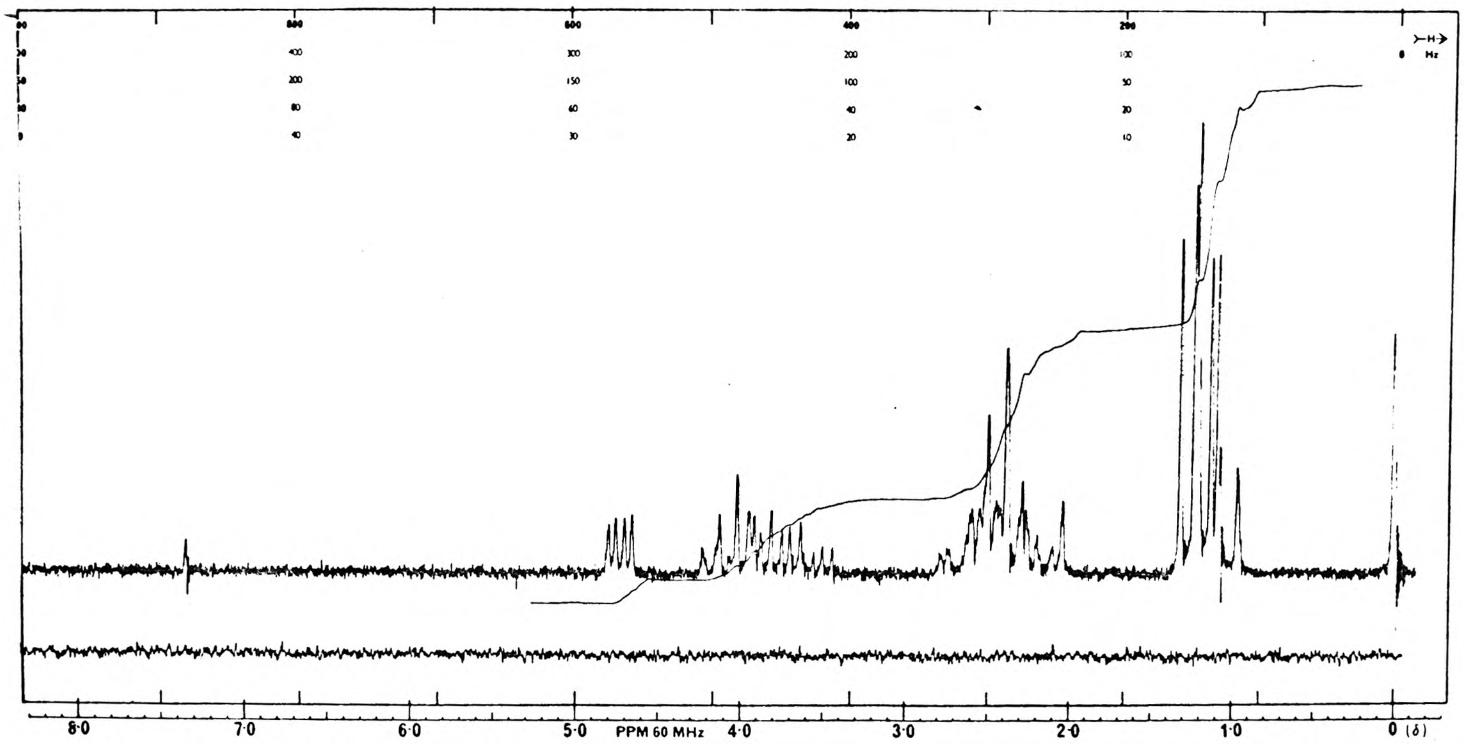
Triethylenediamine,:
Bromine, 1:2



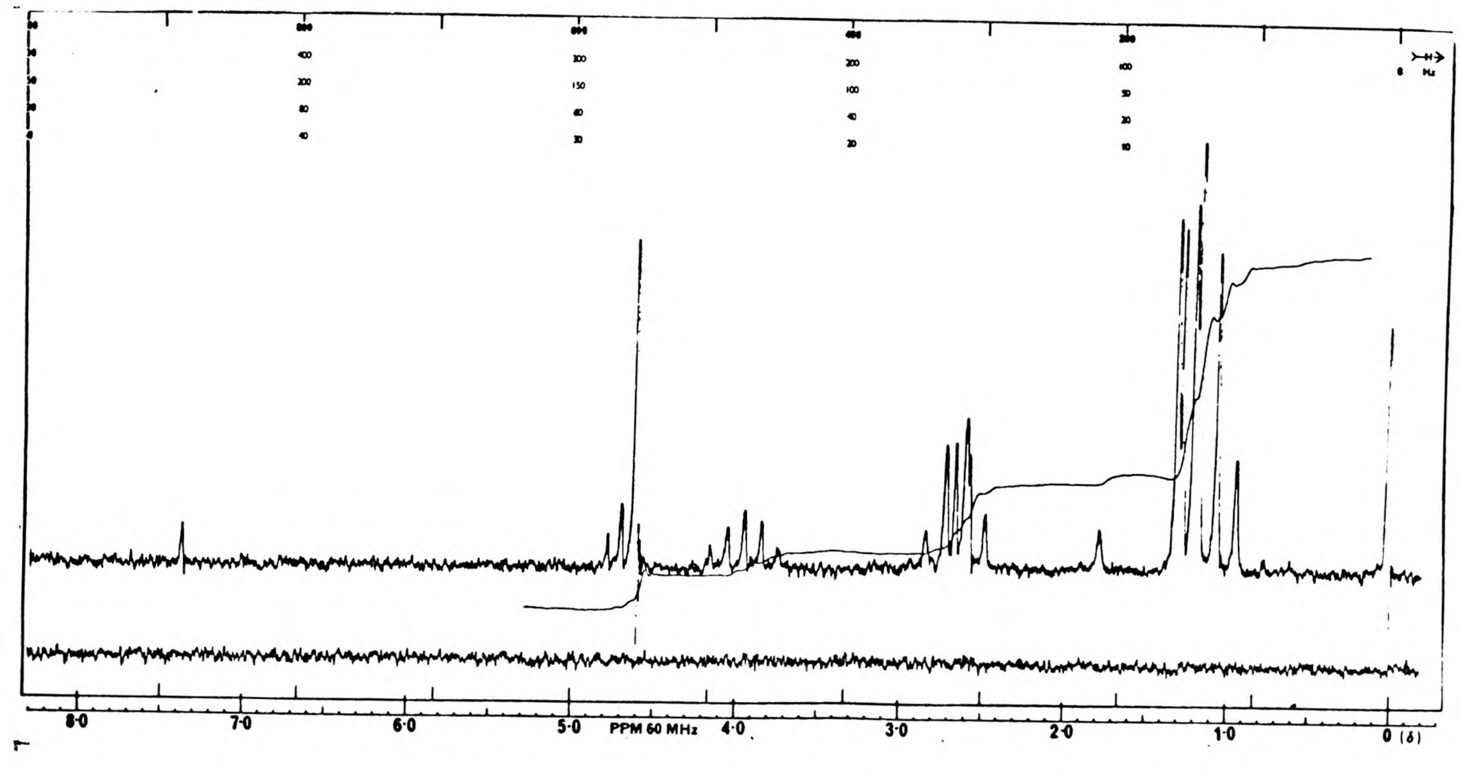
PMR No. 1. Oxidation product of C2DEA (XIX)



PMR No. 3. Oxidation product of C3DEA (XX)



PMR No. 2. Oxidation product of Diethylaminoethanol (XXI)



PMR No. 4. Oxidation product of of triethylamine (XXII)

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