## *The preparation and reactions of highly chlorinated indoles*

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UNIVERSITY OF DURHAM

A Thesis

entitled

# THE PREPARATION AND REACTIONS OF HIGHLY CHLORINATED INDOLES

Submitted by

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A Candidate for the Degree of Master of Science

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Thanks are also due to many technical and laboratory staff for their help, and to Durham University for a maintenance grant.

## MEMORANDUM

The work described in this thesis was carried out in the University of Durham between October 1970 and September 1973. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

## Summary

The action of sodium bisulphite and then acetic anhydride on indole gave sodium N-acetyl indoline-2-sulphonate. Chlorination of this compound has been shown to give a trichloroindole or a mixture of polychlorinated indoles depending on the conditions employed. Investigation of this reaction has shown that a 5,7-dichloroindole and a 5,6,7-trichloroindole could be isolated, again depending on the reaction conditions.

5,6,7-Trichloroindole was chlorinated further using sulphuryl chloride, chlorine, or phosphorus pentachloride to yield 3,5,6,7-tetrachloroindole, 2,3,3,5,6,7-hexachloroindolenine and 2,3,3,4,5,6,7-heptachloroindolenine respectively.

A synthetic route to 2,3,3,4,5,6,7-heptachloroindolenine was devised starting with the ammination of hexachlorobenzene to give pentachloroaniline. The ammination reaction was dropped in favour of the reduction of pentachloronitrobenzene as the yields of the latter proved much higher and the product easier to purify. The pentachloroaniline was heated with trichloroacetyl chloride at reflux to give octachloroacetanilide which was heated with phosphorus pentachloride at 170° for 6 hrs. to produce N-pentachlorophenyl trichloroacetimidoyl chloride. This product was dechlorinated at 380-400° for 8 hrs. in a stream of nitrogen to give 2,3,3,4,5,6,7-heptachloroindolenine.

The action of oxygen or nitrogen nucleophiles on heptachloroindolenine displaced a chlorine atom at C-(2) to give 2-substituted hexachloroindolenines, whereas the action of nucleophiles such as sodio diethyl malonate, sodium thiophenoxide, or thiophenol reduce heptachloroindolenine to 2,3,4,5,6,7-hexachloroindole as does lithium aluminium hydride.

Similarly heptachloroindolenine is reduced and alkylated by trimethyl phosphite to 1-methyl-2,3,4,5,6,7-hexachloroindole.

The action of magnesium or n-butyl-lithium in tetrahydrofuran on heptachloroindolenine gave N-metallohexachloroindoles which were either hydrolysed to 2,3,4,5,6,7-hexachloroindole or alkylated by dimethyl sulphate to 1-methyl-2,3,4,5,6-hexachloroindole.

The reaction of antimony pentachloride with heptachloroindolenine was expected to produce the anti-aromatic hexachloroindole cation which could be quenched with methanol. The reaction however gave a moderate yield of pentachloroaniline indicating the five membered ring had broken up.

Catalytic hydrogenation of heptachloroindolenine and 2,3,4,5,6,7-hexachloroindole gave 4,5,6,7-tetrachloroindole and catalytic hydrogenation of 1-methyl-2,3,4,5,6,7-hexachloroindole gave 1-methyl-4,5,6,7-tetrachloroindole.

# CONTENTS

## General Introduction

In the past very few papers have been published on the synthesis of highly chlorinated indoles and indolenines.

Work on the chlorination of sodium N-acetyl indoline-2-sulphonate initially started by workers for E. Merck A.-G.[51,52] was followed up by workers at Durham University[54] who showed that a trichloroindole could be isolated and chlorinated further to what was incorrectly believed to be 1,2,3,4,5,6,7-heptachloroindole, but was shown by the author to be 2,3,3,4,5,6,7-heptachloroindolenine.

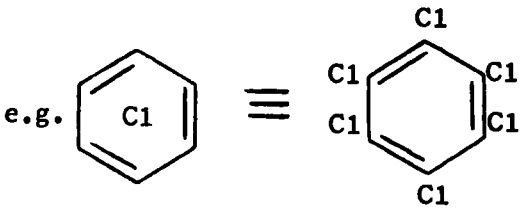
Heptachloroindolenine had already been prepared by the pyrolitic cyclisation of N-pentachlorophenyl trichloroacetimidoyl chloride by workers for Farbenfabriken Bayer A.-G.[103]

A synthesis of heptachloroindolenine was devised starting from cheap and readily available materials using the pyrolitic cyclisation of N-pentachlorophenyl trichloroacetimidoyl chloride as the last step.

The remainder of the work in this thesis is concerned with the further chlorination of 5,6,7-trichloroindole and the metallation, catalytic reduction of heptachloroindolenines and its reaction with various nucleophiles and some other reagents.

Note.

In the structures which contain the symbol Cl in the centre of a ring, this is intended to represent the fact that the carbon atoms of the ring are attached to chlorine, except where otherwise indicated.



# CHAPTER I

## PREPARATION OF HALO-INDOLES AND HALO-INDOLENINES

## 1.1. PREPARATION OF HALO-INDOLES.

### 1.1.1. INTRODUCTION OF HALOGEN INTO INDOLE COMPOUNDS.

#### 1.1.1.1. Halogenation of Indole.

Although halogenation of indoles has not been studied extensively from a mechanistic viewpoint, synthetic studies show halogenation largely follows the normal pattern of electrophilic substitution.

Substitution generally takes place at the 3-position and when this is blocked, at the 2-position, except when the substituent at the 3-position is strongly electron withdrawing in which case substitution will take place at the 5- or 6-position.[1,2] When both the 2- and 3-positions are blocked further substitution takes place in the benzene ring.

Nitration and Friedel-Crafts acylation studies amongst others have established the general order of positional reactivity for electrophilic aromatic substitution in the neutral indole molecule as:

$$3 > 2 > 6 > 4 > 5 > 7$$

Substitution at C-7 is rare.

Numbering system for indole and indolenines

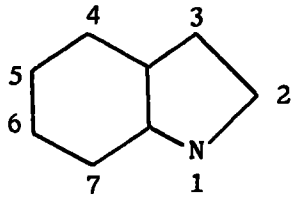
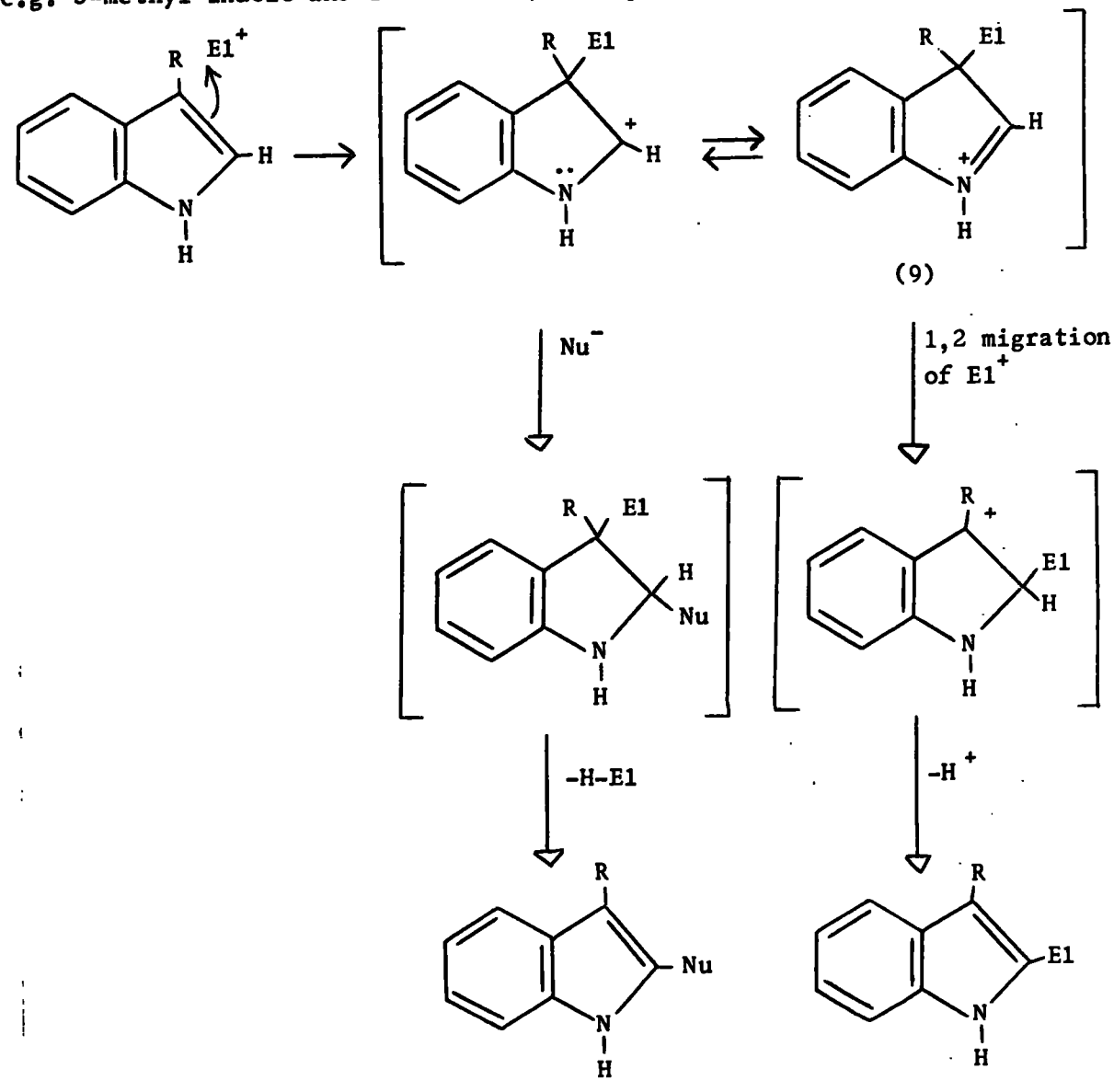



FIG. 1.

Theoretical approaches to the problem give the correct choice for the most reactive site in the indole ring (C-3) and often the second most reactive site (C-2) correctly; however the theoretical order of reactivity of the benzo-positions is at variance with that observed.

Jackson[3] has shown that all electrophilic substitution reactions of 3-alkyl indoles take place at C-3 to give an indolenium ion (9) which

rearranges to give a 2,3-disubstituted indole (Eqn. 1). However if nucleophiles are present these may attack at C-2 to give an indoline which eliminates H-El to give a 2,3-disubstituted indole different to that above (e.g. 3-methyl indole and IC1 Table 1). (Eqn. 1.).




Eqn. 1.

A list of selected chlorination reactions of indoles is given in Table 1.

Table 1.

Chlorination of Indoles

| Substitution | Reagent, Position (Reference) |
|---|---|
| - | $Cl_2O/CHCl_3$, 1(4) |
| - | Sulphuryl chloride, 3(5c,6,8) then 2(5c,6) |
| 1-Methyl | Sulphuryl chloride, 3 and 2(5c) |
| 1-Benzoyl | Chlorine, 3(7,8) |
| 2-Methyl | N-chlorosuccinimide, 3(6)<br>Sulphuryl chloride, 3(5a) |
| 2-Carbethoxy | Phosphorus pentachloride, 3(9) then 6(9)<br>Sulphuryl chloride, 3(9) |
| 3-Methyl | Sulphuryl chloride, 2(5b)<br>Iodine monochloride, 2(5c) |

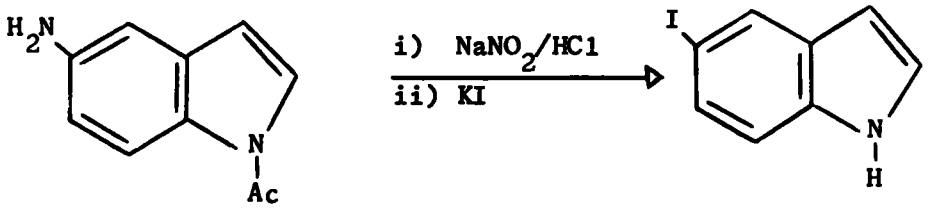
3-Halo-indoles can be obtained from their N-acyl derivatives by treatment with sodium ethoxide in ethanol[7,8,10] or with dilute ammonia.[7]

Bromination of indole[12,13,14] or 1-benzoyl indole[7a,15] takes place at C-3 as expected. However bromination of indoles with strongly electron withdrawing substituents at C-3, e.g. formyl,[16] acetyl,[17] or carbethoxy[18,19,20] do not substitute at C-2 but at C-5 and/or C-6.

Iodination of indole,[7a,14,21,22b,23] 1-benzoyl indole,[7a] or some 2-substituted indoles[14,22a,23,24] with iodine or iodine monochloride places an iodine at C-3, whereas the action of iodine on 3-methyl indole places an iodine at C-2.[5b] The action of iodine monochloride on 3-methyl indole gives 2-chloro-3-methyl indole and the reaction is thought to proceed via a 3-iodoindolenium ion which is attacked at C-2 by chloride ion.[25]

1.1.1.2. Preparation by the Sandmeyer Reaction.

5-Iodoindole (4) has been prepared by the Sandmeyer Reaction[27,28] with 1-acetyl-5-aminoindole (3). (Eqn. 2).

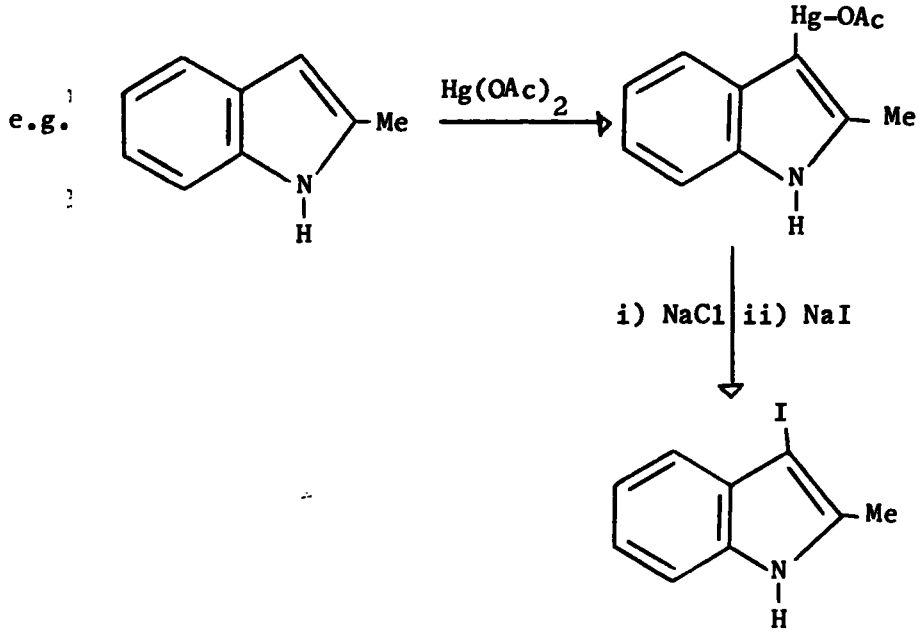



(3) (4) Ref. 27,28

Eqn. 2.

1.1.1.3. Preparation by Mercuration.

Indoles react with mercuric chloride[29] and mercuric acetate[30,31,32] to give chloromercuri- and acetoxymercuri-derivatives respectively. Sodium chloride converts acetoxymercuri-derivatives to chloromercuri-derivatives which in turn yield iodoindoles on treatment with sodium iodide.[30,33,34]



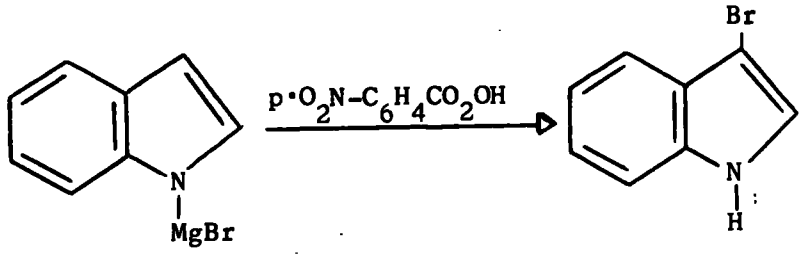

Ref. 34

Eqn. 3.

1.1.1.4. Preparation from Grignards.

Oxidation of indolyl magnesium bromides with paranitroperbenzoic acid gives indoles brominated in the pyrrole ring.[35,36]

e.g.




(5) (6) Ref. 35

Eqn. 4.

Treatment of indolyl magnesium bromide (5) with di-iodoacetylene gave 3-iodoindole.[37]

1.1.1.5. Halogen Exchange.

4-Bromo- and 6-bromo-indoles have been converted to the respective chloroindole by refluxing the bromoindole or bromoindole-2-carboxylic acid with cuprous chloride and quinoline.[38]

1.1.2. INTRODUCTION OF HALOGEN INTO OXINDOLE, DIOXINDOLE AND INDOLINE COMPOUNDS.

1.1.2.1. Halogenation of Oxindoles and Oxindole Derivatives.

The presence of the acyl amino group on the aromatic ring in oxindole activates positions 5 and 7 towards electrophilic substitution reactions.

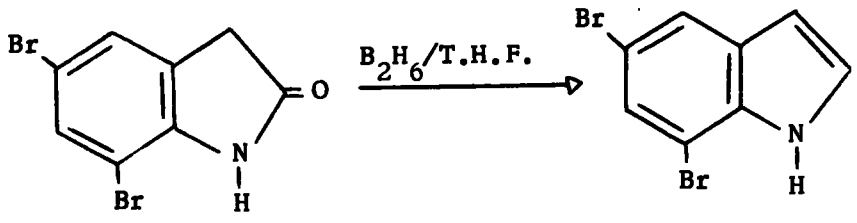
Bromination of oxindole[39,40] and some N-substituted derivatives[40,41] in water yield 5-bromo-oxindoles with one equivalent of bromine,[39,40,41] and 5,7-dibromo-oxindoles with two equivalents of bromine[39,41] in water. Three molecular proportions of bromine with oxindole in water gave 3,5,7-tribromo-oxindole.[39]

The products of chlorination of oxindole derivatives have been assumed to be the 5,7-dichloro derivative by analogy with the structure of the

bromination products.[42]

The action of iodine monochloride on oxindole produced a mono iodo-oxindole of unknown structure, but the action of potassium iodide and potassium iodate in acetic acid gave 5-iodo-oxindole.[43]

5,7-Dibromo-oxindole (7) and 5-iodo-oxindole have been reduced with borane in tetrahydrofuran to 5,7-dibromoindole (8) and 5-iodoindole respectively.[44] (Eqn. 5).



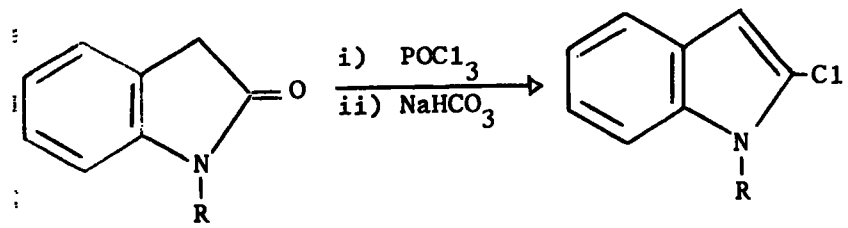

(7) (8) Ref. 44

Eqn. 5.

Indoles chlorinated in the pyrrole ring have been prepared directly from oxindole and dioxindole.

The action of phosphorus pentachloride on either oxindole or dioxindole was reported to give 2,3-dichloroindole.[26]

2-Chloroindoles (2) has been prepared from oxindoles (1) by the action of phosphorus oxychloride and sodium bicarbonate.[6] (Eqn. 5a).



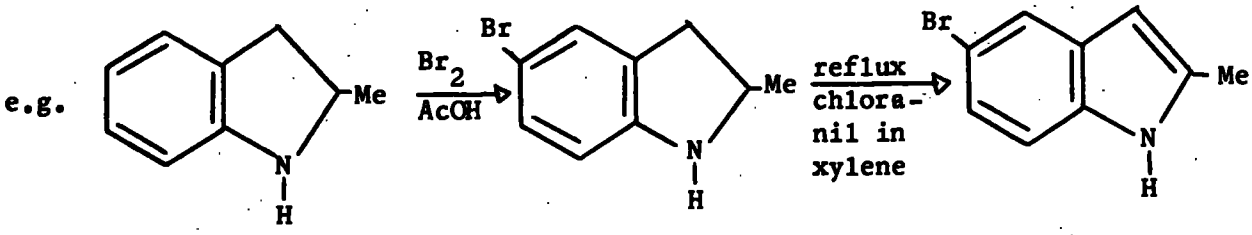

Ref. 6

R = H, PhCO

Eqn. 5a.

1.1.2.2. Halogenation of Indolines and Subsequent Dehydrogenation to Indole.

The indoline system is a substituted aniline system and as such the amino system directs electrophilic agents primarily para, to the 5-position, and ortho, to the 7-position as a secondary site in the neutral amine and N-acyl derivative. When coupled with a suitable method of subsequent dehydrogenation of the indoline to indole, it is a useful synthetic route to substituted indoles.[45] (Eqn. 6).



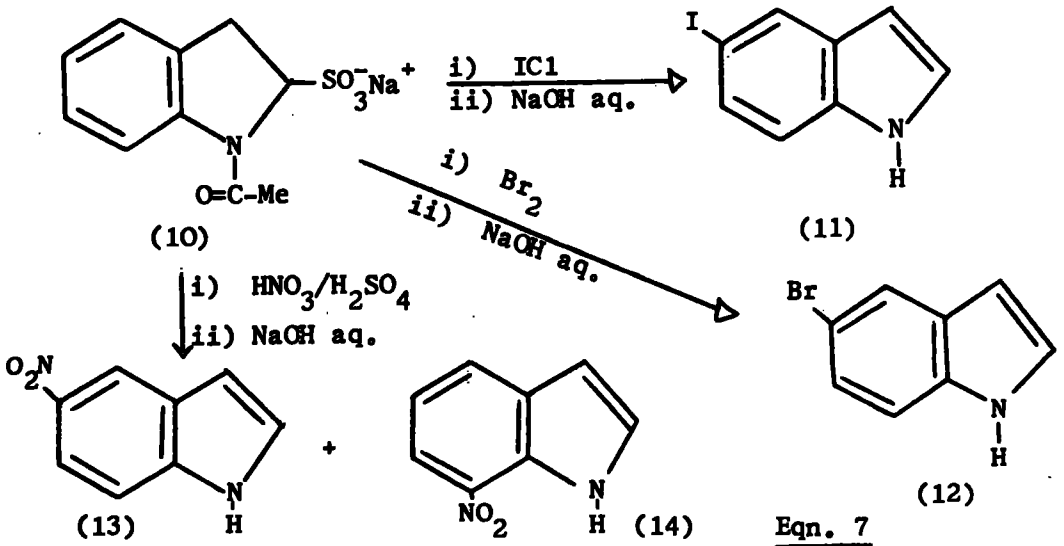

Ref. 45

Eqn. 6.

A number of halo-indoles have been prepared in this way.[45-50]

1.1.2.3. Halogenation of Sodium N-acetyl Indoline-2-Sulphonate and Subsequent Hydrolysis to Indoles.

This synthetic route involves the addition of sodium bisulphite to indole to give sodium indoline-2-sulphonate[51-53,55-57] followed by acetylation to sodium N-acetyl indoline-2-sulphonate[51-54] (10). This on treatment with iodine monochloride or bromine gives on alkaline hydrolysis 5-iodoindole[51-53] (11) and 5-bromoindole[51-53] (12) respectively. Nitration of sodium N-acetyl indoline-2-sulphonate with conc. nitric acid and conc. sulphuric acid gives on alkaline hydrolysis a mixture of 5-nitroindole (13) and some 7-nitroindole (14).[51-53] (Eqn. 7).




Eqn. 7

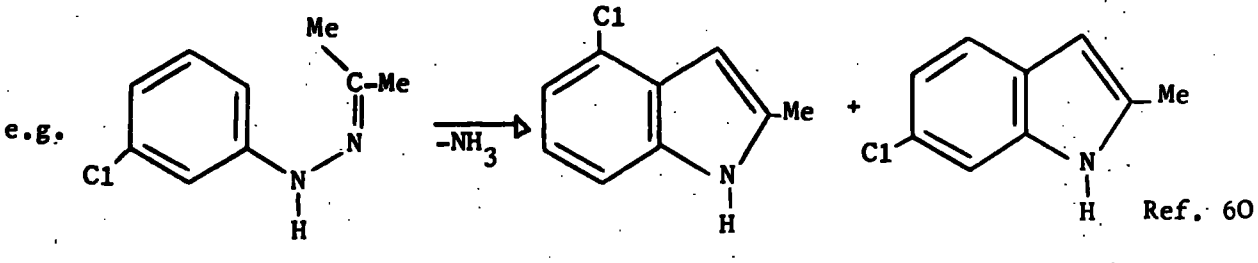
Chlorination of (10) in water[52] gives on alkaline hydrolysis a trichloroindole[54] which the author has shown to be 5,6,7-trichloroindole.

### 1.1.3. CYCLISATION METHODS.

#### 1.1.3.1. Fischer Cyclisation.

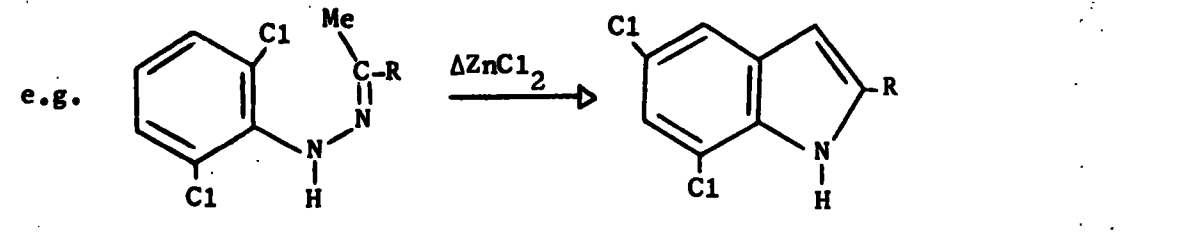
The cyclisation of aryl hydrazones to indoles known as the Fischer Indole Synthesis remains the most versatile and widely applied reaction for the formation of the indole ring system, and much work has been done regarding the mechanism of the reaction.

If the aryl hydrazone has only one orthoaryl hydrogen the order of the benzo ring substituents in the product is unambiguous, but if there are two orthoaryl hydrogen atoms then only if both meta substituents are the same[62] will the substitution in the benzo ring be unambiguous; otherwise two products may form.[60] (Eqn. 8). However some reactions give one product only.




Eqn. 8.

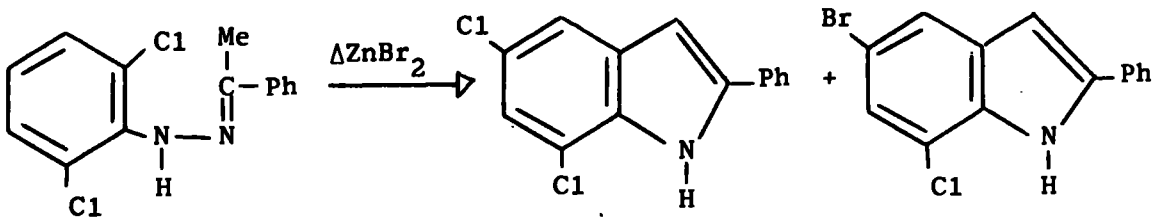
When the meta substituent is ortho-para directing in electrophilic substitution (e.g. halogen) the formation of 6-substituted indoles is favoured over 4-substituted indoles,[79] and the reverse is usually true of meta directing groups. Those reactions which do not give the predicted substitution ratio can probably be accounted for by steric hindrance.[58] If there are no orthoaryl hydrogens in the aryl hydrazone then an unusual substituent migration may occur. (Eqn. 9).




R = Ph, pCl-$C_6H_4$.

Eqn. 9.

When this reaction was repeated using zinc bromide in place of zinc chloride catalyst the 'migrating chlorine' suffered halogen exchange. (Eqn. 10).




1:3

Eqn. 10

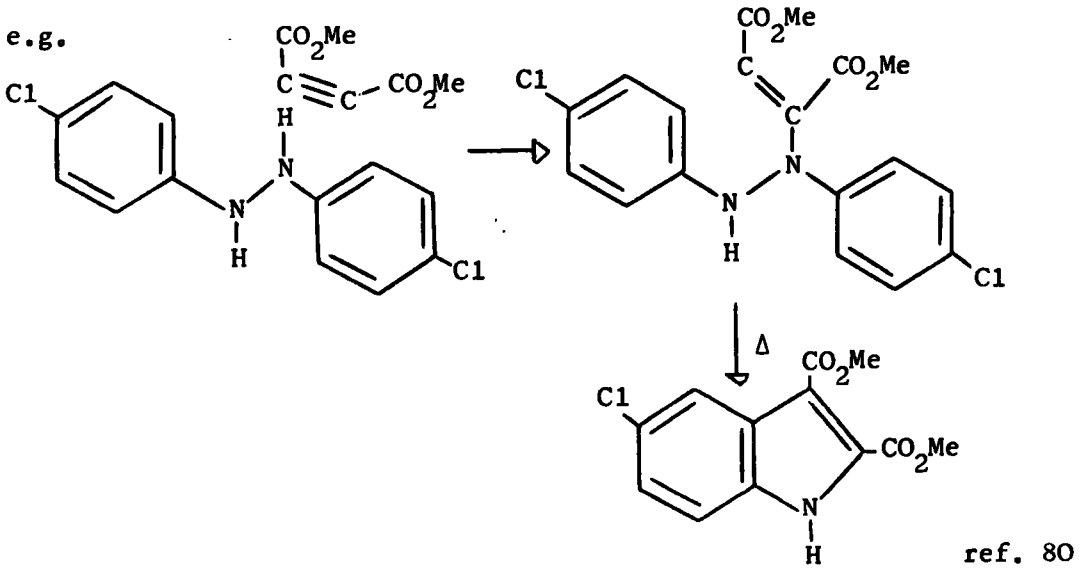
Using stannous chloride as catalyst the 'migrating chlorine' was lost through reduction to yield 7-chloroindoles.[61] This reduction indicates that the 'migrating chlorine' is in a positive condition.[59]

Catalysts for the Fischer cyclisation are either proton sources or Lewis acids, e.g. zinc chloride, polyphosphoric acid, but often no catalyst is necessary only inert solvent at elevated temperatures.[70]

The Fischer Indole Synthesis has been used to prepare chloroindoles,[58,60-62,64-74] bromoindoles,[18,72-79] and chlorobromoindoles.[71]

1.1.3.2. Diels and Reese Synthesis.

In the Diels and Reese Synthesis which resembles the Fischer Synthesis, hydrazobenzenes and acetylene dicarboxylic esters react to give intermediates which on heating give indoles. (Eqn. 11).



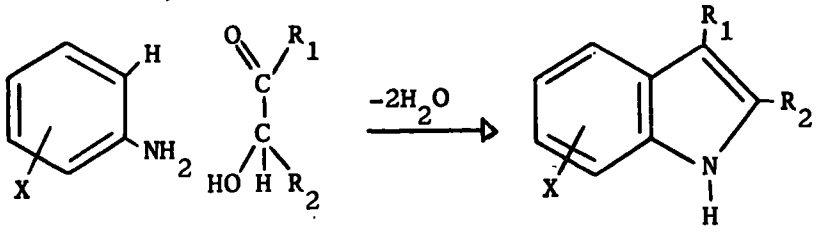

ref. 80

Eqn. 11.

Halo-indole esters formed by the Fischer, Diels and Reese, and Reissert synthesis have been saponified and the halo-indole acid decarboxylated at its melting point or by refluxing with the appropriate copper halide in quinoline.[8,81-84]

1.1.3.3. Bischler Synthesis.

The Bischler Synthesis makes use of the condensation reaction between aryl amines and α-halo-ketones or α-hydroxy-ketones.[85] Cyclisation occurs by electrophilic attack at the ortho position of the aniline ring by the carbonyl or imine group which can be enhanced by co-ordination by a proton or Lewis acid, followed by aromatisation. (Eqn. 12).



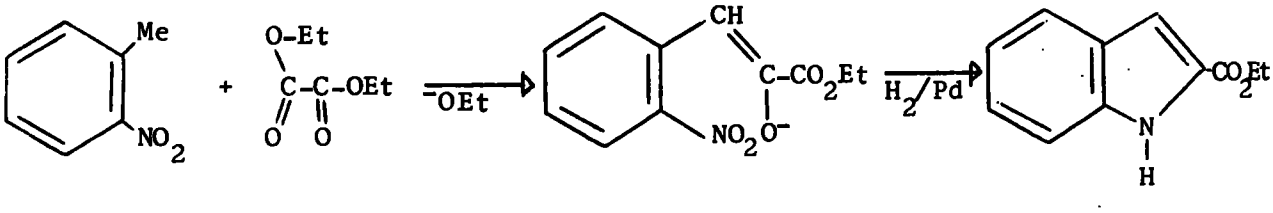
Eqn. 12.

This synthesis has been used to prepare a limited number of halo-indoles.[86,87]

1.1.3.4. Reductive Cyclisations.

1.1.3.4.1. Reissert Synthesis.

The Reissert Synthesis is the most widely known reductive indole cyclisation and involves base catalysed condensation of an orthonitrotoluene with an oxalate ester followed by reduction to give an indole 2-carboxylic ester. (Eqn. 13).



Eqn. 13.

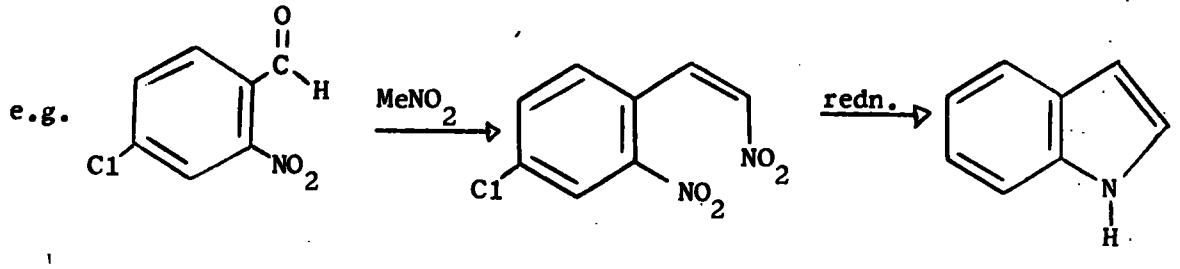
The common reducing agent for the final stage is hydrogen on palladium, however this reagent would result in dehalogenation and zinc and acetic acid[60,88] or ferrous sulphate and ammonia are preferred.

Ambiguity in the Reissert Synthesis and other listed reductive cyclisations is precluded through formation of the pyrrole moiety by reactions that occur external to the benzene ring.

Many halo-indoles have been prepared via this cyclisation.[18,38,60,64,66,83,89-92]

1.1.3.4.2. Cyclisation of Ortho Omega Dinitrostyrenes.

Orthonitrobenzaldehydes can be condensed with nitromethane to give ortho omega dinitrostyrenes which have been reductively cyclised to indoles. (Eqn. 14).



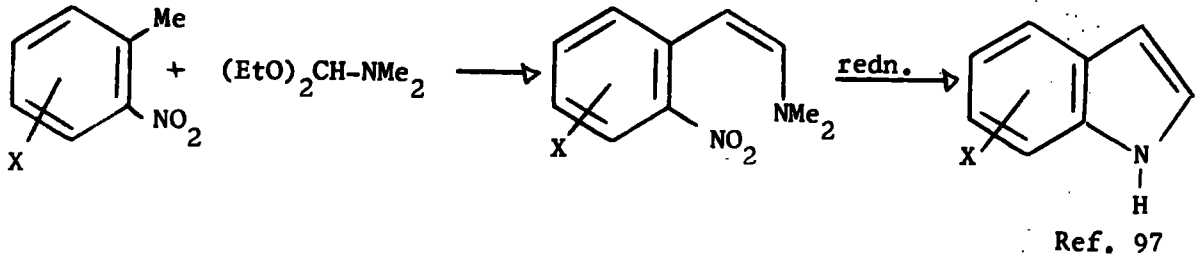

Ref. 64

Eqn. 14.

The cyclisation does not generally lead to structural ambiguity,[64,93,94] though iodine migration has occurred in some cyclisations[95] and dehalogenation has been observed in catalytic cyclisations.[95,96]

1.1.3.4.3. Cyclisation of Beta-amino Orthonitrostyrenes.

Orthonitro beta-amino styrenes, prepared by condensation of an ortho-nitrotoluene and a formamide acetal, has been reduced to indoles. (Eqn. 15).



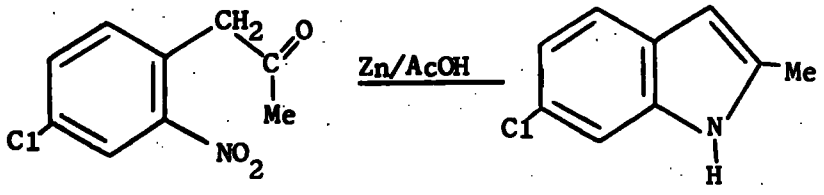

Ref. 97

Eqn. 15.

Three chloroindoles have been prepared in this way.[97]

1.1.3.4.4. Cyclisation of Orthonitrophenyl Beta Ketones.

A reaction similar to the Reissert Synthesis is the reductive cyclisation of orthonitrophenyl beta ketones. (Eqn. 16).

e.g. 


Ref. 60

Eqn. 16.

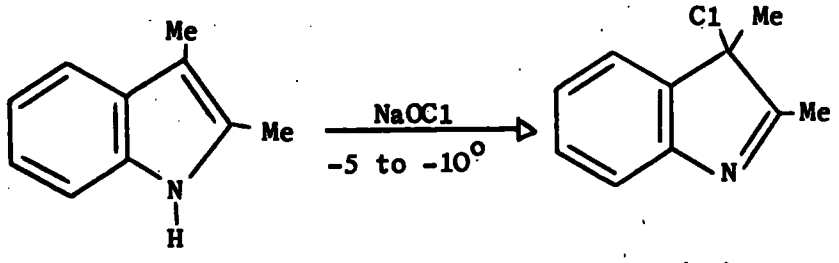
Other halo-indoles have been prepared by this method.[60]

1.2. PREPARATION OF HALO-INDOLENINES.

1.2.1. DIRECT HALOGENATION.

1.2.1.1. Halogenation of Indoles.

A 3-chloroindolenine has been prepared by the action of sodium hypochlorite on 2,3-dimethyl indole (15) but the product, 2,3-dimethyl-3-chloroindolenine (16)[98] is unstable above 15°C. (Eqn. 17).




Ref. 98

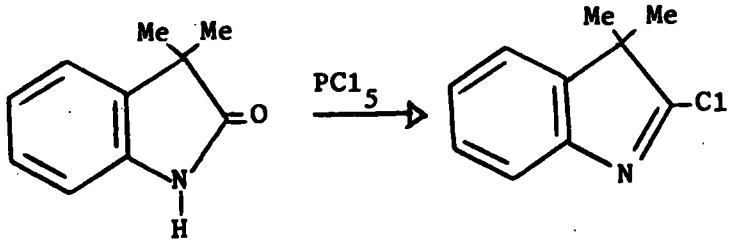
(15) (16)

Eqn. 17.

1.2.1.2. Halogenation of Oxindoles.

A 2-chloroindolenine has been prepared by the action of phosphorus pentachloride on 3,3-dimethyl oxindole (17)[99,100] to give 2-chloro-3,3-dimethyl

indolenine (18). (Eqn. 18).



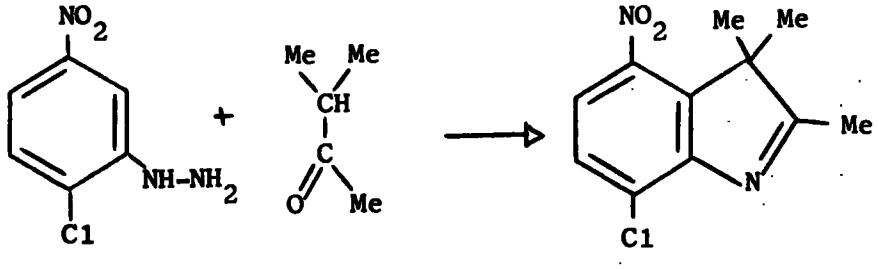

(17) (18) Ref. 99,100

Eqn. 18.

1.2.2. CYCLISATION METHODS.

1.2.2.1. Fischer Cyclisation.

The Fischer Cyclisation can be used to prepare indolenines though examples of the preparation of halo-indolenines by this route are limited. (Eqn. 19).

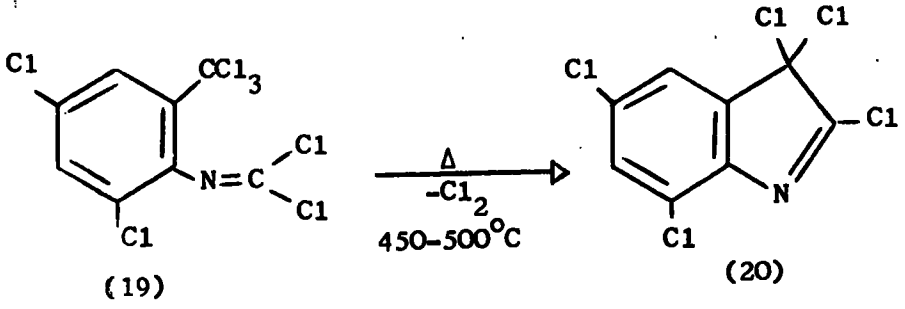



Ref. 101

Eqn. 19.

1.2.2.2. Pyrolytic Cyclo-dechlorination.

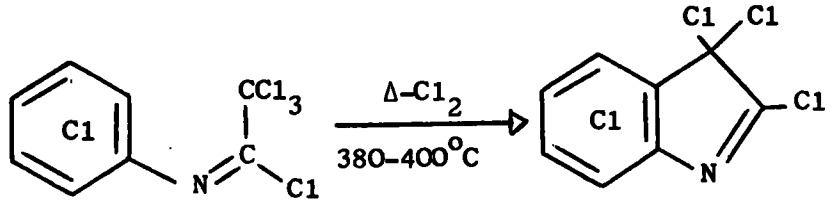
2,3,3,5,7-Pentachloroindolenine (20) has been prepared by the pyrolytic cyclisation of 2,4-dichloro-6-trichloromethyl phenyl chloroformimidoyl chloride.[102] (19) (Eqn. 20).




(19) (20) Ref. 102

Eqn. 20.

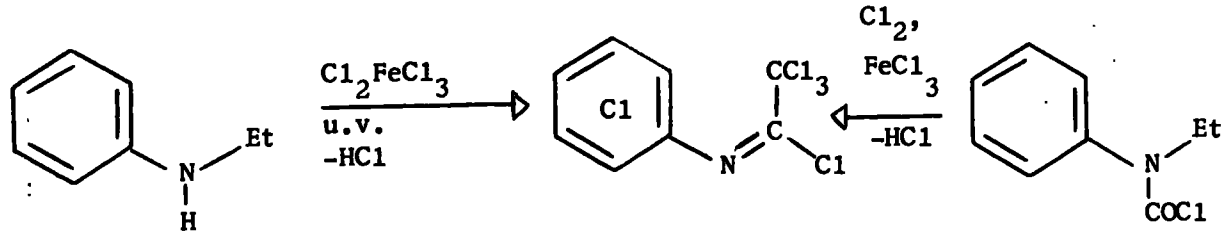
N-Pentachlorophenyl trichloroacetimidoyl chloride (21) has been pyrolytically cyclised to heptachloroindolenine (22) in a weak stream of nitrogen at 380 - 400°C.[102] (Eqn. 21).




(21) (22) Ref. 102

Eqn. 21.

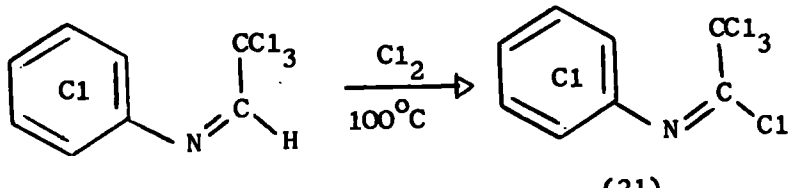
The exhaustive chlorination of N-ethyl, N-phenyl carbamic acid chloride[103] (23) or N-ethyl aniline[104] (24) using chlorine, ultraviolet light and halogen transfer agent (e.g. $FeCl_3$ or $AlCl_3$) gives N-pentachlorophenyl trichloroacetimidoyl chloride (21). (Eqn. 22).




(24) (21) (23)

Eqn. 22.

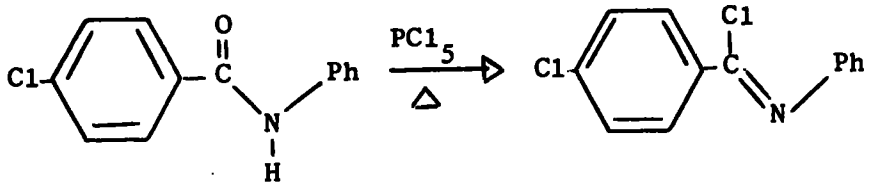
(21) has also been prepared by the chlorination of N-pentachlorophenyl trichloroacetaldimine.[105] (25) (Eqn. 23).




(25) (21) Ref. 105

Eqn. 23.

Imidoyl chlorides can be prepared in several ways but the most important route starts with the corresponding amide which is heated with phosphorus pentachloride either alone or in an anhydrous inert solvent.[106] (Eqn. 24). Other useful chlorinating agents are sulphuryl chloride, carbonyl chloride, and phenyl phosphorus tetrachloride.

e.g. 

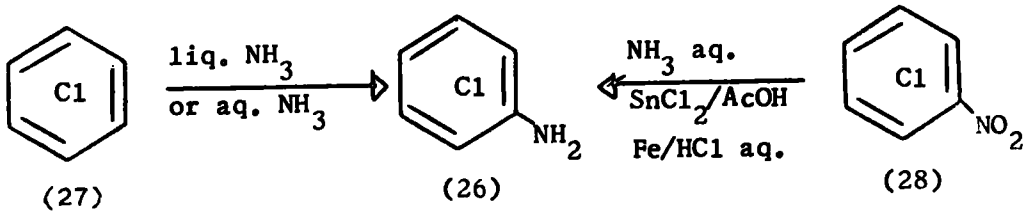
Eqn. 24.

The appropriate amide for chlorination to (21) is 2',2',2',2 ,3,4,5,6-octachloroacetanilide, however little is known about this compound.

Highly chlorinated acetanilides have been prepared by refluxing acid anhydrides or chloro-acetyl chlorides with chloroanilines either together or in benzene with or without barium carbonate or pyridine as catalyst.[106-112]

2',2',2',2,4,6-Hexachloroacetanilide has been prepared by refluxing 2,4,6-trichloroaniline with trichloroacetic acid and phosphorus oxychloride.[113] Highly chlorinated acetanilides have also been prepared by the action of mixed anhydride of di- or tri-chloroacetic acid and acetic acid on a chloroaniline.[111,114]

Pentachloroaniline (26) has been prepared from hexachlorobenzene (27) by the action of aqueous ammonia[115,116] or liquid ammonia,[117,118] or from pentachloronitrobenzene[119,120] (28) by reduction, or the action of aqueous ammonia.[118] (Eqn. 25).



(27) (26) (28)

Eqn. 25.

# CHAPTER II

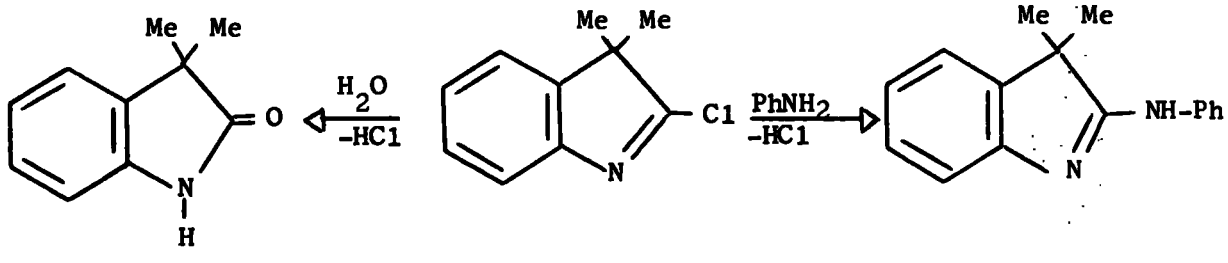
## REACTIONS OF HALO-INDOLENINES AND AZO-METHINES

In this chapter there are described reactions of imidoyl chlorides and azo-methines which have direct relevance to reactions which were carried out on heptachloroindolenine.

## 2.1. REACTIONS OF HALO-INDOLENINES.

### 2.1.1. NUCLEOPHILIC DISPLACEMENT OF HALOGEN.

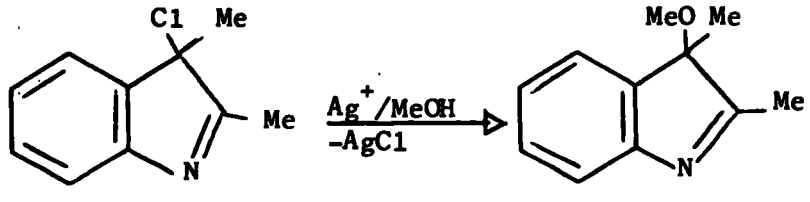
The 2-chlorine atom in 2-chloro-3,3-dimethyl indolenine (29) has been displaced by aniline to give 3,3-dimethyl-2(phenyl amino)indolenine (30).[99] (Eqn. 26). Hydrolysis of (29) gave 3,3-dimethyl oxindole (31).[99] (Eqn. 26).




(31) (29) (30) Ref. 99

Eqn. 26.

The 3-chlorine atom in 3-chloro-2,3-dimethyl indolenine (16) has been displaced by methoxide generated by silver trifluoroacetate in methanol.[98] (Eqn. 27).

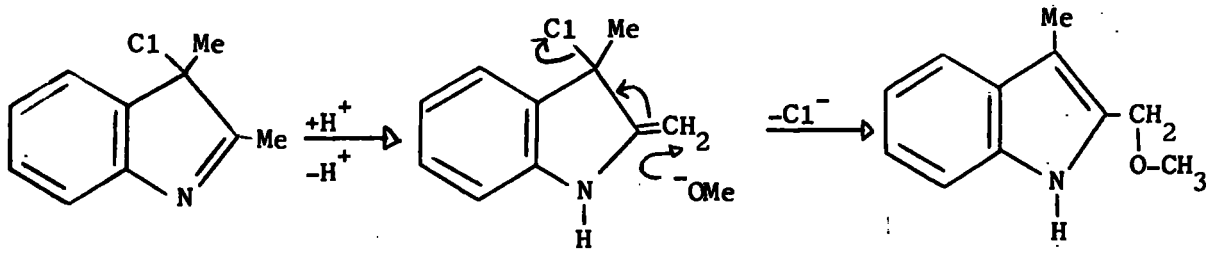



(16) Ref. 98

Eqn. 27.

This reaction contrasts with Taylor's generalisation for nucleophilic displacement of 3-halo-2,3-dialkyl indolenines.[122] Taylor's generalisation states that 3H-indoles with potential leaving groups at C-3 give products of nucleophilic substitution at the C-2 substituent. If the reaction obeyed

this generalisation then (32) would be the expected product. (Eqn. 28).



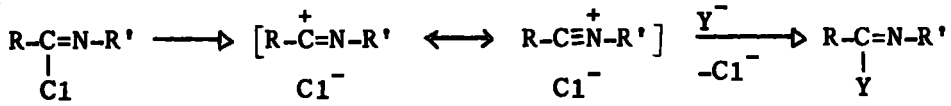
(32)

Eqn. 28.

## 2.2. REACTIONS OF IMIDOYL CHLORIDES AND SOME AZO-METHINES.

### 2.2.1. THE ACTION OF NUCLEOPHILES.

Nucleophilic substitution at the carbon atom of the polarised carbon nitrogen double bond is probably the most characteristic reaction of imidoyl halides. The mechanism is thought to proceed via a $S_N1$ process as follows.



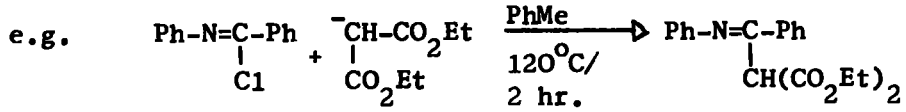
$Y^-$ nucleophile

Eqn. 29.

However there is no reason why the reaction could not proceed by an addition-elimination, or $S_N2$ mechanism.

In addition reactions of azo-methines the nucleophilic moiety of the reagent bonds to the carbon atom of the azo-methine linkage.

Compounds containing active methylene groups readily condense with imidoyl halides in the presence of base.[123] (Eqn. 30).

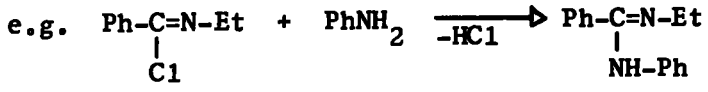


Ref. 123

Eqn. 30.

The products are generally formulated with C-substitution though there is evidence for O-substitution in certain cases.

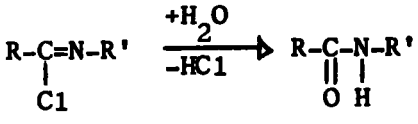
Ammonia and primary and secondary amines react with imidoyl halides to give amidines.[124,125] (Eqn. 31).



Ref. 125

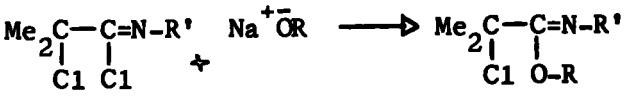
Eqn. 31.

Hydrolysis of imidoyl halides leads rapidly to the amide in most cases. (Eqn. 32).



Eqn. 32.

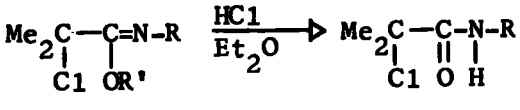
Imidoyl halides react with alkoxides and phenoxides to give the corresponding imidates.[125-128] (Eqn. 33).



Ref. 128

Eqn. 33.

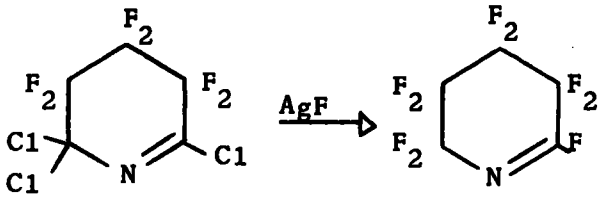
Imidates can be readily hydrolysed with hydrochloric acid to the corresponding amide.[126,128] (Eqn. 34).



Ref. 128

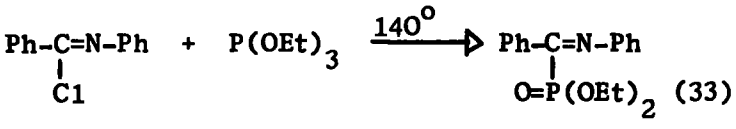
Eqn. 34.

The halogen exchange process has been used to prepare an imidoyl fluoride from imidoyl chlorides.[129] (Eqn. 35).

e.g.  71% Ref. 129

Eqn. 35.

N-Phenyl and N-methyl benzimidoyl chlorides react with trialkyl phosphites to give the corresponding dialkyl phosphonates.[130,131] (Eqn. 36).

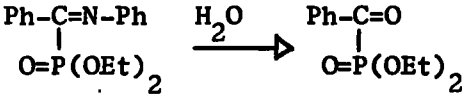


(33)

Ref. 131

Eqn. 36.

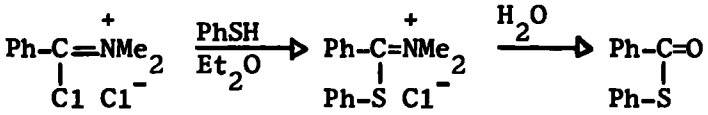
(33) is readily hydrolysed to benzoyl phosphonate (34). (Eqn. 37).



(33) (34)

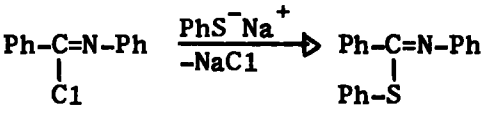
Eqn. 37.

Thiols react with N,N-dialkyl immonium chlorides to give intermediates which may be cleaved by water.[132] (Eqn. 38).

 Ref. 132

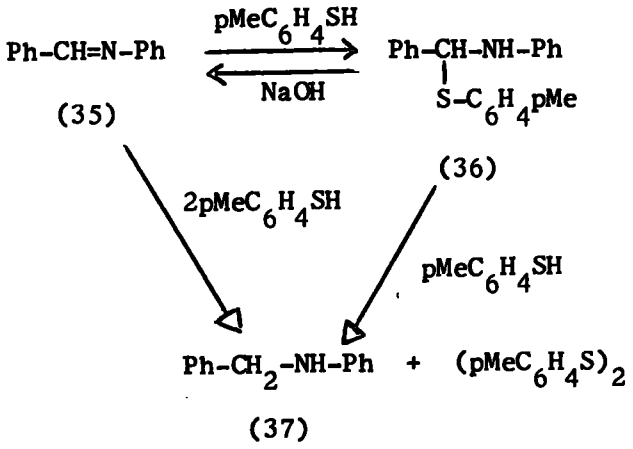
Eqn. 38.

The thiophenoxide ion reacts in a similar way with imidoyl chlorides.[133] (Eqn. 39).

e.g.  Ref. 133

Eqn. 39.

A few reactions of nucleophilic addition to azo-methines have been described. Benzaldehyde anil (35) has been found to form an addition product (36) with a thiol, which decomposes on addition of dilute sodium hydroxide.[134] (Eqn. 40).



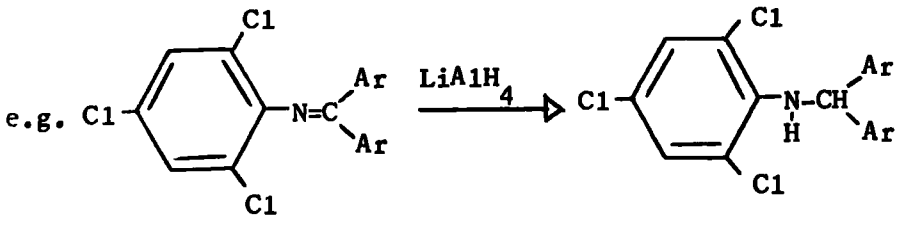

Eqn. 40.

The action of another molecule of para-toluene thiol on (36) causes reduction of the addition compound to give a secondary amine[134] (37). (Eqn. 40).

Benzaldehyde anil can be reduced directly to (37) by excess para-toluene thiol,[134] but other anils may require heating.[135]

2.2.2. THE ACTION OF SOME METAL COMPOUNDS.

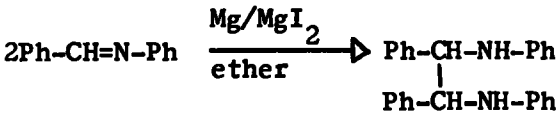
Lithium aluminium hydride reduces aromatic and aliphatic Schiff's bases easily to secondary amines without removal of any aryl halogen atoms.[136,137] (Eqn. 41).




Ref. 136

Eqn. 41.

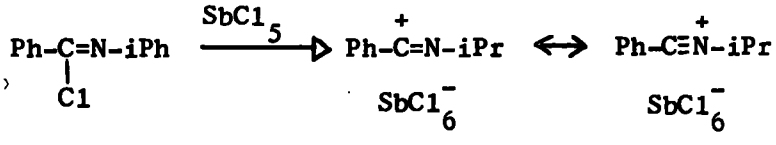
Benzylidene alkyl amines and benzylidene aryl amines reacted with magnesium-magnesium iodide mixture in ether or benzene to give ethylene diamine derivatives.[138,139] (Eqn. 42).




Ref. 139

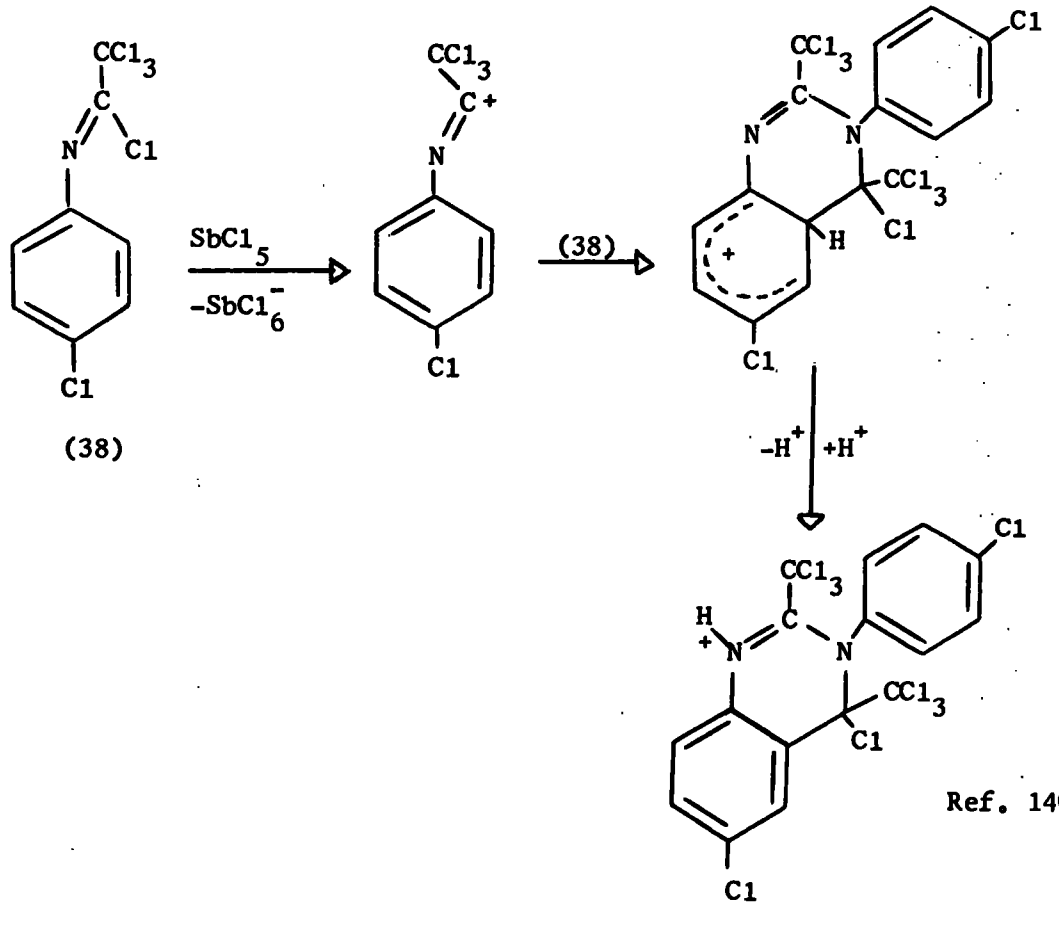
Eqn. 42.

Lewis acids are capable of complexing the halide of imidoyl halides to give nitrilium salts.[140,141] (Eqn. 43 and 44).




Ref. 141

Eqn. 43.




Ref. 140

Eqn. 44.

2.2.3. CATALYTIC HYDROGENATION.

Aldimines or ketimines are readily hydrogenated to the corresponding secondary amine. (Eqn. 45). Raney nickel, platinum and palladium catalysts are often used for the hydrogenation.

e.g. $Me\text{-}N{=}CH\text{-}Ph \xrightarrow{H_2/Ni} Me\text{-}NH\text{-}CH_2\text{-}Ph$ 100% Ref. 142

Eqn. 45.

# CHAPTER III

## THE CHLORINATION OF SODIUM N-ACETYL INDOLINE-2-SULPHONATE AND 5,6,7-TRICHLOROINDOLE, AND THE SYNTHESIS AND REACTIONS OF HEPTACHLOROINDOLENINE

## 3.1. STRUCTURE DETERMINATION IN INDOLES AND INDOLENINES FROM SPECTRAL DATA.

### 3.1.1. Mass Spectra.

The mass spectrum of indole[143] and substituted indoles[144,145] have been recorded. Examination of the fragmentation modes for alkyl indoles[145] shows that the principle mode involves 2-3 bond cleavage followed by loss of stable HCN.

The number of chlorine atoms in a molecule can be readily found from the isomeric distribution of molecular peaks in the mass spectrum.[174]

### 3.1.2. Infrared Spectra.

The N-H stretching frequency of indole has been measured[146] and shows a shift to longer wavelengths when the solvent contains combined oxygen[147] due to hydrogen bonding between the nitrogen hydrogen and solvent oxygen,[148] and a shift to shorter wavelength when the solvent contains combined halogen.[147] The N-H stretching frequency shows a large shift to longer wavelength on changing from solution to solid spectra. The N-H stretching frequency is lower for 3-substituted indoles than for 2-substitution,[149] and it has been shown that electron withdrawing groups, e.g. formyl[150] in the 2- or 3-position lower the stretching frequency[149] whilst inductive electron releasing groups in the 2- or 3-position raise the N-H stretching frequency.[149] This effect is larger for 3-substituents than 2-substituents.

It has been observed that a peak at 1095 $cm.^{-1}$ is present in 3-substituted indole derivatives whereas this peak is not present in 2-substituted indoles.[150]

Overtones in the band 2000-1650 $cm.^{-1}$ have been studied but have not been correlated with substitution orientation[151] as is possible with substituted benzenes.

The infrared spectrum of substituted 2-alkyl indolenines shows νC=N at 1640-1600 cm.$^{-1}$ in chloroform,[152] and substituted 2-aminoindolenines in dichloromethane at 1642 cm.$^{-1}$ with a ring mode at 1615 cm.$^{-1}$.[153]

3.1.3. Ultraviolet Spectra.

Three bands are observed in the ultraviolet spectrum of indole and all are due to the transition $\pi \rightarrow \pi^*$.[154] The ultraviolet spectra of monochloroindoles is essentially the same as that of indoles[155] and the nature of the solvent and pH do not appreciably influence the spectra.[155] The introduction of a methyl group into the benzene ring of indole has no influence on the band positions but increases the intensity.[156] Substitution of a methyl group in the pyrrole ring causes a bathochromic shift.[154,156]

The ultraviolet spectra of 2,3,3-trimethyl indolenine,[157-159] is due to three modified electronic transitions in the benzene chromophore.[157]

The ultraviolet spectra of indoles, indolenines and 2-alkylidene-indolines are sufficiently different to allow for structural identification.[160]

3.1.4. $^1$H N.M.R. Spectra.

The chemical shifts and coupling constants for the protons in indole have been measured[161-167] (Appendix 2).[161] Indolenine tautomerism is excluded by the spectrum.[164] The chemical shifts and coupling data of indole and substituted indoles have been evaluated[162-164,168,169] and show a trans-ring coupling between the 2- and 6-protons which appears in some data[168,169] but does not appear in indole itself.

The chemical shift of the 3-proton appears upfield of the remaining protons in indole and this can often be used to distinguish it from the other ring protons.

Marked differences are observed in the chemical shift of the 2-proton in indole and substituted indoles in polar and non-polar solvents.[170-172] An

increase in the polarity of the solvent causes a downfield shift of the signal.[171]

In contrast only small differences in the chemical shift of the 3-proton have been observed.[170] This solvent effect can be used to distinguish between 2- and 3-protons and hence between 2- and 3-substitution in the indole nucleus.[170] The 7-proton[171] also shows a small solvent effect whereas the N-(1)-proton shows a very large solvent effect.[173] The resonance positions of the 1,2- and 3-protons is concentration dependent to varying degrees, as well as solvent dependent.[171,173] The chemical shift of the 3-proton remains approximately constant although this depends on the solvents, whilst the 2-proton moves to higher field at increasing concentration.[171] This concentration effect might be useful in distinguishing between 2- and 3-protons[171] and ought to be taken into consideration when structural interpretation is based on solvent effects.

## 3.2. THE CHLORINATION OF SODIUM N-ACETYL INDOLINE-2-SULPHONATE AND 5,6,7-TRICHLOROINDOLE.

### 3.2.1. THE REACTION OF CHLORINE WITH SODIUM N-ACETYL INDOLINE-2-SULPHONATE.

Introduction.

Sodium N-acetyl indoline-2-sulphonate has been prepared previously by shaking indole with sodium bisulphite in a mixture of water, ether and ethanol[52-54] for ca. 3 days, to give sodium indoline-2-sulphonate, and stirring this product with an equal weight of sodium metabisulphite in acetic anhydride at 45-50° for 3 to 30 hrs.[51-54]

The first reported chlorination of sodium N-acetyl indoline-2-sulphonate in water at 0-5° gave on alkaline hydrolysis a mixture of polychlorinated indoles containing on average 2·3 chlorine atoms per indole nucleus.[52]

Later work in which the chlorination was carried out at ca. 10° and

the chlorinated mixture allowed to warm to room temperature before alkaline hydrolysis, gave a trichloroindole in good yield.[54]

Investigation of the chlorination of sodium N-acetyl indoline-2-sulphonate showed that two products could be obtained depending on the reaction conditions.

(a) The chlorination of aqueous sodium N-acetyl indoline-2-sulphonate was carried out at -2 to +2° and when excess chlorine passed unabsorbed, nitrogen was bubbled rapidly through the solution to remove excess chlorine. The chlorinated solution was then carefully made alkaline, at <10° to prevent the precipitate from darkening. The product was recovered by filtration and sublimation. However the sublimate contained an amount of a trichloro-indole as shown by mass spectrometry, and was purified with difficulty by several recrystallisations from pet. ether (b.p. 40-60°) to give 5,7-dichloroindole, m.p. 53·5 - 54·0, (lit., m.p.[7] 58·0 - 58·5, m.p.[65] 55°).

Assignment of Structure.

The microanalysis and, mass and isomeric distribution of the molecular peaks in the mass spectrum gave the molecular formula $C_8H_5Cl_2N$.

The infrared spectrum (Appendix 1) had a single strong band at 3400 $cm.^{-1}$ assigned to νN-H showing the compound was not an indolenine and could be an indole.

The $^1H$ N.M.R. spectrum (Appendix 2) was recorded in both carbon tetrachloride and in acetone as solvent.

The broad band whose chemical shift was highly solvent dependent was assigned to the N-(1) proton.

Of the remaining sharp signals one shows a solvent shift almost twice that of any of the other protons and was assigned to the 2-proton. One doublet of doublets appeared upfield of the majority of protons and was assigned to the 3-proton. This feature is characteristic of a 3-proton in an indole.

The signals assigned to the 2- and 3-protons had a mutual coupling constant and each signal had a coupling constant not found elsewhere in the spectrum and so must therefore be coupled with the N-(1)-proton.

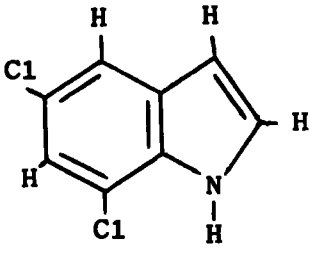
One more absorption appeared as a doublet of doublets and coupling constant not found elsewhere in the spectrum. This proton signal was assigned to the 4-position as it is the only unassigned position remaining from which a proton is known to couple with the N-(1)-proton.[161-167]

A proton at C-(7) would be expected to couple with the proton at C-(3) however all the couplings of the 3-proton have been accounted for, therefore there is a chlorine atom at C-(7).

The 4-proton and the remaining proton signal, a doublet of doublets, have a mutual coupling constant consistent with meta coupling in a benzenoid ring, thus assigning the remaining proton to the 6-position. The remaining coupling constant of the 6-proton and incomplete resolution of a fine splitting in the 2-proton signal indicate that a trans-ring coupling is occurring between the 2- and 6-protons.

The chemical shifts, solvent effects of the protons and the coupling constants between them are consistent with previous data. (Appendix 2).

The remaining benzo-positions are occupied by chlorine atoms which gives the product the structure (Fig. 2).



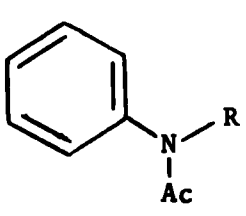

5,7-dichloroindole
(VII)

Fig. 2.

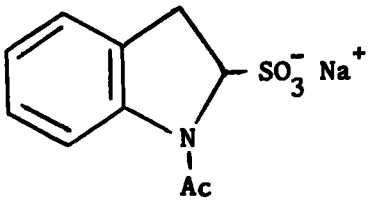
Theoretical Considerations.

The structure of the product 5,7-dichloroindole can readily be accounted for on the basis of simple electrophilic aromatic substitution.

Sodium N-acetyl indoline-2-sulphonate (10) behaves as a N-acetyl anilide or more accurately as N-alkyl acetanilide (39) directing electrophilic reagents (i.e. $Cl\text{-}\overset{+}{O}H_2$) into para and/or ortho positions, i.e. the 5- and 7-positions of the indoline ring by mesomeric electron release (+M effect) (Fig. 3).



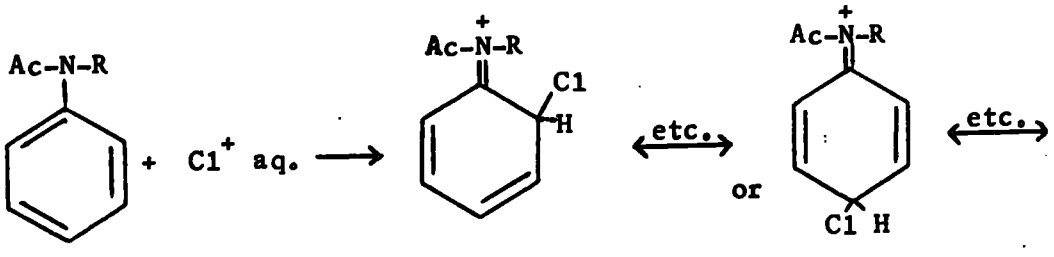

(39)




(10)

Fig. 3.

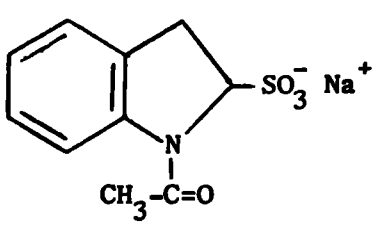
A $CH_3CONR$ group on a benzene ring directs electrophilic reagents to para- and ortho-positions due to mesomeric electron release (Eqn. 46).



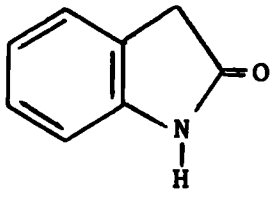

(39)

Eqn. 46.

The electrons which conjugate with the aromatic benzene ring in mesomeric electron release are normally located as lone pairs on the nitrogen atom. In order that the best overlap with ring orbitals is achieved the Ac-N-R bonds have to become planar with the benzene ring. In sodium N-acetyl indoline-2-sulphonate the N-(1) — C-(2) bond is held approximately in the same plane as the benzene ring by the constraint imposed on it by the rigidity of the five membered ring. Thus part of the activation energy barrier has been surmounted.




(10)




(40)

Fig. 4.

Sodium N-acetyl indoline-2-sulphonate (10) can be compared to oxindole (40) which is also a N-acyl aniline and is believed to chlorinate in the 5- and 7-position[42] with chlorine in water (Chapter 1, Section 1.1.2.1.) (Fig. 4).

(b) The chlorination of aqueous sodium N-acetyl indoline-2-sulphonate (10) was also carried out under more severe conditions.

The initial chlorination was carried out at +2 to -2° until excess chlorine was passing through the solution as described previously, then the mixture allowed to warm to 15°C whilst chlorine was being passed slowly for a further 30 mins. before removing excess chlorine by bubbling nitrogen through the solution, and then carefully hydrolysing with sodium hydroxide solution as described previously. The product was purified by vacuum sublimation and recrystallisation to give 5,6,7-trichloroindole.

Assignment of Structure.

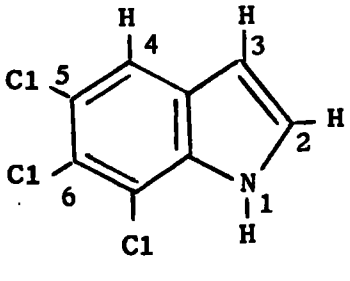
The microanalysis and, mass and isomer distribution of molecular peaks in the mass spectrum gave the molecular formula $C_8H_4Cl_3N$.

The infrared spectrum (Appendix 1) which is almost identical to that of 5,7-dichloroindole had a band at 3400 $cm.^{-1}$ which was assigned to νN-H, and the ultraviolet spectrum (Appendix 1) was similar in position and intensity to that of indole but dissimilar to indolenines.

Due to the similarity in preparation of this compound and 5,7-dichloroindole one might expect the 5- and 7-positions to be occupied by chlorine in this trichloroindole.

The $^{1}H$ N.M.R. spectrum (Appendix 2) was recorded in both carbon tetrachloride and acetone and bears many resemblances to the $^{1}H$ N.M.R. of 5,7-dichloroindole.

Three of the bands in the $^{1}H$ N.M.R. spectrum which corresponded almost exactly to three bands in the $^{1}H$ N.M.R. spectrum of 5,7-dichloroindole were assigned to protons in the corresponding positions in trichloroindole by virtue of essentially identical chemical shifts, coupling data and solvent dependence of chemical shift positions. These protons were the N-(1) proton which appears as a broad band, the C-(2) proton a doublet of doublets whose chemical shift is fairly solvent dependent, and the C-(3) proton a doublet of doublets at a relatively high field position. The remaining absorption was a doublet whose coupling constant did not appear elsewhere in the spectrum and so must be coupling with the N-(1) proton. This absorption is assigned to the 4-proton as it is the only remaining position from which a proton is known to couple with the N-(1) proton.[161-167] This doublet has the same coupling constant and almost the same chemical shift as the 4-proton in 5,7-dichloroindole. Thus the chlorines are located at the 5-, 6- and 7-positions (Fig. 5).



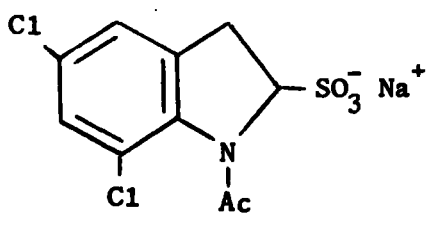

5,6,7-trichloroindole
(IV)

Fig. 5.

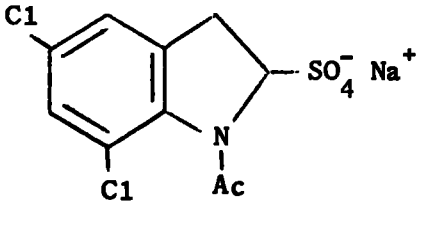
Theoretical Considerations.

Substitution at the 5- and 7-positions of 5,6,7-trichloroindole can be accounted for as in the case of 5,7-dichloroindole, although further substitution at the 6-position of indole whilst the 4-position remains unsubstituted, cannot be explained as easily.

The chlorination of sodium N-acetyl indoline-2-sulphonate to both 5,7-dichloroindole and 5,6,7-trichloroindole is thought to pass through the intermediate sodium N-acetyl-5,7-dichloroindoline-2-sulphonate (41) or if the chlorine has oxidised the sulphonate group sodium N-acetyl-5,7-dichloroindoline-2-sulphate (42), but this has not been proven (Fig. 6).




(41)




(42)

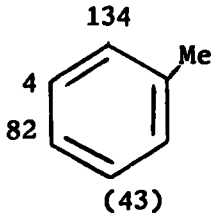
Fig. 6.

It seems likely however that the initial effect of the chlorine is to oxidise the sulphonate group at C-(2) to sulphate and (42) is more likely than (41) as an intermediate.

It is unlikely that the nitrogen atom or the C-(5) chlorine atom have any biased directive effect on further substitution as they are meta and ortho respectively with respect to the two remaining unsubstituted positions in the benzene ring. The remaining substituent effects are then due to the five membered ring residue and the chlorine atom at C-(7). These will be discussed separately.

The partial rate factors for the chlorination of toluene (43) by positive chlorine in water[175] show a bias towards substitution at the ortho

position. The methyl group activates the ortho and para positions by a weak electron releasing inductive effect (Fig. 7).



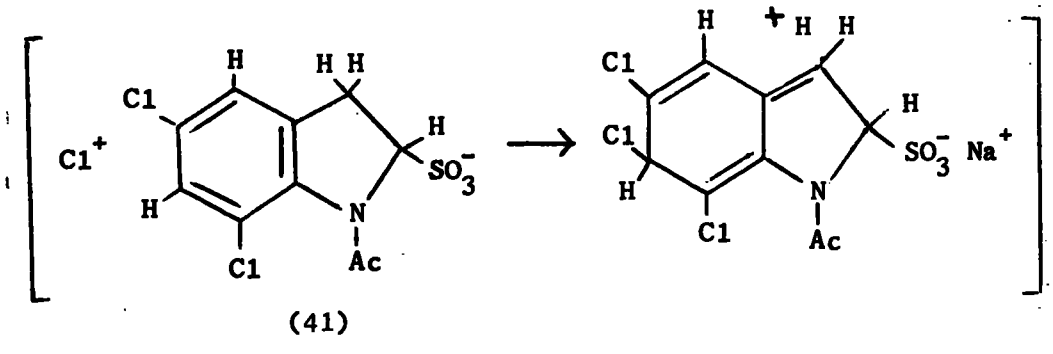

(43)

$Cl^+$, $H_2O$ partial rate factors
ortho para ratio 1·64

Fig. 7.

An ethyl group on a benzene ring also activates the ortho- and para-positions towards electrophilic substitution by an electron releasing inductive effect plus an electron releasing hyperconjugative effect which favours activating the para-position rather than the ortho-position.

The proposed hyperconjugative electron release effect could occur in sodium N-acetyl-5,7-dichloroindoline-2-sulphonate (41) as indicated (Eqn. 47).




(41)

Eqn. 47.

Bromination and chlorination of ethyl, isopropyl and tertiary butyl benzenes in a variety of solvents always favours para-halogenation over ortho-halogenation although the ortho-para ratio varies widely.[176] Conformational requirements of an alkyl group ought also to be considered when discussing proposed hyperconjugative electron release.

The percentage isomer distribution for positive chlorination of chlorobenzene[177-179] is shown in Table 2.

Table 2

| | |
|---|---|
| Ortho substitution | 36•4% |
| Meta " | 1•3% |
| Para " | 62•3% |

Allowing for two ortho-positions and only one para the ortho para ratio is 0•292. Thus a chlorine on a benzene ring directs positive chlorine largely para. This factor indicates the sodium N-acetyl indoline-2-sulphonate might chlorinate largely at the 4-position with some chlorination at the 6-position.

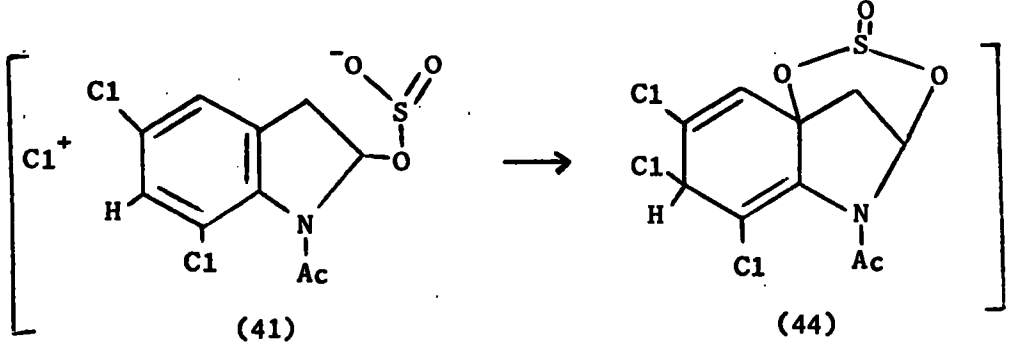
The steric crowding at the 4- and 6-position has also to be considered along with the electronic effects particularly with polysubstituted benzenes.

Conclusion.

Thus on consideration of the structure of sodium N-acetyl indoline-2-sulphonate in the light of theories of electrophilic substitution and examples of electrophilic aromatic chlorination no firm reason can be found for the exclusive chlorination at C-(6) over C-(4).

Alternative Explanation.

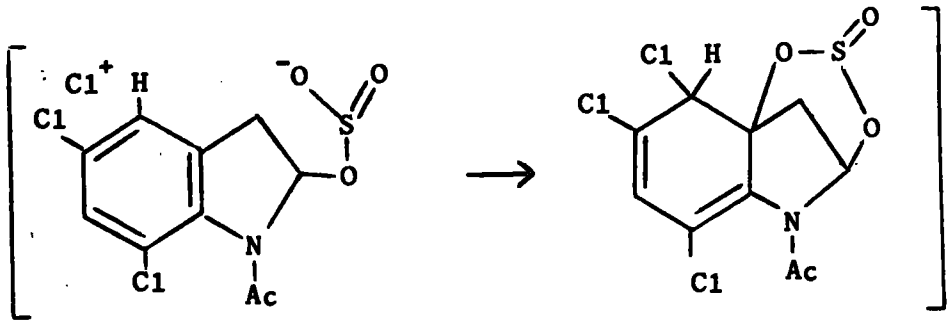
The attack of electrophilic chlorine could be assisted by neighbouring group participation by the nucleophilic sulphonate group (Eqn. 48 and 49).




Eqn. 48.

The attack of positive chlorine and neighbouring group participation by the sulphonate group results in an uncharged intermediate (44).

Similarly a mechanism can be postulated for attack at C-(4) to give (45) (Eqn. 49).



(41) (45)

Eqn. 49.

This still does not account for the apparently exclusive chlorination at C-(6) over C-(4) as both mechanisms seem equally likely superficially. However other factors such as steric hindrance and conformation requirements may come into play which prevent substitution at C-(4), but do not hinder substitution at C-(6).

3.2.2. THE CHLORINATION OF 5,6,7-TRICHLOROINDOLE.

3.2.2.1. The Action of Sulphuryl Chloride on 5,6,7-Trichloroindole.

The action of sulphuryl chloride on indole gives a mixture of 2,3-dichloroindole and 3-chloroindole.[5b,c, 6] The reaction of 5,6,7-trichloroindole was repeated under similar conditions but the product was separated by column chromatography.

Assignment of Structure.

The microanalysis and, mass and isomeric distribution of molecular peaks in the mass spectrum gave the molecular formula $C_8H_3Cl_4N$.

The infrared spectrum (Appendix 1) had a single strong band at 3400 $cm.^{-1}$ assigned to $\nu$N-H and the ultraviolet spectrum (Appendix 1) was similar in shape, intensity, and position to that of indole but was dissimilar to that of indolenines.

The $^{1}H$ N.M.R. spectrum (Appendix 2) was recorded in both carbon tetrachloride and acetone.

The spectrum consisted of a broad band whose position was very solvent dependent, assigned to the N-(1) proton, and two doublets of differing coupling constants which must both be coupling with the N-(1)-proton. The chemical shift of one of the doublets was markedly solvent dependent and the coupling constant indicative of (1,2) coupling rather than (1,3) or (1,4) (Table 3). The other splitting is characteristic of 1,4-coupling in indoles. (Table 3).

Table 3

| | J(1,2) | J(1,3) | J(1,4) | Ref. |
|---|---|---|---|---|
| Indole | 2·5 | 2·0 | 0·7 | 161 |
| 2-Chloroindole | - | 2·0 | | 6 |
| 3-Chloroindole | 2·5 | - | | 6 |
| Product | (2·7) | - | (0·8) | |
| 5,6,7-Trichloroindole | 2·6 | 2·0 | 0·8 | |

The solvent dependence of chemical shift has been used to differentiate between protons at C-(2) and C-(3) since downfield shift on changing from a non-polar to polar solvent is greater for a 2-proton than a 3-proton.[170] This solvent dependence of chemical shift is in turn somewhat dependent on the nature of the adjacent substituent.[170]

Indoles with a methyl group or a bromine atom at the 3-position show a slightly decreased solvent dependence of chemical shift whereas indoles with a carbethoxy group at the 3-position show less than half the solvent dependence of chemical shift of indole (Table 4).

The introduction of a bromine atom at the 3-position in indole results in a very small decrease in the solvent dependence of chemical shift of the 2-proton from 0·44 to 0·41. Introduction of groups at the 2-position do not

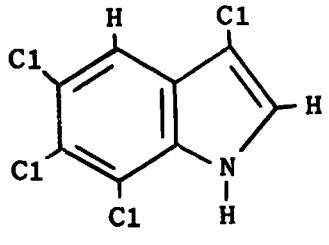
Table 4.[170]

| | $CDCl_3$ | Acetone | Δ | Proton |
|---|---|---|---|---|
| Indole | 3·26 | 2·72 | 0·44 | 2 |
| Indole | 3·59 | 3·52 | 0·07 | 3 |
| 3-Methyl indole | 3·39 | 3·0 | 0·39 | 2 |
| 2-Methyl indole | 3·95 | 3·86 | 0·09 | 3 |
| Ethyl indole 3-Carboxylate | 2·18 | 1·99 | 0·19 | 2 |
| Ethyl indole 2-Carboxylate | 2·77 | 2·78 | 0·01 | 3 |
| 3-Bromoindole | 2·98 | 2·57 | 0·41 | 2 |

seem to increase solvent dependency of chemical shift much more than for indole.

Introduction of a further chlorine atom into 5,6,7-trichloroindole causes a slight increase in the solvent dependence of chemical shift from 0·35 to 0·40 p.p.m. (Appendix 2) if substitution at C-(3) is suspected, or a large increase from 0·13 to 0·40 p.p.m. if substitution at C-(2) is suspected. In the light of the above data the latter possibility seems very remote.

The $^1H$ N.M.R. of the tetrachloroindole in undried acetone consisted of a broad band due to the N-(1) proton, and two sharp singlets caused by the collapse of the doublets in the above spectrum. The collapse indicates that the N-(1) proton is exchanging rapidly with the solvent. The structure of the tetrachloroindole is given in Fig. 8.




3,5,6,7-tetrachloroindole
(VI)

Fig. 8.

Theoretical Considerations.

No pentachloroindole was detected in the product under the conditions employed. Further chlorination probably did not take place due to the deactivating effect of the chlorine atoms already present.

3.2.2.2. The Action of Chlorine of 5,6,7-Trichloroindole in Carbon Tetrachloride

Chlorine gas was bubbled through a solution of 5,6,7-trichloroindole with a trace of iodine as a catalyst. Iodine reacts with chlorine to form iodine monochloride (Eqn. 50) which is more polar than chlorine and chlorinates at C-(2) in indoles, (1.1.1.1., Table 1, p.4).

$$I_2 + Cl_2 \longrightarrow 2ICl$$

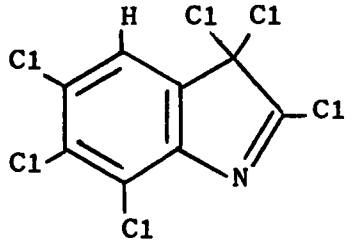
Eqn. 50.

Structural Assignment.

The microanalysis and, mass and isomeric distribution of the mass spectrum gave the molecular formula $C_8HCl_6N$.

The infrared spectrum showed no bands in the νN-H region but showed a strong band at 1570 cm.$^{-1}$ due to νC=N, characteristic of indolenines. The ultraviolet spectrum (Appendix 1) was characteristic of indolenines in shape, position and intensity, but is unlike that of indoles.

The $^1H$ N.M.R. (Appendix 2) consists of a singlet absorption at exactly the same position as the 4-proton in 5,6,7-trichloroindole and it is assumed that the single proton occupies the same position in this compound (Fig. 9).



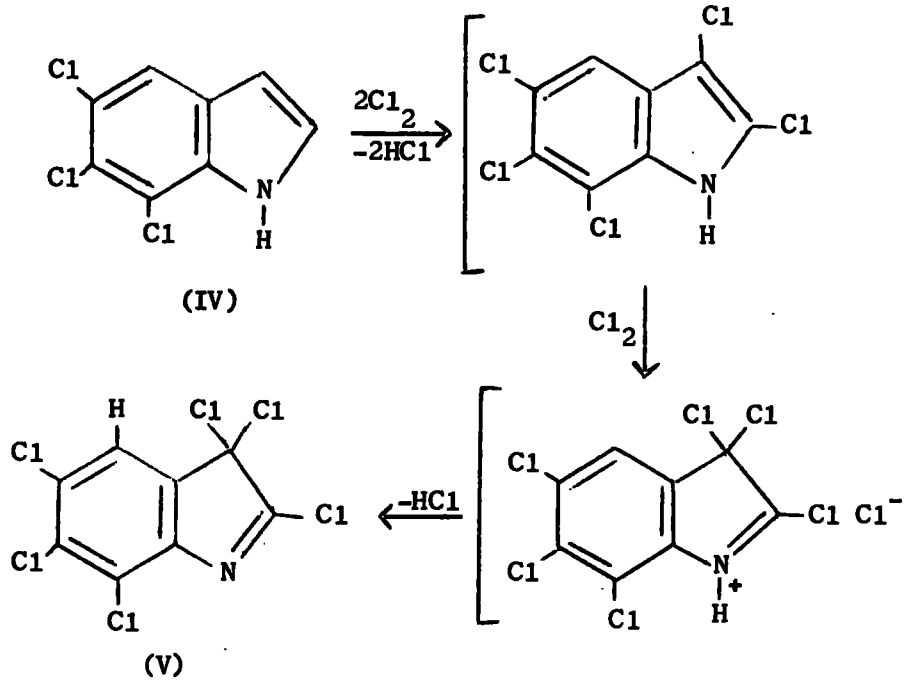

2,3,3,5,6,7-hexachloroindolenine
(V)

Fig. 9.

Theoretical Considerations.

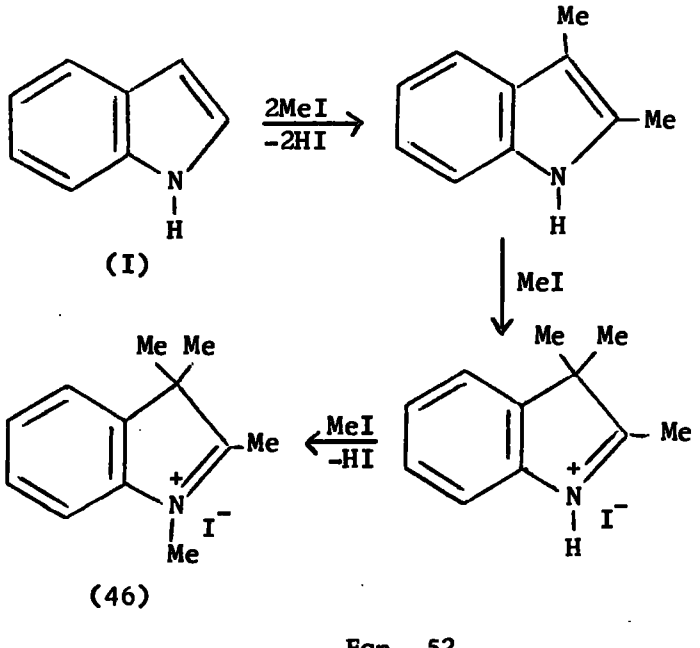
When positions 3 and 2 have been filled by electrophilic reagents or are already blocked further substitution takes place in the six membered ring usually at the 5- or 6-position.

The action of chlorine on 5,6,7-trichloroindole places an extra chlorine atom at C-(3) ignoring the site at C-(4).




Eqn. 51.

A similar sequence of reactions occurs in the polyalkylation of indole with methyl iodide to give finally 1,2,3,3-tetramethyl indolenium iodide (46).[180]

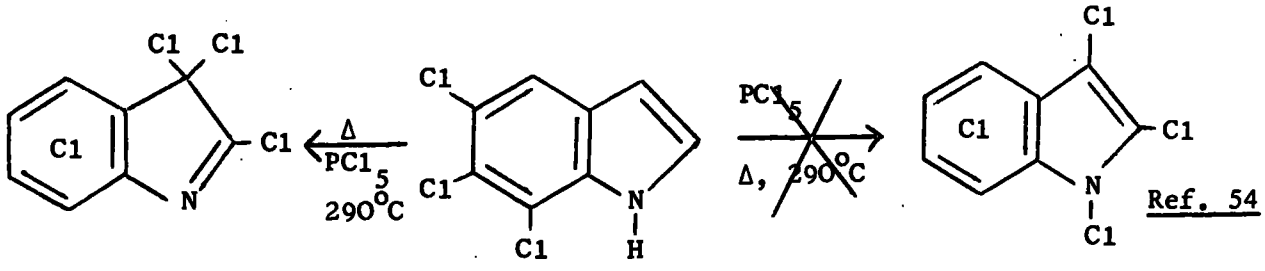



Eqn. 52.

The reaction can also be compared with the chlorination of 2,3-dimethyl indole with t-butyl hypochlorite (1.2.1.1., Eqn. 17, p.13).

3.2.2.3. The Chlorination of 5,6,7-Trichloroindole with Phosphorus Pentachloride.

The chlorination of 5,6,7-trichloroindole (IV) with phosphorus pentachloride has been reported in the literature[54] and the product was stated to be heptachloroindole (47) (Eqn. 53). Repetition of this work by the author has shown the chlorination product to be heptachloroindolenine (22) (VIII).




(22) (VIII) (IV) (47)

Eqn. 53.

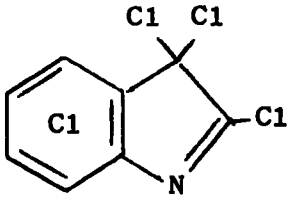
The optimum reaction temperature was confirmed at ca. 290°C.

Assignment of Structure.

The microanalysis and, mass and isomeric distribution of molecular peaks in the mass spectrum gave the molecular formula, $C_8Cl_7N$.

The infrared spectrum (Appendix 1) shows a strong band at 1570 $cm.^{-1}$ assigned to νC=N, characteristic of indolenines. The ultraviolet spectrum (Appendix 1) is almost identical with that of 2,3,3,5,6,7-hexachloro-indolenine, and is characteristic in shape and intensity of indolenines.

There is only one structure for heptachloroindolenine (Fig. 10).




2,3,3,4,5,6,7-heptachloroindolenine
(VIII)

Fig. 10.

5,6,7-Trichloroindole like tertiary amines when heated with phosphorus pentachloride yields an imidoyl chloride on chlorination.

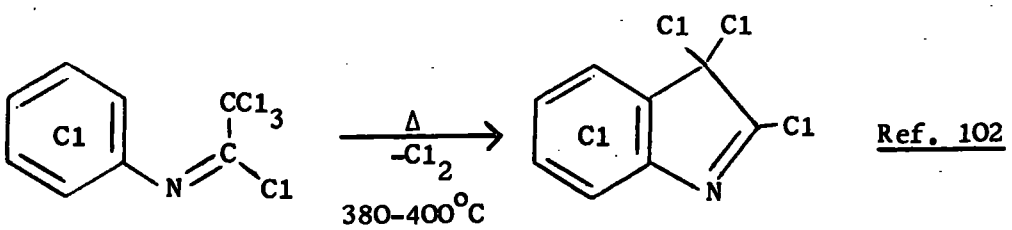
Overall Yield.

Starting from indole to prepare heptachloroindolenine by the route just described the synthesis can be done with 19% yield but it is felt there is a little hope for improving the yield.

## 3.3. SYNTHETIC ROUTE TO HEPTACHLOROINDOLENINE.

Introduction.

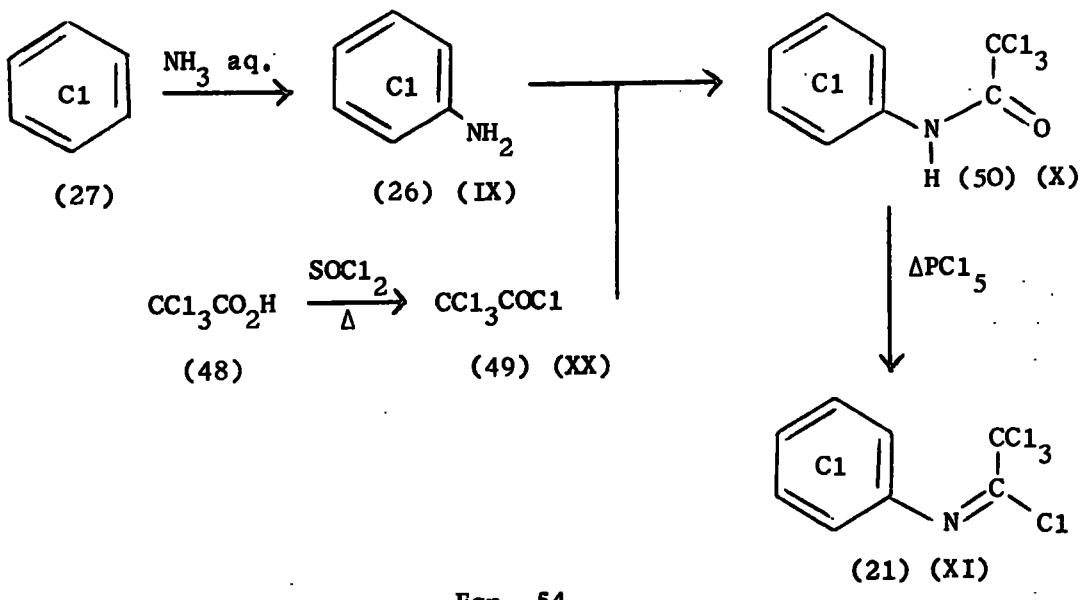
Heptachloroindolenine has been prepared by the pyrolitic cyclisation of N-pentachlorophenyl trichloroacetimidoyl chloride.[102] (Eqn. 21).




(XI) (21) (22) (VIII)

Eqn. 21.

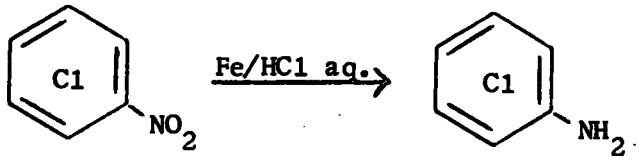
It was proposed to prepare N-pentachlorophenyl trichloroacetimidoyl chloride by the route indicated below (Eqn. 54).




(27) (26) (IX) (50) (X) (48) (49) (XX) (21) (XI)

Eqn. 54.

The preparation of pentachloroaniline (26) from hexachlorobenzene (27) was abandoned in favour of the reduction of pentachloronitrobenzene (28) as the latter reaction was more convenient and gave higher yields of product which was easier to purify (Eqn. 55).




(28) (26) (IX) Ref. 120

Eqn. 55.

The reduction of pentachloronitrobenzene by El-Hewehi and Runge[120] was reported to give a higher yield (75%) than the method of Clark and Hams[119] (46%) and so was favoured.

3.3.1. Preparation of Trichloroacetyl Chloride from Trichloroacetic Acid.

Trichloroacetyl chloride (49) was prepared by the action of thionyl chloride on trichloroacetic acid (48) by a procedure similar to that used for the preparation of butyryl chloride[121] except that it was necessary to reflux the mixture for ca. 2 days for almost complete reaction. The product was purified by distillation and fractionation.

3.3.2. Preparation of Pentachloroaniline from Pentachloronitrobenzene.

The reaction method was identical to El-Hewehi and Runge[120] but the work up was modified and involved on ether extraction.

Structure Determination.

The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_6H_2Cl_5N$.

The infrared spectrum (Appendix 1) showed two bands at 3480 and 3380 $cm.^{-1}$ assigned to symmetric and assymmetric $\nu$N-H, and no bands in the $\nu$C-H region, m.p. 231·5 - 232·5°C, (m.p. lit.[119] 229°C, lit.[120] 232-4°C).

The product must then be pentachloroaniline.

### 3.3.3. Preparation of Octachloroacetanilide by Reaction of Trichloroacetyl Chloride and Pentachloroaniline.

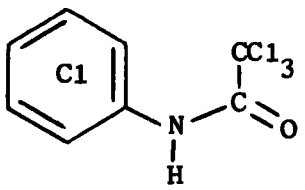
Reaction between acetyl chloride and aniline proceeds rapidly from room temperature, however, the reaction between trichloroacetyl chloride and pentachloroaniline was more reluctant. The reaction in boiling ether, benzene or toluene produced little reaction, but reaction at reflux temperature without any solvent and with either powdered barium carbonate or 0·5 - 1 ml. of concentrated sulphuric acid gave a high yield of product after ca. 2 days reaction.

Structure Determination.

The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_8HCl_8NO$.

The infrared spectrum (Appendix 1) showed a band at 3300 $cm.^{-1}$ assigned to νN-H and a strong band at 1720 $cm.^{-1}$ assigned to νC=O.

The data for the product is consistent with the structure in Fig. 11.




2',2',2',2,3,4,5,6-octachloroacetanilide
(X)

Fig. 11.

### 3.3.4. The Preparation of N-Pentachlorophenyl Trichloroacetimidoyl Chloride from Octachloroacetanilide.

The most common method used for preparing imidoyl chlorides is to heat the corresponding amide with phosphorus pentachloride.[106] The reaction of octachloroacetanilide with phosphorus pentachloride was carried out in a Carius tube and the best reaction conditions were found to be ~170° for ca. 6 hrs. Higher reaction temperatures (e.g. ~320°C) result in a product which proved difficult to purify.

Structure Determination.

The microanalysis and, mass and isomeric distribution of the molecular peaks in the mass spectrum gave the molecular formula $C_8Cl_9N$.

The mass spectrum showed peaks at (P-35) (-Cl), (P-70) ($-Cl_2$), (P-105) ($-Cl_3$), (P-117) ($-CCl_3$), (P-152) ($-CCl_4$), and (P-178) ($C_6Cl_5$).

The infrared spectrum (Appendix 1) showed a strong band at 1690 $cm.^{-1}$ assigned to νC=N, m.p. 127·5 - 128·5°C, (m.p.[103] 131-3°C, m.p.[104] 129-30°C, m.p.[105] 131-3°C)

3.3.5. The Preparation of Heptachloroindolenine by the Pyrolysis of N-Pentachlorophenyl Trichloroacetimidoyl Chloride.

Heptachloroindolenine was prepared from N-pentachlorophenyl trichloroacetimidoyl chloride (XI) by a procedure almost identical to workers for Farbenfabriken Bayer A.-G.[102] Molten (XI) was refluxed at 380-400°C in flask with a fairly slow stream of dry nitrogen for 7½ hrs. to yield (VIII), which was purified by vacuum sublimation and recrystallisation.

Structure Determination.

The infrared and mass spectra were identical to authentic heptachloroindolenine, m.p. 122-3°C, (lit.[102] m.p. 122-4°C), authentic material m.p. 123·5-4·5°C.

Theoretical Considerations.

The reaction probably proceeds by loss of chlorine radical from N-pentachlorophenyl trichloroacetimidoyl chloride followed by cyclisation and loss of a further chlorine radical.

Overall Yield.

The overall yield of the synthesis starting from pentachloroaniline is 13%. It is thought that this could be doubled as the workers[102] who originally carried out the last stage claim a 100% yield compared to 53% for this work.

## 3.4. REACTIONS OF HEPTACHLOROINDOLENINE.

### 3.4.1. NUCLEOPHILIC SUBSTITUTION IN HEPTACHLOROINDOLENINE.

#### 3.4.1.1. OXYGEN NUCLEOPHILES.

The alkoxides used were found to react readily with heptachloroindolenine in the appropriate alcohol at room temperature, reaction being completed in five to ten minutes. The limiting factor in reaction rate is thought to be the limited solubility of heptachloroindolenine in alcohols. Addition of 20% tetrahydrofuran to isopropanol made heptachloroindolenine immediately soluble and the reaction was completed in under one minute.

The reaction of sodium methoxide with heptachloroindolenine gave a low yield of methoxy substituted product and a large amount of carbonyl containing mixture. Due to this low yield the reaction was repeated using potassium isopropoxide as nucleophile.

The reaction of sodium methoxide in methanol with heptachloroindolenine gave a bright red colouration which faded away shortly after the starting material had dissolved, but the reaction with potassium isopropoxide in isopropanol gave no transient colourations.

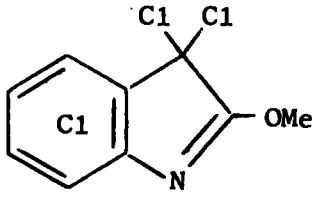
#### 4.1.1.1. Reaction with Sodium Methoxide.

Structural Assignments.

The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_9H_3Cl_6NO$.

The infrared spectrum (Appendix 1) showed no $\nu$N-H bands but did show weak bands at 2980 and 2900 $cm.^{-1}$ and 1400 and 1330 $cm.^{-1}$ which can be assigned to a methyl group attached to oxygen. There are two strong bands at 1630 and 1600 $cm.^{-1}$ which can be assigned to $\nu$C=N and the ring mode respectively. The mass spectrum shows large peaks at (P-15) and (P-35) due to loss of methyl and chlorine respectively.

The ultraviolet spectrum (Appendix 1) is similar in shape and intensity to heptachloroindolenine but shows a hypsochromic shift of 2·5 nm (blue shift) with respect to heptachloroindolenine. This spectral shift cannot be explained by substitution at the 3-position as this would be expected to produce no change as it would be remote from the π system. Substitution of methoxy in the benzo ring is unlikely as a bathochromic shift would be expected. By a process of elimination it appears that the methoxy group is at the 2-position and the most likely structure of the monomethoxy hexachloroindolenine indicated in Fig. 12.




2-methoxy-3,3,4,5,6,7-hexachloroindolenine (XIX)

Fig. 12.

4.1.1.2. Reaction with Potassium Isopropoxide.

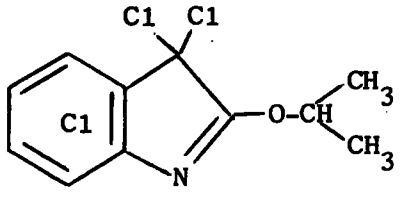
The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_{11}H_7Cl_6NO$.

The infrared spectrum (Appendix 1) showed no νN-H but had some weak bands at 2980 and 2920 $cm.^{-1}$ due to aliphatic νC-H and a doublet at ca. 1380 $cm.^{-1}$ characteristic of isopropyl group, and bands at 1100 and 1020 $cm.^{-1}$ were assigned to νC-O. Strong bands at 1610 and 1580 $cm.^{-1}$ were assigned to νC=N and the ring mode respectively.

The ultraviolet spectrum (Appendix 1) was very similar in shape and intensity to that of heptachloroindolenine, and almost identical to the spectrum of methoxy hexachloroindolenine, and had nearly the same hypsochromic shift of 3·5 nm. with respect to heptachloroindolenine. The hypsochromic shift can only be explained by substitution at C-(2) as with methoxy hexachloroindolenine (XIX).

The $^{1}H$ N.M.R. (Appendix 2) consists of a doublet at $\delta$ = 1·57 with a coupling constant of 6 Hz assigned to the two equivalent isopropyl methyls, plus a multiplet at ca. 4·4 ($\delta$) assigned to the tertiary isopropyl hydrogen. The methyl proton signal position is in good agreement with typical values however the tertiary hydrogen is at a chemical shift position similar to the $\alpha$ alkyl proton in an alkyl ester. The mass spectrum showed a peak at (P-42) indicating a loss of propene $C_3H_6$ which can be accounted for by a McLafferty rearrangement.

The most probable structure of the compound is given in Fig. 13.

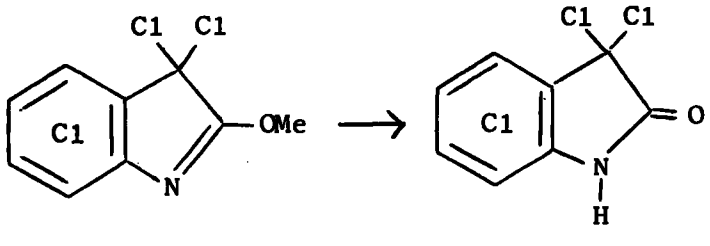



2-isopropoxy-3,3,4,5,6,7-hexachloro-indolenine
(XII)

Fig. 13.

3.4.1.1.3. Theoretical Considerations.

The low yield of the reaction [32%] may be caused by demethylation of the product or acid hydrolysis on work up. In either case the product expected is 3,3,4,5,6,7-hexachloro-oxindole (Eqn. 56).




(XIX) (51)

Eqn. 56.

The structure of the other product was not established but it was thought to be a mixture. The reaction with potassium isopropoxide gave far better yields, and no major side products.

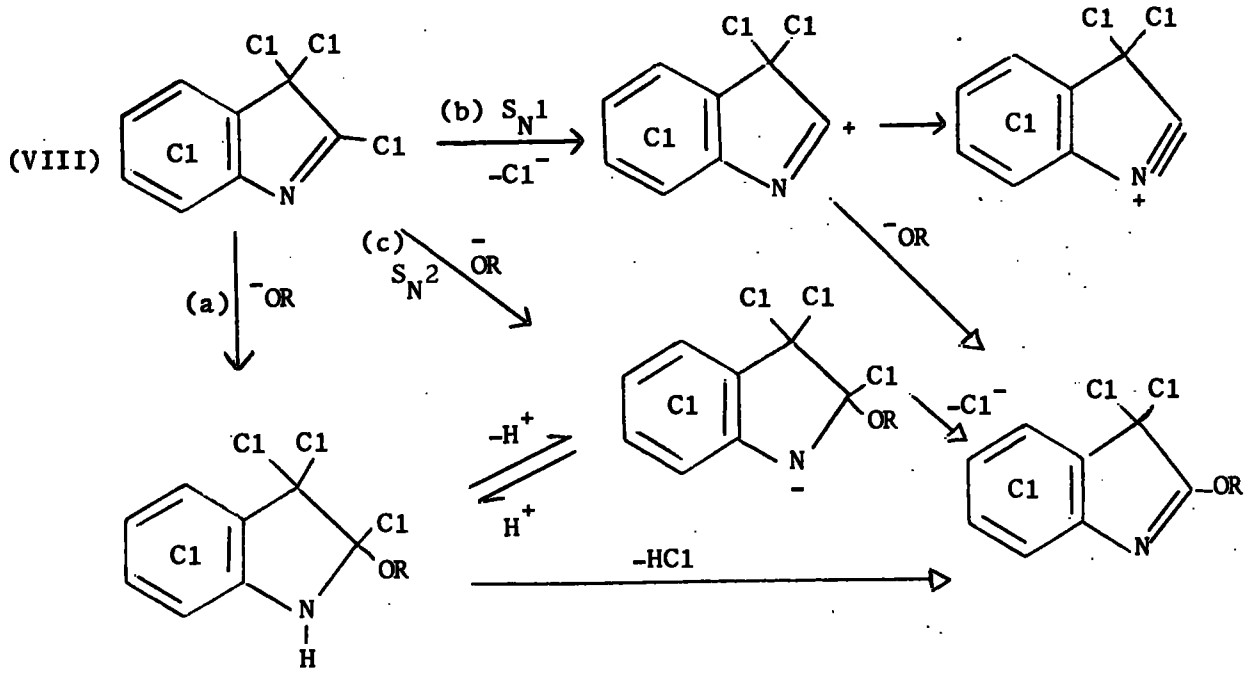
Mechanism.

There are three basic possibilities for the reaction pathway. These are:

(a) Nucleophilic addition-elimination.

(b) Nucleophilic substitution unimolecular $S_N1$.

(c) Nucleophilic substitution bimolecular $S_N2$.




Eqn. 57.

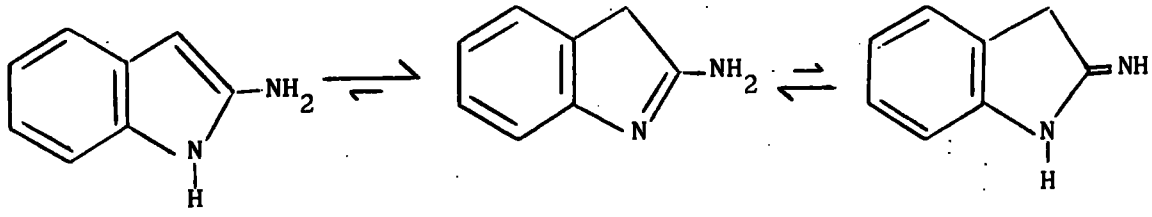
The action of nucleophiles on imidoyl chlorides is thought to proceed by a $S_N1$ mechanism, but this is much less likely with 2-chloroindolenines as strain in the five membered ring is likely to raise the activation barrier.

Nucleophilic displacement of C-(2) in indolenines in such circumstances is presumed to proceed by nucleophilic addition elimination reaction.[210] The intermediate addition compound is a 2-chloroindoline and as such, readily eliminates hydrogen chloride.

3.4.1.2. NITROGEN NUCLEOPHILES.

The aliphatic amines were found to react readily with heptachloroindolenine in ethanol at room temperature. The reaction of methyl amine with heptachloroindolenine gave a bright red colouration when more than ca. 2 molar excess of methyl amine was added and proved difficult to remove on chromatography.

It has been shown that the 2-aminoindole (52) is unstable relative to 2-aminoindolenine[162,183,184] (53) and that the latter is more stable than 2-iminoindoline (54) (Eqn. 58).

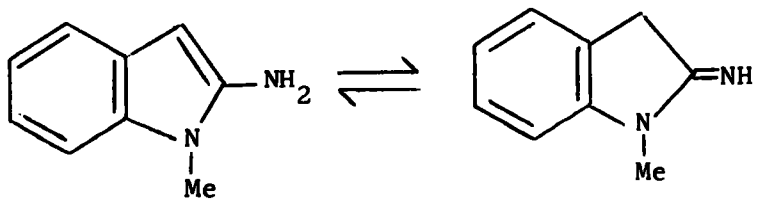


(52) (53) (54)

Eqn. 58.

Preference of (53) over (54) indicates that conjugation of the phenyl ring with iminonitrogen of the amidine system is energetically more favourable than conjugation with the amino system.

With 1-methyl-2-aminoindole only two tautomers are possible (Eqn. 59).

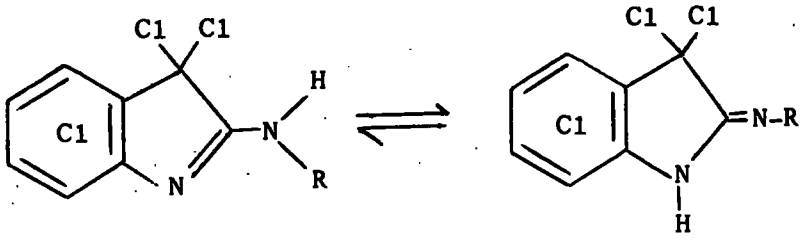


(55) (56)

Eqn. 59.

On the basis of ultraviolet spectral data it was concluded that tautomer (55) was more stable in ether solution, but in more polar solvents tautomer (56) is favoured.[183]

In the case of aminoindolenines with two chlorine atoms at C-(3) (e.g. (57), Eqn. 60) an indole tautomer is precluded.



(57) Eqn. 60. (58)

When there are two alkyl groups attached to the nitrogen at C-(2) then the 2-iminoindoline tautomer is precluded.

3.4.1.2.1. Methyl Amine and Heptachloroindolenine.

The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_9H_4Cl_6N_2$.

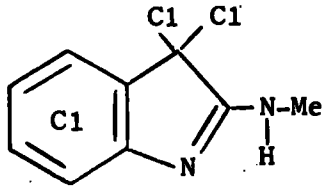
The infrared spectrum (Appendix 1) showed a band at 3200 and 3150 $cm.^{-1}$ assigned to νN-H and bands at 3000 to 2900 $cm.^{-1}$ to νC-H (Aliphatic). The bands at 1650 and 1590 $cm.^{-1}$ were assigned to νC=N and the ring mode respectively.[153]

The ultraviolet spectrum (Appendix 1) was similar in shape and intensity to that of heptachloroindolenine but shows a bathochromic shift(9 nm). The bathochromic shift can be accounted for by substitution at C-(2) or the benzene ring but not by substitution at C-(3).

The $^1H$ N.M.R. spectrum (Appendix 2) consists of a doublet at δ = 3·27 with a coupling constant of ca. 4 Hz but when deuterium exchange was carried out the doublet collapsed to a singlet at δ = 3·27. The doublet was assigned to methyl protons attached to nitrogen and the collapse of the doublet on deuterium exchange indicates that the methyl group can couple with an adjacent labile proton probably on a nitrogen atom. This coupling indicates the presence of an intact methyl amino group $CH_3NH$-.

The doublet appears at an unusually low field position for a methyl group attached to nitrogen and can best be explained by substitution of $CH_3NH$- at the electron deficient 2-position.

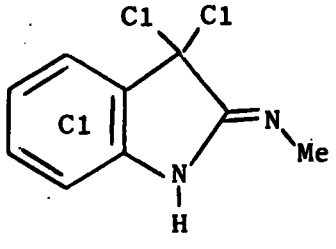
The most probable structure of the product is given in Fig. 14.




2-methylamino-hexachloroindolenine
(XIII)

Fig. 14.

The ultraviolet spectrum indicates that (XIII) exists largely in the aminoindolenine form, in cyclohexane solution at least, as opposed to the iminoindoline form (60) (Fig. 15).




(60)

Fig. 15.

3.4.1.2.2. Dimethyl Amine and Heptachloroindolenine.

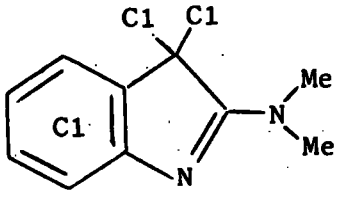
The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_{10}H_6Cl_6N_2$.

The infrared spectrum (Appendix 1) showed no νN-H but did show aliphatic νC-H. The spectrum also had a strong band at 1640 and 1590 $cm.^{-1}$ assigned to νC=N and the ring mode respectively, characteristic of indolenines.[153]

The $^1H$ N.M.R. (Appendix 2) showed a sharp singlet at δ = 3·43 due to two equivalent methyl groups on nitrogen. The ultraviolet spectrum (Appendix 1) was similar in shape in intensity to heptachloroindolenine but showed a bathochromic shift of 10·5 nm. This shift can be accounted for by substitution at the 2-position or in the benzene ring.

The methyl group is at an unusually low field position in the $^1H$ N.M.R. spectrum compared to typical values of the chemical shift of methyl protons attached to nitrogen. These can be accounted for by substitution of $Me_2N$- at the electron deficient 2-position.

The most likely structure for the product is given in Fig. 16.

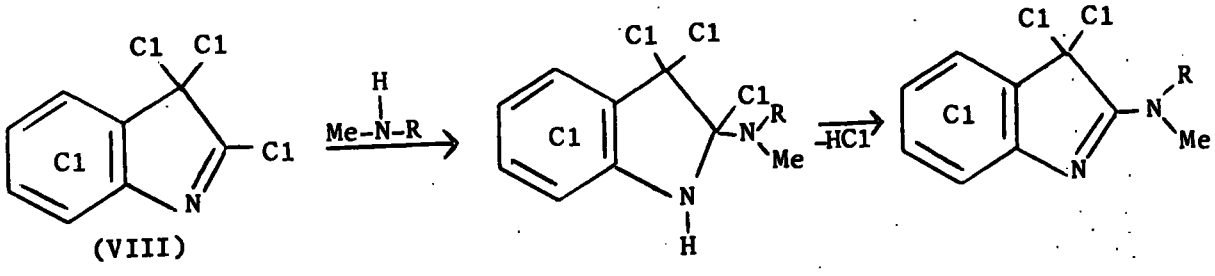


2-dimethylamino -3,3,4,5,6,7-hexachloro-indolenine, (XVIII)

Fig. 16.

3.4.1.2.3. Mechanism for the Reactions with Methyl Amine and Dimethyl Amine.

The reaction between heptachloroindolenine and methyl amine or dimethyl amine probably occurred by an addition-elimination reaction[182] (Eqn. 59a).



(VIII)

R = H, Me

Eqn. 59a.

The hydrogen chloride evolved reacts with unreacted amine necessitating the use of a two molar excess of amine for complete reaction.

3.4.1.2.4. Trimethyl Amine and Heptachloroindolenine.

Trimethyl amine reacts with heptachloroindolenine in tetrahydrofuran to produce the same product as the reaction between heptachloroindolenine and dimethyl amine, i.e. (XVIII).

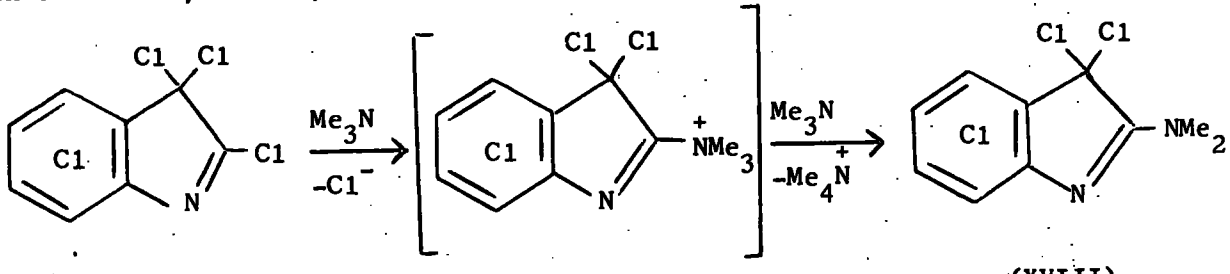
Structure Assignment.

The microanalysis and, mass and isomeric distribution of parent peaks in the mass spectrum gave the molecular formula $C_{10}H_6Cl_6N_2$.

The infrared spectrum and mass spectrum were identical to the product formed between dimethyl amine and heptachloroindolenine which is thought to be 2-dimethylamino-3,3,4,5,6,7-hexachloroindolenine (XVIII).

Mechanism.

The reaction is thought to proceed by nucleophilic attack at C-(2) eliminating chloride ion to give a quaternary ammonium salt (59) which can be demethylated by excess trimethyl amine. (Eqn. 61).



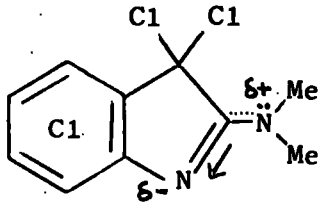

(VIII) (59) (XVIII)

Eqn. 61.

3.4.1.2.5. General Conclusion and Theoretical Considerations on Amino-indolenines.

The fact that the ultraviolet spectra of 2-methylamino-hexachloro-indolenine and 2-dimethylamino-hexachloroindolenine are almost identical, indicated that they have the same 2-aminoindolenine structure as this is the only tautomer possible for 2-dimethylamino-hexachloroindolenine.

The unusually low field position of the N-methyl-protons in the $^{1}H$ N.M.R. of the alkylamino-hexachloroindolenines prepared are probably caused by overlap of the lone pairs on the nitrogen at C-(2) with the polar double bond causing a shift of electronic charge away from the aminonitrogen to the ring nitrogen thus deshielding the methyl-protons. The methyl proton signal chemical shift is in good agreement with a methyl group attached to the nitrogen atom of an amide or to a nitrogen bearing a full positive charge. Greater electron availability at the ring nitrogen and consequent increase in extended conjugation with the aromatic ring would explain the bathochromic shift relative to heptachloroindolenine.




(XVIII)

Fig. 17.

3.4.1.3. CARBON AND SULPHUR NUCLEOPHILES.

3.4.1.3.1. Sodio Diethyl Malonate and Heptachloroindolenine.

The diethyl malonate carbanion reacts readily with compounds containing reactive halogen atoms displacing halide ion (Eqn. 62 and 63).

e.g. $RX + {}^{-}CH(CO_2Et)_2 \longrightarrow RCH(CO_2Et)_2 + X^{-}$

Eqn. 62.

$RCOX + {}^{-}CH(CO_2Et)_2 \longrightarrow RCOCH(CO_2Et)_2 + X^{-}$

Eqn. 63.

When iodine is added to sodio diethyl malonate a redox reaction occurs and tetraethyl dimalonate forms. (Eqn. 64).

$$I_2 + {}^{-}CH(CO_2Et)_2 \xrightarrow[-I^{-}]{} ICH(CO_2Et)_2 \xrightarrow[-I^{-}]{{}^{-}CH(CO_2Et)_2} (CH(CO_2Et)_2)_2$$

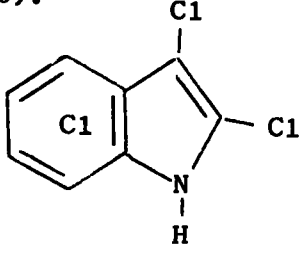
Eqn. 64.

The action of two moles of sodio diethyl malonate on heptachloroindolenine produced 2,3,4,5,6,7-hexachloroindole and an unidentified pale yellow oily product.

Structure Determination of the Product.

The microanalysis and mass spectrum gave the molecular formula $C_8HCl_6N$.

The infrared spectrum was identical to that of the product formed from hydrolysis of the reaction between heptachloroindolenine and magnesium in tetrahydrofuran. This product was shown to be 2,3,4,5,6,7-hexachloroindole, (Fig. 18).




2,3,4,5,6,7-hexachloroindole
(XIV)

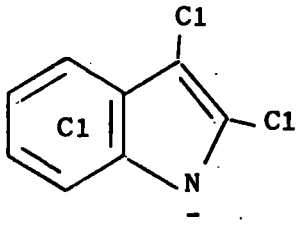
Fig. 18.

m.p. 190-190·5°C (authentic m.p. 189·5 - 190·5°C).

The infrared spectrum of the pale yellow oily product showed a very strong C=O band but the mass spectrum was uninformative.

3.4.1.3.2. Action of Dimethyl Sulphate on the Reaction Mixture Formed from Sodio Diethyl Malonate and Heptachloroindolenine.

To test the hypothesis that the reaction between sodio diethyl malonate and heptachloroindolenine formed a hexachloroindole anion (61) it was




(61)

Fig. 19.

proposed to add dimethyl sulphate to the reaction mixture to trap the ion as 1-methyl-2,3,4,5,6,7-hexachloroindole.

Structural Assignment of the Product.

The infrared and mass spectra were identical to the product formed between trimethyl phosphite and heptachloroindolenine in tetrahydrofuran which was shown to be 1-methyl-2,3,4,5,6,7-hexachloroindole (XV), m.p. 235-6°C (authentic m.p. 236·5 - 237·0°C).

Conclusion.

The formation of 1-methyl hexachloroindole indicates the formation of the hexachloroindole anion (61).

Reaction mechanisms will be discussed later.

3.4.1.3.3. Action of Sodium Thiophenoxide on Heptachloroindolenine.

The reaction of sodium thiophenoxide with heptachloroindolenine was expected to give a thiophenoxy hexachloroindolenine by analogy with the reaction between sodium methoxide and heptachloroindolenine. Instead the action of two moles of sodium thiophenoxide on heptachloroindolenine gave 2,3,4,5,6,7-hexachloroindole.

Structural Assignment.

The infrared and mass spectra of one product was identical to authentic 2,3,4,5,6,7-hexachloroindole. The mass spectrum of the mixture of other products indicated the presence of diphenyl disulphide.

2,3,4,5,6,7-hexachloroindole, m.p. 189·5 - 190·5°C (authentic m.p. 189·5 - 190·5°C).

Conclusion.

Sodium thiophenoxide reduced heptachloroindolenine to 2,3,4,5,6,7-hexachloroindole. (Eqn. 65).

$$2PhSH + C_8NCl_7 \longrightarrow (PhS)_2 + C_8NHCl_6 + HCl$$

Eqn. 65.

3.4.1.3.4. Action of Dimethyl Sulphate on the Reaction Mixture Formed Between Sodium Thiophenoxide and Heptachloroindolenine.

Dimethyl sulphate was added to the reaction mixture formed from sodium thiophenoxide and heptachloroindolenine in tetrahydrofuran and turned cloudy over 30 mins. to give a colourless crystalline solid on work up.

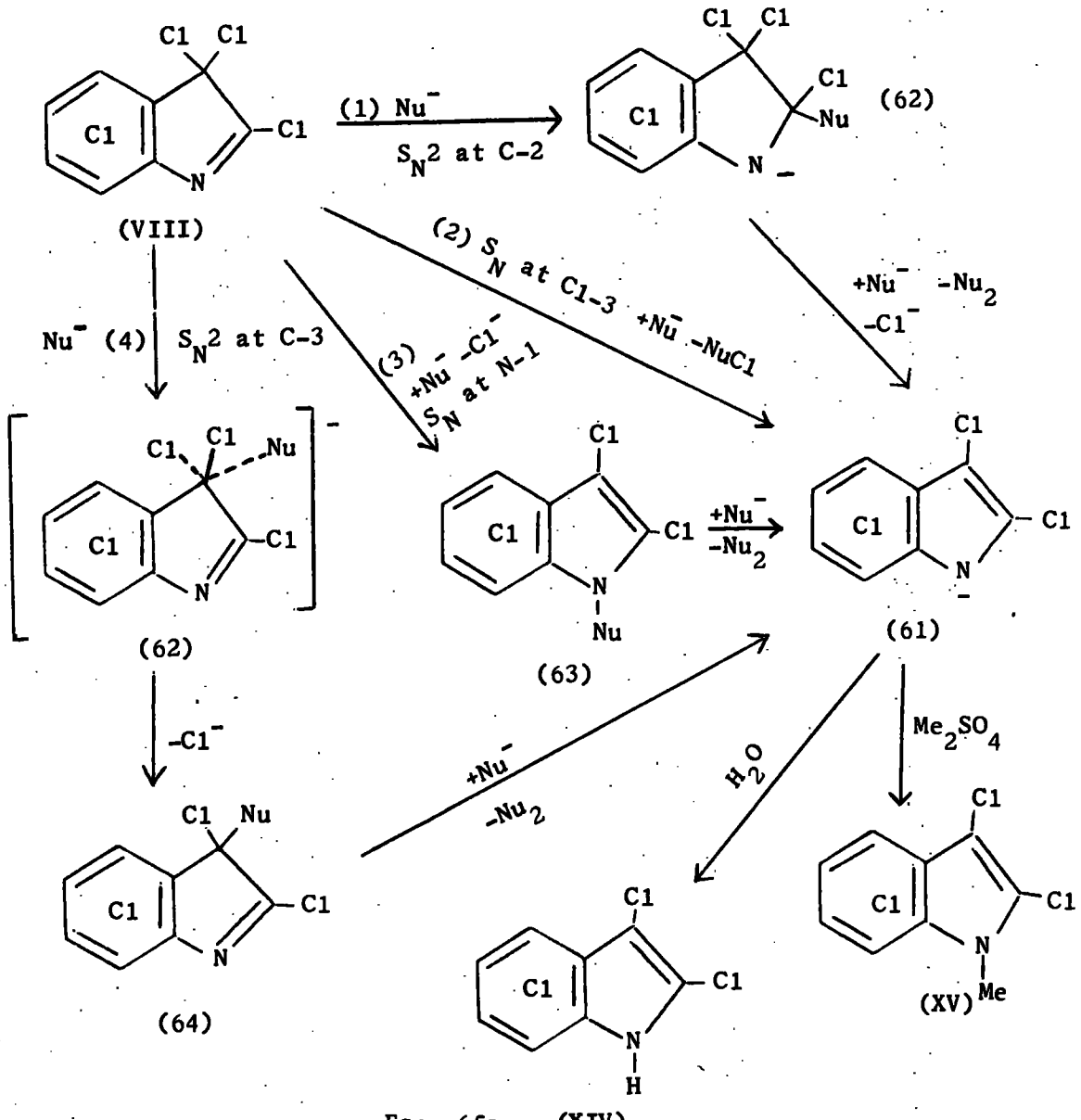
Structure Determination.

The infrared and mass spectra were identical to authentic 1-methyl-2,3,4,5,6,7-hexachloroindole (XV), m.p. 235-6°C (m.p. authentic 236·5 - 237·0°C).

The preparation of 1-methyl-2,3,4,5,6,7-hexachloroindole indicated the presence of a hexachloroindole anion (61) in the reaction mixture.

3.4.1.3.5. Mechanisms.

Sodio diethyl malonate or sodium thiophenoxide could react with heptachloroindolenine by any of the four reaction sequences shown below. (Eqn. 65a).




Eqn. 65a

(1) Nucleophilic substitution at C-(2) to give (62) followed by attack of nucleophile at new substituent.

(2) Nucleophilic attack on a chlorine atom at C-(3) to give (61) directly.

(3) Nucleophilic attack at N-(1) to give (63) followed by attack of a further nucleophile at the N-substituent.

(4) Nucleophilic attack at C-(3) displacing chloride ion to give (64) followed by attack of a further nucleophile at the new substituent.

Reaction route (3) is unlikely as it involves the attack of a negative species at an electron-rich site.

The chlorine atoms at C-(3) displaced by the nucleophile in reaction route (4) are both benzylic and allylic. The developing p orbital at C-(3) containing two electrons is attracted towards:

(a) the electron attracting aromatic 6-membered ring,

(b) the other chlorine atom at C-(3),

(c) the polar C=N which behaves like an allylic system with a strongly electron-withdrawing substituent at the γ(N-(1)) position.

The detection of diphenyl disulphide ($Nu_2$) in the product supports the mechanisms proposed. However the corresponding oxidation product of sodio diethyl malonate, i.e. tetraethyl dimalonate was not identified by mass spectrum in the remaining oily product.

3.4.1.3.6. The Action of Thiophenol on Heptachloroindolenine in Tetrahydrofuran.

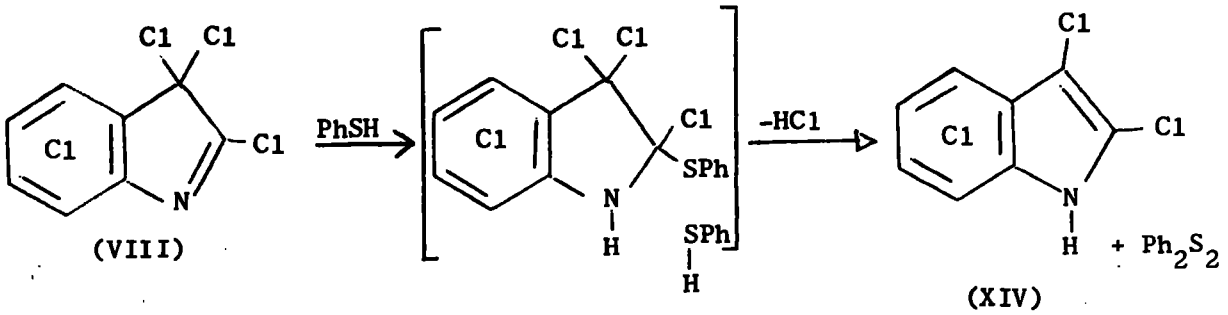
The addition of two moles of thiophenol to heptachloroindolenine in tetrahydrofuran reduced it to hexachloroindole. The addition of three moles of thiophenol failed to produce more product and the addition of one mole of thiophenol produced a little over half as much product. This indicates that two moles of thiophenol are sufficient to reduce one mole of heptachloroindolenine to hexachloroindole.

Structural Determination.

The infrared and mass spectra of the product were identical to authentic 2,3,4,5,6,7-hexachloroindole, m.p. 189·5 - 190·5°C (authentic m.p. 189·5 - 190·5°C).

Theoretical Considerations.

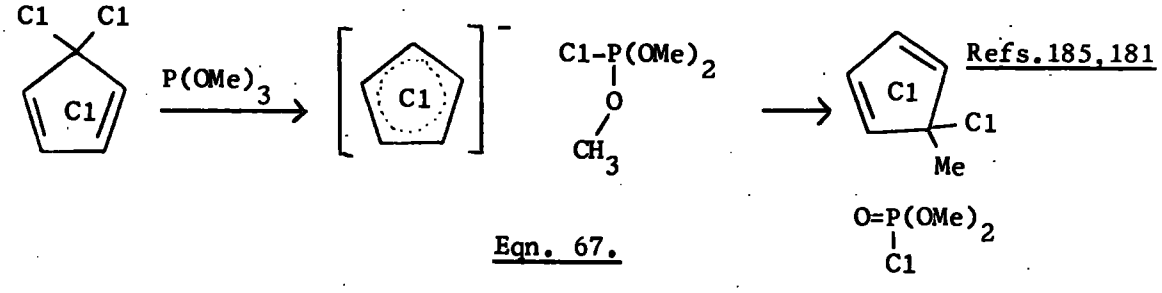
The reaction probably proceeds by nucleophilic addition followed by nucleophilic attack on sulphur. (Eqn. 66).




Eqn. 66.

3.4.1.4. Action of Trimethyl Phosphite on Heptachloroindolenine.

Trimethyl phosphite reacts with hexachlorocyclopentadiene introducing a methyl group at the aliphatic carbon atom.[185,181] The mechanism proposed for the reaction is shown below. (Eqn. 67).




Eqn. 67.

The structure of heptachloroindolenine has the requirements of a chlorine atom on an allylic carbon in a 'cyclopentadiene' ring.[185] One mole of trimethyl phosphite reacts readily with heptachloroindolenine in ether at room temperature to give 1-methyl hexachloroindole.

Structural Assignments.

The microanalysis and, mass and isomeric distribution of molecular peaks in the mass spectrum gave the molecular formula $C_9H_3Cl_6N$.

The infrared spectrum (Appendix 1) showed no bands in νN-H or νC=N regions but did show weak bands in the region 3000 - 2900 $cm.^{-1}$ characteristic of a methyl group.

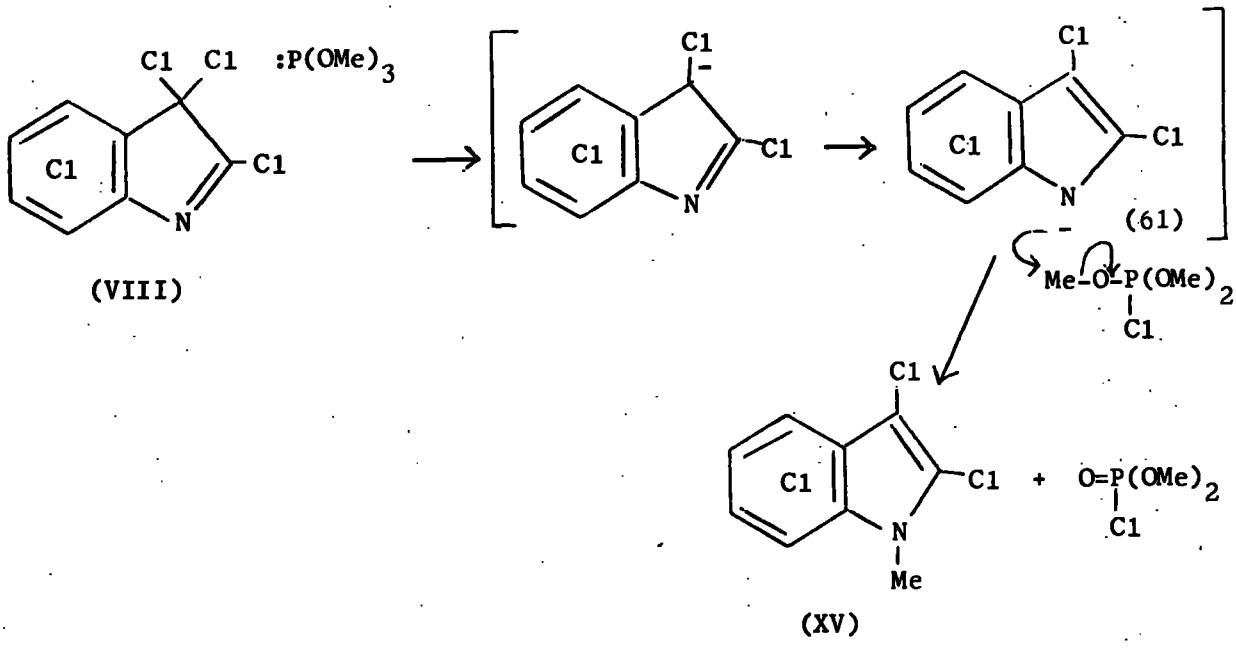
The ultraviolet spectrum (Appendix 1) is similar in shape and position to 5,6,7-trichloroindole.

The $^1H$ N.M.R. (Appendix 2) shows a singlet at 4·10 (δ) which is at a low field position for 1-methyl indoles.[164]

The mass spectrum shows strong peaks at (M-15) and (M-35) due to loss of $CH_3$ or Cl respectively from the parent molecular ion.

Theoretical Considerations.

By analogy with the mechanism proposed for the alkylation of hexachlorocyclopentadiene[185] the following mechanism was devised (Eqn. 68).




Eqn. 68.

The intermediate hexachloroindole anion (61) alkylates at the N-(1) atom as the tautomer with the negative charge on the electronegative nitrogen atom is more stable than the tautomer with the negative charge at C-(3).

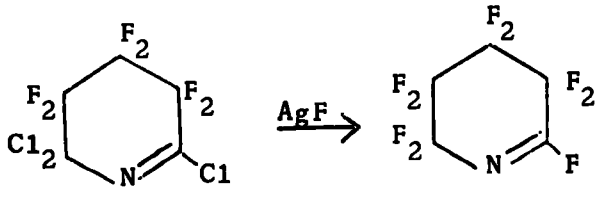
3.4.1.5. INCONCLUSIVE REACTIONS.

3.4.1.5.1. Reaction of Caesium Fluoride and Heptachloroindolenine.

Fluorination of heptachloroindolenine has been attempted by heating it with dry potassium fluoride at 400°C.[188] The conditions employed caused the heptachloroindolenine to break up.

The experiment was repeated by the author at 170°C using dry caesium fluoride as fluorinating agent, but no volatile products were recovered.

Imidoyl chlorides readily exchange chloride for fluoride[182] using silver fluoride (Eqn. 35 ) so it ought to be possible to place at least one fluorine in heptachloroindolenine by halogen exchange.




Ref. 129.

Eqn. 35.

3.4.1.5.2. Reaction of Hydrazine Hydrate and Heptachloroindolenine.

The reaction between hydrazine hydrate and heptachloroindolenine in aqueous dioxan took place rapidly but gave a mixture of three or more products which would prove extremely difficult to separate. If the substitution took place at C-(2) as is believed to happen with the methyl amines then there are several tautomeric structures for the product.

3.4.1.5.3. Reaction of Potassium Hydroxide and Heptachloroindolenine.

The reaction between potassium hydroxide and heptachloroindolenine might be expected to proceed readily and cleanly as does the hydrolysis of imidoyl chlorides,[189] but gave a mixture of coloured products.

3.4.2. METALLATION REACTIONS.

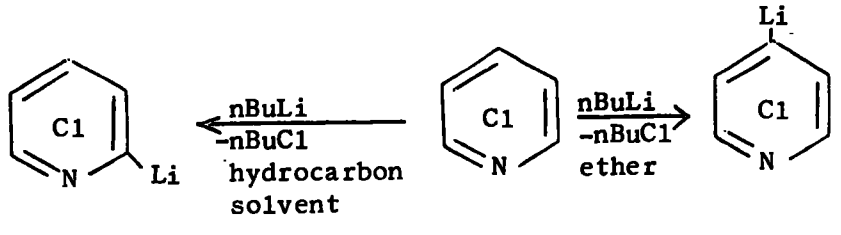
3.4.2.1. The Reaction of n-Butyl-lithium on Heptachloroindolenine in Tetrahydrofuran.

n-Butyl-lithium reacts with aryl halides to give butyl chloride and lithium aryls (Eqn. 69).

$$ArCl + nBuLi \longrightarrow ArLi + nBuCl \xrightarrow{H_2O} ArH + LiOH$$

Eqn. 69.

n-Butyl-lithium reacts with perchloro heteroaromatic compounds displacing the chlorine atom adjacent to the heteroatom[186-7] (Eqn. 70).




Refs. 186,187

Eqn. 70.

If an ether is used as solvent the site most susceptible to nucleophilic attack is lithiated.[186-7] It is thought n-butyl-lithium in hydrocarbon solvents associates with nitrogen lone pairs of the heteroatom and is only capable of attacking in the immediate vicinity. In ether solvents n-butyl-

lithium is well solvated and it is capable of attacking at the site of its choice.[186-7]

n-Butyl-lithium was added to heptachloroindolenine in tetrahydrofuran at -60°C and hydrolysed at -20°C after 30 mins.

Structural Assignment.

The infrared and mass spectra were identical with authentic 2,3,4,5,6,7-hexachloroindole (XIV), m.p. 187-8°C (authentic m.p. 189·5 - 190·5°C). [See 3.4.2.4.].

3.4.2.2. The Action of Dimethyl Sulphate on the Reaction Mixture Formed from Heptachloroindolenine and n-Butyl-lithium.

The reaction between n-butyl-lithium and heptachloroindolenine was repeated but before hydrolysis dimethyl sulphate was added to alkylate the lithio complex.

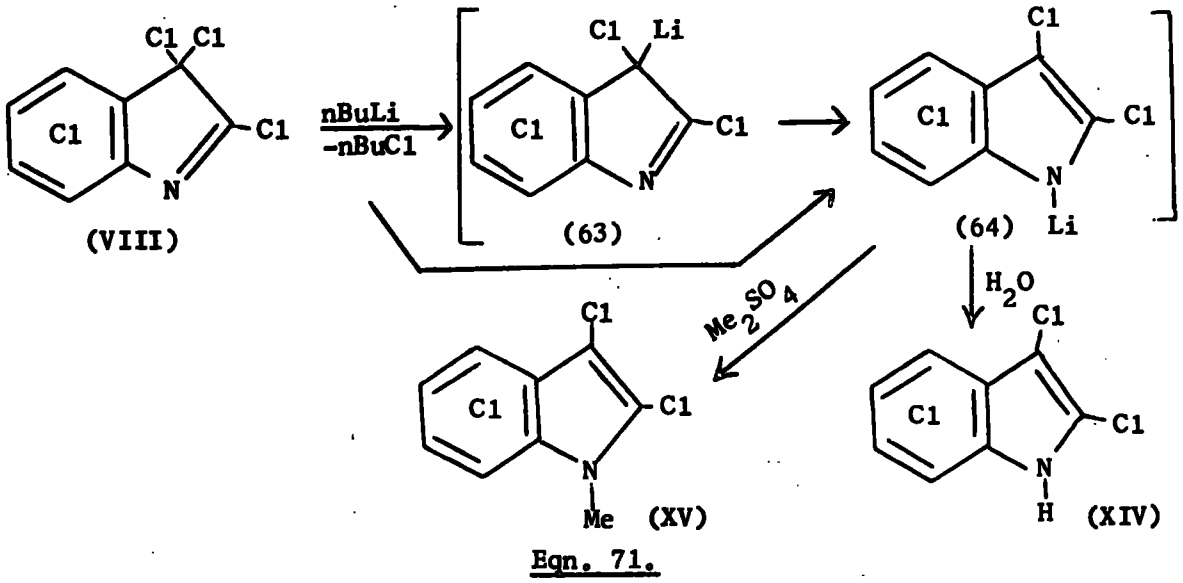
Assignment of Structure.

The mass spectrum indicated the product contained a methyl hexachloro-indole, a methyl pentachloroindole and some methyl tetrachloroindole and hexachloroindole.

3.4.2.3. Theoretical Considerations.

The formation of 2,3,4,5,6,7-hexachloroindole from heptachloroindolenine indicates that a 3-chlorine is transferred by the action of n-butyl-lithium.

The formation of an indole and not an indolenine on alkylation or hydrolysis indicates that the lithio complex exists largely as a N---Li complex (64).




Eqn. 71.

As well as (XV) and (XIV) the mass spectrum of the alkylation mixture indicates the presence of a methyl pentachloroindole and a methyl tetrachloroindole.

The absence of multiple alkylation may indicate that alkylation at other than N-(1) does not occur or is very slow.

The presence of (XIV) formed after reaction with dimethyl sulphate may indicate that the alkylation reaction of (64) is slow.

The absence of a pentachloroindole indicates that dilithiation of (XIV) is unlikely whereas the presence of methyl pentachloroindole and methyl tetrachloroindole indicates that further lithiation of (XV) can occur, including dilithiation.

The detection of further lithiation after alkylation may indicate that n-butyl-lithium did not react readily with dimethyl sulphate.

3.4.2.4. The Action of Magnesium on Heptachloroindolenine in Tetrahydrofuran.

Grignard reagents have been prepared from a series of chlorinated and polychlorinated aromatic compounds using magnesium and tetrahydrofuran.[190] Of many other solvents tried, tetrahydrofuran proved the most efficacious and it was concluded that the reactions were facilitated by the accessibility of the oxygen lone pair of electrons used to solvate and stabilise the magnesium complex.[190]

Indolyl magnesium halides are usually regarded as XMg-N complexes[191] although the alternative XMg-C(3) has been suggested[192-3] but is now firmly ruled out by N.M.R. studies[194] and indole Grignards are thought to mainly exist in an ionic form.[194]

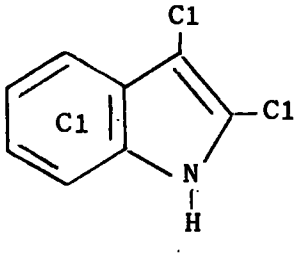
Structural Assignment.

The microanalysis and, weight and isotopic distribution of parent peaks in the mass spectrum gave the molecular formula $C_8HCl_6N$.

The infrared spectrum (Appendix 1) showed a strong sharp band at 3400 $cm.^{-1}$ assigned to νN-H and showed no bands that could be assigned to νC=N indicating the compound was an indole.

The ultraviolet spectrum (Appendix 1) was similar in shape and intensity to 5,6,7-trichloroindole.

The only reasonable structure for the compound is shown in Fig. 20.




2,3,4,5,6,7-hexachloroindole
(XIV)

Fig. 20.

3.4.2.5. Action of Dimethyl Sulphate on the Solution of Hexachloroindole Grignard in Tetrahydrofuran.

Dimethyl sulphate was added to the reaction mixture formed between magnesium and heptachloroindolenine in tetrahydrofuran to confirm the presence of a Grignard reagent.

Addition of an alkyl sulphate and alkali to indolyl magnesium halides gives 1-monoalkyl indoles.[195]

Magnesium derivatives of indoles show a shift towards alkylation at C-(3) relative to sodium derivatives.[196] If position 3- or positions 2- and 3- of indolyl magnesium halides are blocked by methyl groups, alkylation can take place largely at C-(3).[197-200]

In non-polar solvents such as ethers and hydrocarbons one expects to find a large amount of ion aggregation and a small highly charged magnesium ion is likely to be tightly co-ordinated with the indolyl anion. Free indolyl ions have a strong preference for alkylation at nitrogen by a $S_N2$ mechanism as the anions negative charge is normally thought to be located in a $sp^2$ orbital on nitrogen. When the pair of electrons on nitrogen is

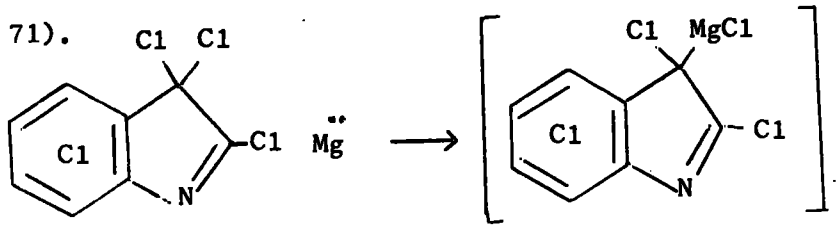
extensively co-ordinated to a metal ion its availability to act as a nucleophile is limited.

Structure Determination.

The infrared and mass spectrum were identical to authentic 1-methyl-2,3,4,5,6,7-hexachloroindole, m.p. 235·0 - 235·5°C (m.p. authentic 236·5 - 237·0°C).

3.4.2.6. Theoretical Considerations.

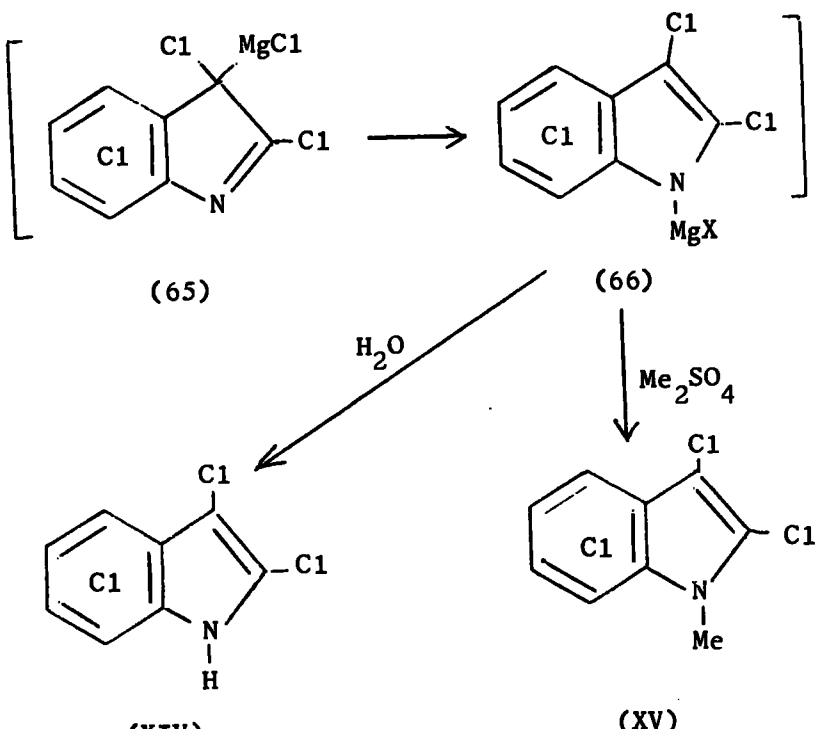
The mechanism of the reaction probably proceeds via displacement of a chlorine at C-(3) by magnesium to give a C-(3) magnesium derivative (65). (Eqn. 71).




(VIII) (65)

Eqn. 71.

As most indolyl Grignard reagents are believed to be N-MgX complexes it seems likely (65) rearranged to (66) (Eqn. 72), or 66 forms directly.



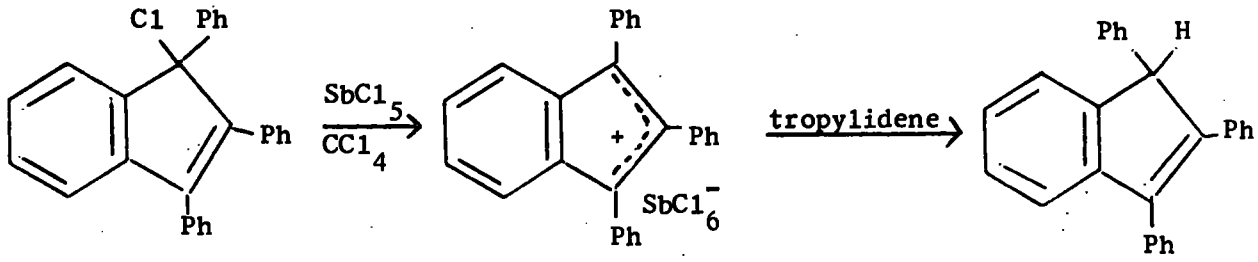

Eqn. 72.

No methyl tetrachloroindoles or methyl pentachloroindoles were detected in the mass spectrum of the product indicating the excess magnesium did not remove any further chlorine atoms from the indole ring as was the case with butyl-lithium.

3.4.3. Action of Antimony Pentachloride on Heptachloroindolenine.

Antimony pentachloride is a strong chloride ion acceptor[201-2] and will accept chloride ion from organic chlorides such as triphenyl methyl chloride[202] and imidoyl chlorides (2.2.2., p.23).

The salts formed from the reaction of organic halides with antimony pentachloride can be quenched with alkoxides,[203] alcohols[203-4] to give ethers or with tropylidene[204-6] to give the corresponding hydrocarbon (e.g. Eqn. 73).




Ref. 205

Eqn. 73.

The reaction was performed in order to form the antiaromatic cation analogous to the reaction in Equation 73.

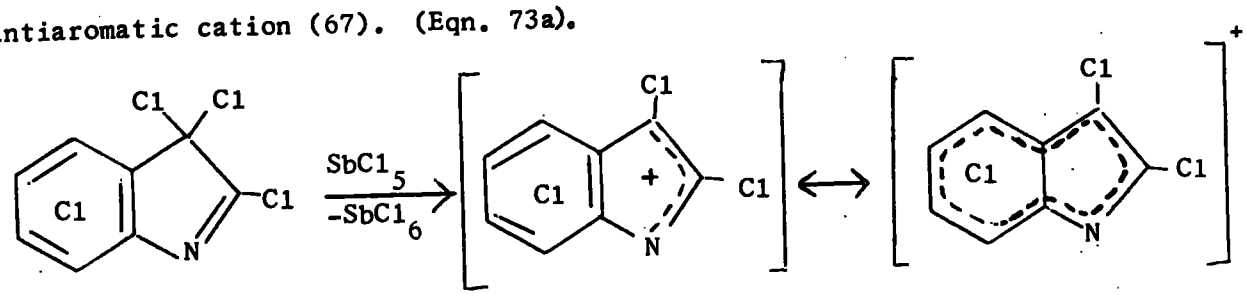
Antimony pentachloride was added to heptachloroindolenine without any solvent at -60°C and cold methanol (-60°C) was added dropwise to quench the salt formed.

Structure Determination of the Products.

The infrared and mass spectra of one product was identical to authentic pentachloroaniline but the other golden yellow carbonyl containing compound was not identified.

3.4.3.1. Theoretical Considerations.

The most likely positions from which a chloride ion can be taken are C-(2) and C-(3). Abstraction of a chloride ion from C-(3) results in an antiaromatic cation (67). (Eqn. 73a).

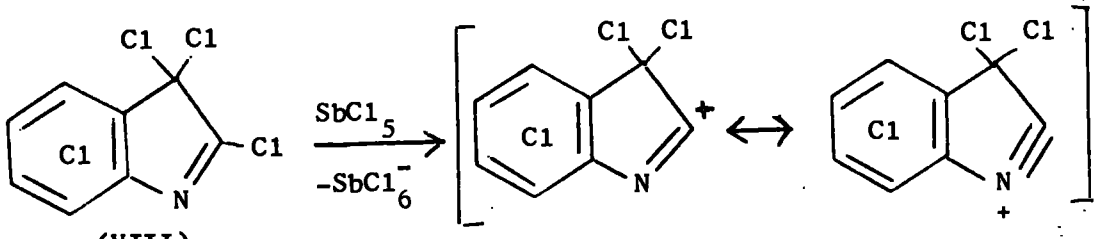



(VIII) (67)

Eqn. 73a.

By valence bond tautomerism it can be shown that (67) can locate the positive charge on any ring atom.

Abstraction of a chloride ion from C-(2) gives (68) (Eqn. 74).




(VIII) Eqn. 74. (68)

The observation that the addition of methanol produced a product, i.e. pentachloroaniline which resulted from the break-up of the five membered ring indicates that the indole cation is not very stable whatever form it takes. An insight into the structure of the anion might be gained from a knowledge of the structure of the unidentified compound/mixture formed along with pentachloroaniline.

3.4.4. REDUCTION OF HEPTACHLOROINDOLENINE.

3.4.4.1. Action of Lithium Aluminium Hydride on Heptachloroindolenine.

Lithium aluminium hydride is used for the selective reduction of carbonyl groups and various polar functions. The actual mechanism is believed

to be stepwise by transfer of a hydride ion and co-ordination of the aluminium hydride with the more electronegative atom of the polar group. Hydrolysis replaces the aluminium hydride by hydrogen.

For an example see Chapter II, 2.2.2.

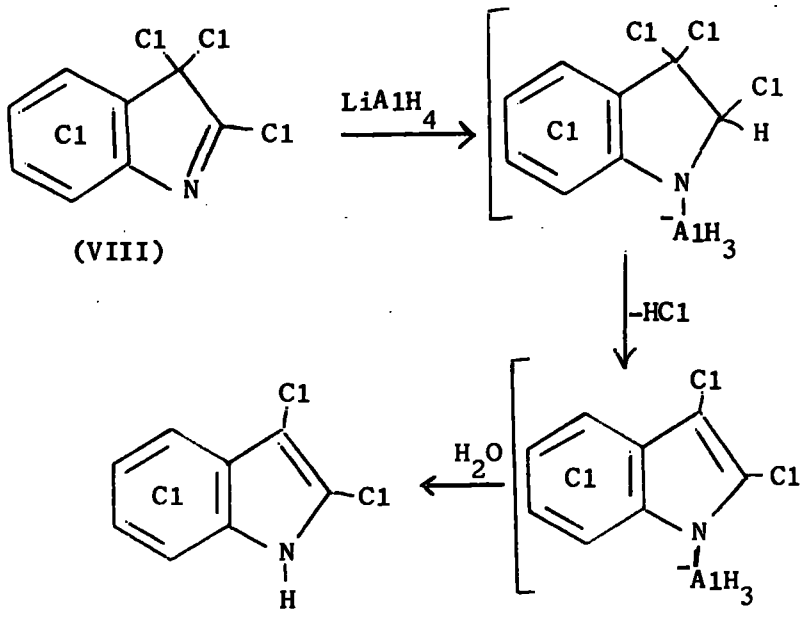
The action of lithium aluminium hydride on heptachloroindolenine produced 2,3,4,5,6,7-hexachloroindole.

Structural Determination.

The infrared and mass spectrum were identical to authentic 2,3,4,5,6,7-hexachloroindole, m.p. 187-190°C, (m.p. authentic 189·5 - 190·5°C).

Theoretical Considerations.

The aluminium hydride is thought to add across the carbon nitrogen double bond as shown followed by elimination of hydrogen chloride to give (69) (Eqn. 75).




(VIII) (XIV) (69)

Eqn. 75.

Hydrolysis of (69) gives (XIV).

3.4.4.2. CATALYTIC HYDROGENATION OF HEPTACHLOROINDOLENINE AND SOME OF ITS REACTION PRODUCTS.

For the dehalogenation of heterocyclic halogen compounds the catalyst of choice is palladium on charcoal as it is least poisoned by halide ions and

promotes carbon halogen bond cleavage.

The rate of reaction can be increased by the use of base and a more polar hydroxylic solvent, although increased reactivity means decreased selectivity.[207]

3.4.4.2.1. Catalytic Hydrogenation of Heptachloroindolenine in Tetrahydrofuran.

Heptachloroindolenine contains three basic types of chlorine atom, an imidoyl chloride at C-(2), benzylic or even 'allylic' chlorines at C-(3) and aryl chlorines in the benzene ring. Hydrogenolysis of benzyl, vinyl and allyl halides is known to occur readily but aryl chlorides are stable to hydrogenolysis in neutral media and require the presence of base to facilitate reaction.[207] The presence of more than one halogen atom on a carbon, or the presence of ring heteroatom promotes dehalogenation.[207]

Heptachloroindolenine was hydrogenated at room temperature and atmospheric pressure in tetrahydrofuran, and magnesium oxide to accelerate the reaction, and the reaction was stopped when three equivalents of hydrogen had been absorbed.

Structure Determination.

The microanalysis and, mass and isomeric distribution of molecular peaks in the mass spectrum gave the molecular formula $C_8H_3Cl_4N$.

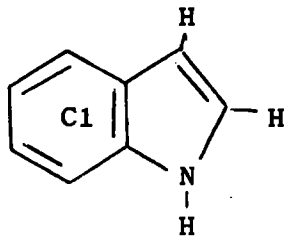
The infrared spectrum (Appendix 1) showed a strong sharp band at 3400 $cm.^{-1}$ due to νN-H but no band that could be assigned to νC=N.

The ultraviolet spectrum (Appendix 1) is similar in shape, position and intensity to 5,6,7-trichloroindole.

The $^1H$ N.M.R. spectrum (Appendix 2) consists of two doublets of doublets with a mutual coupling constant, and each coupled to the N-(1) hydrogen which was too weak to observe. The mutual coupling between all three protons means that they are all in the same ring, i.e. the pyrrole ring.

The chemical shift of the doublet of doublets at a relatively high field position is assigned to the 3 proton as it shows little solvent dependence of chemical shift. The chemical shift of the other doublet of doublets showed appreciable solvent dependence and was assigned to the 2-proton. The coupling data was consistent with the structural assignments made.

The chlorine atoms are at positions 4,5,6, and 7 (Fig. 21).

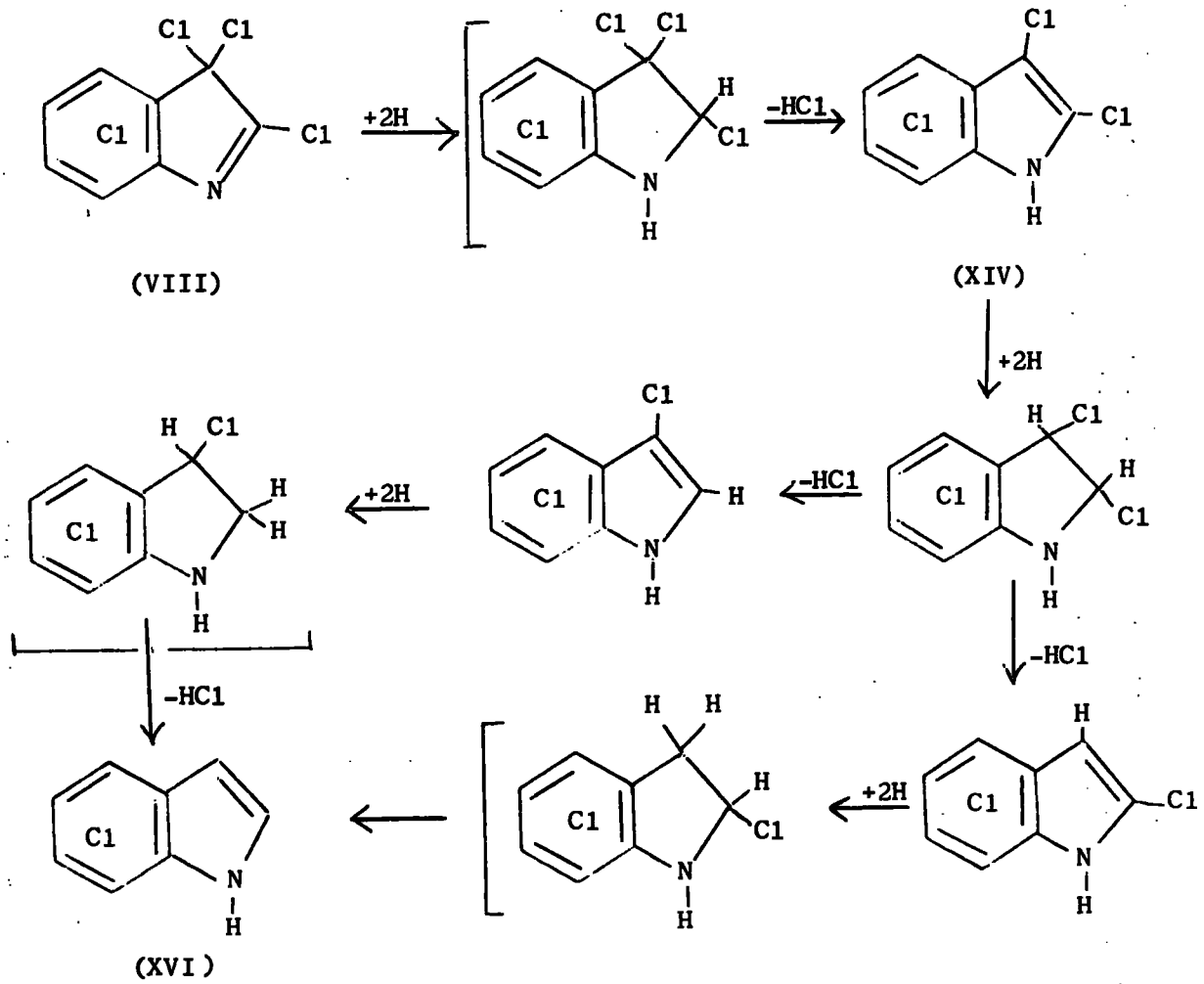


4,5,6,7-Tetrachloroindole
(XVI)

Fig. 21.

Theoretical Considerations

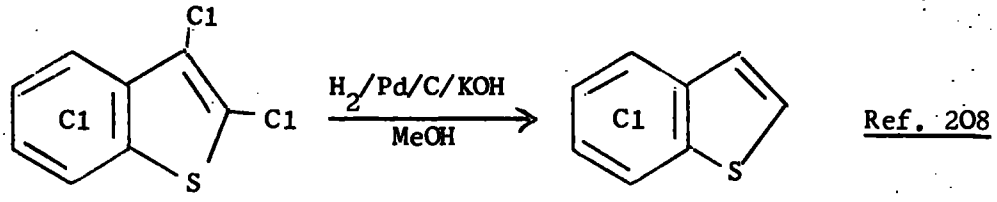
The reaction probably proceeds by successive addition of hydrogen across a double bond followed by elimination of hydrogen chloride (Eqn. 76).




Eqn. 76.

3.4.4.2.2. Catalytic Hydrogenation of Hexachloroindole.

By analogy with the catalytic hydrogenation of hexachlorobenzo[b]-thiophene (70) to 4,5,6,7-tetrachlorobenzo[b]thiophene[208] (71) (Eqn. 76a), hexachloroindole was expected to hydrogenate to 4,5,6,7-tetrachloroindole.




(70) (71) Ref. 208

Eqn. 76a.

It has been observed that the indole ring undergoes facile catalytic hydrogenation in strongly acidic solution[209] and it is thought that the indolenium ion is involved in the reaction.

2,3,4,5,6,7-Hexachloroindole was hydrogenated under the same conditions as heptachloroindolenine but the reaction was stopped after two equivalents of hydrogen had been absorbed.

Structure Determination.

The infrared and mass spectra were identical to the product of catalytic hydrogenation of heptachloroindolenine, i.e. 4,5,6,7-tetrachloroindole (XVI), m.p. 177·0 - 177·5°C (authentic m.p. 177·0 - 177·5°C).

The reaction probably occurred by a route from (XIV) to (XVI) in Eqn. 76.

3.4.4.2.3. Catalytic Hydrogenation of 1-Methyl-2,3,4,5,6,7-Hexachloroindole.

1-Methyl-2,3,4,5,6,7-hexachloroindole was hydrogenated to confirm the structure given to it. The conditions employed were similar to those used for the hydrogenation of heptachloroindolenine and the reaction was stopped after two equivalents of hydrogen had been absorbed.

Structure Determination.

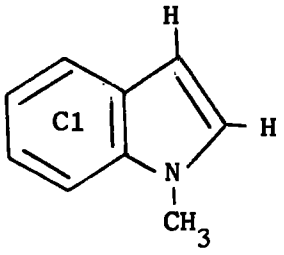
The microanalysis and, mass and isomeric distribution of parent molecular peaks gave the molecular formula $C_9H_5Cl_4N$.

The infrared spectrum (Appendix 1) showed no νN-H or νC=N but did show weak bands in the νC-H region.

The ultraviolet spectrum (Appendix 1) was similar in shape, position and intensity to 5,6,7-trichloroindole.

The mass spectrum shows a strong peak at (P-15) due to loss of a methyl group.

The $^1H$ N.M.R. (Appendix 2) consists of a singlet at 4·05(δ) due to methyl protons on the nitrogen atom of indole, and two doublets which are mutually coupled. The doublet at high field was assigned to the 3-proton and as the coupling constant was consistent with 2 - 3 coupling indicating that the other proton is at C-(2). The chlorine atoms are therefore at the 4-, 5-, 6- and 7-positions (Fig. 22).




1-Methyl-4,5,6,7-tetrachloroindole
(XVII)

Fig. 22.

# CHAPTER IV

## EXPERIMENTAL DETAILS FOR CHAPTER III

## EXPERIMENTAL

### Sodium Indoline-2-Sulphonate (II).

A solution of indole (I) (100 g.) in ether (200 ml.) and absolute alcohol (600 ml.) was added with stirring to sodium metabisulphite (112 g.) in water (288 mls.) and the mixture was shaken vigorously for 72 hrs. The white crystals were filtered off, washed with methanol (300 ml.) and dried under suction. The filter-cake was broken up, and dried in vacuo over $P_2O_5$ to give II (16·1 g.) (85% yield). The infrared spectrum showed two sharp bands at 3430 and 3220 $cm.^{-1}$ due to the N-H stretch.

### Acetylation of Sodium Indoline-2-Sulphonate (II).

A mixture of II (100 g.) and sodium metabisulphite (100 g.) was stirred with acetic anhydride (900 ml.) at 45 - 49°C for 30 hrs. ensuring that the mixture remained fluid. The thick white slurry was filtered and the solid washed with dry ether, broken up and dried in vacuo over $P_2O_5$ to give crude sodium N-acetyl indoline-2-sulphonate (III) (224 g.).

### 5,7-Dichloroindole (VII).

Crude III (212·1 g.) was dissolved in a mixture of water (2 l.) and ice (500 g.) filtered at the pump and the filtrate placed in a 3 l. flask with an efficient stirrer. The solution was cooled to -2 to 0°C and chlorine passed through the solution with rapid stirring at -2 to +2°C. When the chlorine passed unabsorbed through the mixture the chlorine was stopped and nitrogen passed to remove excess chlorine. The green solution was transferred to a large beaker and aqueous NaOH (600 ml., 20% $^{w}/_{w}$) was added slowly with rapid stirring at $< 10^{o}C$. The precipitate

which formed was filtered off, washed with water and dried in vacuo over $P_2O_5$ (57·6 g.) and sublimed in vacuo (80°, 0·05 mm.) to give crude product (54·4 g.). The crude product (10 g.) was recrystallised [petroleum ether (b.p. 40 - 60°)] several times to give VII (1 g.), m.p. 53·5 - 54·0°C (12% yield), (Found: C, 51·49; H, 2·92; Cl, 37·66; N, 7·37%; $M^+$, 185), $C_8H_5Cl_2N$ requires C, 51·65; H, 2·71; Cl, 38·11; N, 7·53%; $M^+$, 185). The infrared spectrum showed a single band at 3400 $cm.^{-1}$ due to N-H stretch. $^1H$ n.m.r. in acetone (δ values): 1, ~10·3; 2, 7·45; 3, 6·56; 4, 7·57; 6, 7·22. Coupling data: $J_{1,2}$, ~2·5; $J_{1,3}$, 2·0; $J_{1,4}$, 0·7; $J_{2,3}$, 3·2; $J_{2,6}$, 0·4; $J_{4,6}$, 1·8 Hz. $^1H$ n.m.r. in carbon tetrachloride (δ values): 1, ~7·9; 2, 6·95; 3, 6·32; 4, 7·35; 6, 7·05. Coupling data: $J_{1,2}$, ~2·4; $J_{1,3}$, 2·1; $J_{1,4}$, 0·7; $J_{2,3}$, 3·1; $J_{2,6}$, 0·4; $J_{4,6}$, 1·7 Hz.

5,6,7-Trichloroindole (IV).

The acetylation product (III) (from 100 g. II) was dissolved in a mixture of water (2 l.) and ice (500 g.) and filtered at the pump. The filtrate was transferred to a 3 l. flask with an efficient stirrer and cooled to -2 to 0°. Chlorine was bubbled slowly through the solution with rapid stirring at +2 to -2°C until excess chlorine passed through unabsorbed. The temperature was allowed to rise to 15°C whilst slowly passing chlorine for a further 30 mins. Nitrogen was then passed through the solution to remove excess chlorine and the solution transferred to a large beaker and cooled to ca. 0°C. Aqueous sodium hydroxide (600 ml., 20% $^w/_w$) was added slowly with stirring to the solution at < 10°C and stirred for 1 hr. The precipitate was filtered off and washed with water and dried in vacuo

over $P_2O_5$. The dry solid (61·1 g.) was sublimed in vacuo (90° and 0·03 mm.) to give crude IV (58·4 g.). The crude product was recrystallised from petroleum ether (b.p. 60-80°) to give pure IV (47 g.), m.p. 97·5 - 98·0° (47% yield) (calculated from II), (Found: C, 43·46; H, 1·90; Cl, 48·33; N, 6·49%; $M^+$, 219, $C_8H_4Cl_3N$ requires C, 43·58; H, 1·83; Cl, 48·24; N, 6·35%; $M^+$, 219). $\lambda_{max}$ 279, 292 and 304 nm [$\epsilon$, 7100, 5600 and 3200 (in cyclohexane)]. The infrared spectrum shows a sharp band at 3400 $cm.^{-1}$ due to N-H stretch. $^1H$ n.m.r. spectra ($\delta$ values) in acetone: 1, ~10·5; 2, 7·43; 3, 6·50; 4, 7·65 p.p.m. Coupling data: $J_{1,2}$, 2·6; $J_{1,3}$, 2·0; $J_{1,4}$, 0·7; $J_{2,3}$, 3·1 Hz. $^1H$ n.m.r. spectra ($\delta$ values) in carbon tetrachloride: 1, ~8·0; 2, 7·08; 3, 6·36; 4, 7·48 p.p.m. Coupling data: $J_{1,2}$, 2·4; $J_{1,3}$, 2·1; $J_{1,4}$, 0·7; $J_{2,3}$, 3·1 Hz.

3,5,6,7-Tetrachloroindole (VI).

A solution of sulphuryl chloride (0·4 ml.) in dry ether (100 ml.) at 5° was added dropwise with stirring to a solution of IV (0·5 g.) in dry ether (100 ml.) at 0°. The solution was stirred at 0° for 1 hr., heated under reflux (30 mins.), cooled to < 10°, and poured onto ice-water with stirring. The organic phase was washed with water (2 x 100 ml.), then excess aq. $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a dark red solid (0·54 g.). The crude product (159 mg.) was separated by chromatography on silica gel (using chloroform as eluate) and recrystallised from petroleum ether (b.p. 60-80°), to give 3,5,6,7-tetrachloroindole (107 mg.) (63% yield), (Found: C, 37·87; H, 1·37; Cl, 55·34; N, 5·59%; $M^+$, 253, $C_8H_3Cl_4N$ requires: C, 37·69; H, 1·19; Cl, 55·63; N, 5·49%; $M^+$, 253).

$\lambda_{max}$ 286, 294, 302, and 307 nm [$\epsilon$, 6100, 5800, 4700, and 4200 (in cyclohexane)]. The infrared spectrum showed a sharp band at 3400 cm.$^{-1}$ due to N-H stretch. $^{1}$H n.m.r. spectrum in acetone ($\delta$ values): 1, ~10·9; 2, 7·50; 4, 7·60. Coupling data: $J_{1,2}$, 2·7; $J_{1,4}$, 0·7 Hz. $^{1}$H n.m.r. spectrum in carbon tetrachloride ($\delta$ values): 1, ~8·1; 2, 7·10; 4, 7·53. Coupling data $J_{1,2}$, 2·5; $J_{1,4}$, 0·7 Hz. m.p. 128·5 - 129·0°C.

2,3,3,5,6,7-Hexachloroindolenine (V).

IV (5 g.) and one small crystal of iodine was dissolved in dry carbon tetrachloride (200 ml.) under $N_2$, and chlorine was bubbled slowly through the stirred solution until excess chlorine had passed for 5 mins. The solution was heated under reflux (30 mins.) then evaporated to dryness and the residue separated by chromatography on silica gel [carbon tetrachloride as eluant] and recrystallised from petroleum ether (b.p. 60 - 80°) to give 2,3,3,5,6,7-hexachloroindolenine (5 g.), m.p. 98·5 - 99·5° (68% yield). (Found: C, 29·97; H, 0·45; Cl, 65·92; N, 4·39%; $M^+$, 321, $C_8HCl_6N$ requires C, 29·67; H, 0·31; Cl, 65·69; N, 4·33%; $M^+$, 321). $\lambda_{max}$ 234, 242, 249 and 257 nm [$\epsilon$, 13,700, 18,700, 25,600 and 26,300 (in cyclohexane)]. The infrared spectrum showed a peak at 1570 cm.$^{-1}$ (characteristic of indolenines) due to C=N stretch. The $^{1}$H n.m.r. showed a sharp singlet at 7·67 ($\delta$ scale) due to a 4 proton, (solvent $CCl_4$).

2,3,3,4,5,6,7-Heptachloroindolenine (VIII).

IV (10 g.) and phosphorus pentachloride (70 g.) were heated in an autoclave to 290°C for 6 hrs. The autoclave was opened, the gases vented and volatile materials evaporated in vacuo. The residue was extracted with benzene, and the solution filtered, and evaporated, and the residue

sublimed (90 - 100°C, 0·03 mm.) to give crude VIII (11·3 g.). The sublimate was recrystallised from petroleum ether (b.p. 60-80°) to give VIII (7·5 g.) (46% yield), m.p. 123·5 - 124·5°. (Found: C, 26·82; Cl, 69·27; N, 3·91%; $M^+$, 355, $C_8Cl_7N$ requires: C, 27·05; Cl, 69·63; N, 4·02%; $M^+$, 355). $\lambda_{max}$ 241, 249 and 257 nm [$\epsilon$, 21,700, 27,600 and 26,600 (in cyclohexane)]. The infrared spectrum showed a single band at 1570 $cm.^{-1}$ due to C=N stretch.

Pentachloroaniline (IX).

Pentachloronitrobenzene (100 g.) and methanol (2 l.) were heated under reflux and hydrochloric acid (50 ml., 11 N) and 85 g. coarse iron filings added with stirring portionwise. Hydrochloric acid (150 ml., 11 N) was added and the mixture stirred under reflux for 5 hrs. Hydrochloric acid (60 ml., 11 N) was added and the mixture stirred and heated under reflux for a further 12 hrs. The methanol was distilled off, water (1 l.) added and the solid filtered off. The residue was dissolved in ether (~1·5 l.), shaken with 500 ml. $H_2O$ and the mixture filtered. The organic layer was separated, dried ($MgSO_4$) evaporated to dryness and the residue recrystallised ($CCl_4$) to give IX (70 g.), m.p. 231·5 - 232·5°C (88% yield). (Found: C, 26·82; H, 1·10; Cl, 67·07; N, 5·32%; $M^+$, 263, $C_6H_2Cl_5N$ requires: C, 27·16; H, 0·76; Cl, 66·80; N, 5·28%; $M^+$, 263). The infrared spectrum showed peaks at 3480 and 3380 $cm.^{-1}$ due to N-H stretch.

Trichloroacetyl Chloride (XX).

A mixture of dry trichloroacetic acid (431·7 g.) and thionyl chloride (500 ml.) was heated under reflux for 3 days and then distilled to 140°C. The distillate was fractionated and the fraction b.p. 115 - 120°C (399·2 g.)

was almost pure IX. The infrared spectrum showed a band at 1800 $cm.^{-1}$ due to C=O stretch.

Preparation of Octachloroacetanilide (X).

A mixture of IX (20 g.), trichloroacetyl chloride (40 ml.) and sulphuric acid (1 ml., d, 1·84) was heated under reflux under $N_2$ for three days. The mixture was cooled, added to ether (400 ml.) and water (200 ml.) and neutralised with sodium bicarbonate. The mixture was filtered and the organic layer, separated, dried ($MgSO_4$), evaporated and the residue recrystallised from carbon tetrachloride to give X (21·7 g.), (silver white platelets), m.p. 233·0 - 233·5°, (70% yield). (Found: C, 23·09; H, 0·23; N, 3·11; Cl, 68·60%; $M^+$, 407, required for $C_8HCl_8NO$: C, 23·40; H, 0·25; Cl, 69·05; N, 3·41%; $M^+$, 407). The infrared spectrum showed a peak at 3300 $cm.^{-1}$ due to N-H stretch.

Preparation of N-Pentachlorophenyl Trichloroacetimidoyl Chloride (XI).

X (1 g.) and phosphorus pentachloride (2 g.) were sealed under vacuum in a Carius tube and heated at 160°C for 5 hrs. The contents of the tube were dissolved in carbon tetrachloride and the solution filtered, evaporated to dryness and chromatographed on silica gel (chloroform as eluate) and recrystallised from petroleum ether (b.p. 60 - 80°) to give XI (456 mg.), m.p. 127·5 - 128·5°C (44% yield), (Found: C, 22·41; Cl, 74·59; N, 3·55%; $M^+$, 425, required for $C_8Cl_9N$: C, 22·39; Cl, 74·35; N, 3·26%; $M^+$, 425). The infrared spectrum showed a peak at 1690 $cm.^{-1}$ due to C=N stretch.

Pyrolysis of N-Pentachlorophenyl Trichloroacetimidoyl Chloride (XI).

XI (1 g.) was heated under reflux at 380 - 400°C in a weak stream of $N_2$ for 7½ hrs. The $N_2$ effluent was passed through a liquid air trap

to collect the evolved chlorine. The residue in the reaction vessel was separated by chromatography on silica gel (carbon tetrachloride as eluate) and the second major component was sublimed (80°C, 0·03 mm.) to give pale yellow crystals which were recrystallised from petroleum ether (b.p. 60 - 80°) to give VIII (443 mg.), m.p. 122 - 123°C (53% yield) which was identified by infrared and mass spectrometry and elemental analysis.

Action of Sodio Diethyl Malonate on Heptachloroindolenine.

Excess sodium hydride was added to diethyl malonate (0·0905 g.) in dry tetrahydrofuran (5 ml.) and when effervescence had ceased the solution was filtered and added with stirring to VIII (179 mg.) in dry tetrahydrofuran (10 ml.). After being stirred for 30 mins., the solution was poured into water, extracted into ether (2 x 100 ml.) and the extracts dried ($MgSO_4$), evaporated and the residue (358 mg.) was separated by chromatography on silica gel (chloroform-carbon tetrachloride 50:50 $^{v}/_{v}$ as eluate). The major component (141 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) to give XIV, m.p. 190 - 190·5° (87% yield), identified by infrared spectroscopy, mass spectrometry and elemental analysis.

Action of Dimethyl Sulphate on the Reaction Mixture of Sodio Diethyl Malonate and Heptachloroindolenine.

Excess sodium hydride was added to diethyl malonate (0·1634 g.) in dry tetrahydrofuran. When the effervescence ceased the solution was filtered and added with stirring to a solution of VIII (190 mg.) in dry tetrahydrofuran (20 ml.). After 30 mins. dimethyl sulphate (0·5 mls.) was

added and the mixture was stirred for 30 mins., then poured into water. The mixture was made slightly acid with hydrochloric acid (4 N) and extracted with ether (2 x 100 mls.) and the combined extracts dried ($MgSO_4$), evaporated and the residue separated by chromatography on silica gel (chloroform as eluate) to give the major component, (156 mg.), recrystallised from petroleum ether (b.p. 60 - 80°) to give XV, m.p. 235-6° (77% yield) and was identified as 1-methyl-2,3,4,5,6,7-hexachloroindole by infrared spectroscopy and mass spectrometry.

The Action of Methyl Amine on Heptachloroindolenine.

Methyl amine in ethanol (~32 ml., 0·0732 M) was added dropwise with rapid stirring under nitrogen to VIII (417 mg.) in ethanol (80 ml.) until a red colour just began to form. The solution was stirred (1 hr.), evaporated to dryness and the residue (521 mg.) separated by chromatography on silica gel (chloroform as eluate) to give two components. The first, major, component (312 mg.) was recrystallised (from petroleum ether (b.p. 60 - 80°) to give a methylaminohexachloroindolenine (XIII) chars ~180°C (76% yield). (Found: C, 31·28; H, 1·09; Cl, 60·5; N, 8·15%; $M^+$, 350, $C_9H_4Cl_6N_2$ requires: C, 30·64; H, 1·14; Cl, 60·28; N, 7·94%; $M^+$, 350). $\lambda_{max}$ 258 and 261 nm [$\epsilon$ 32,000 and 25,600 (in cyclohexane)]. The infrared spectrum shows bands at 3250 and 3300 $cm.^{-1}$ due to N-H stretch. $^1H$ n.m.r. in chloroform ($\delta$ value): methyl proton 3·27; $J_{(Me,N-H)}$, 4 Hz, the N-H proton was not observed.

Deuterium Exchange in XIII.

A mixture of XIII (111 mg.), dry dioxan (20 ml.) and $D_2O$ (10 ml.) was heated under reflux for 1 hr. then evaporated to dryness.

$^1H$ n.m.r. in chloroform ($\delta$ value): methyl protons, 3·27 (singlet).

The Action of Dimethyl Amine on Heptachloroindolenine.

Dimethyl amine (30 ml., 0·0364 M in ethanol) was added dropwise with stirring under $N_2$ to VIII (179 mg.) in ethanol (20 ml.). The pale yellow solution was evaporated and the green yellow solid (227 mg.) separated by chromatography on silica gel (chloroform as eluate). The major component (191 mg.) was recrystallised from carbon tetrachloride to give a dimethylaminohexachloroindolenine XVIII (164 mg.) chars ~180°C (90% yield). (Found: C, 32·57; H, 2·03; Cl, 57·53; N, 7·42%; $M^+$, 364, $C_{10}H_6Cl_6N_2$ requires: C, 32·74; H, 1·65; Cl, 57·98; N, 7·64%; $M^+$, 364). $\lambda_{max}$ 259·5 nm [$\epsilon$, 31,300 (in cyclohexane)]. $^1H$ n.m.r. in chloroform ($\delta$ value): methyl protons, 3·43 singlet.

The Action of Trimethyl Amine on Heptachloroindolenine.

A mixture of VIII (197 mg.), dry tetrahydrofuran (30 ml.) and trimethyl amine (2·185 g.) was sealed in a glass tube and left for 3 days at room temperature in the dark. The contents were dissolved in water, extracted with ether (2 x 100 mls.), and the extracts dried ($MgSO_4$), and evaporated, and the residue separated by chromatography on silica gel (chloroform-carbon tetrachloride 50:50 $^v/_v$ as eluate). The major component (100 mg.) was recrystallised from carbon tetrachloride to give an orange solid XVIII, chars 180°C (52% yield), identical to the product formed between dimethyl amine and VIII identified by infrared and mass spectrometry.

Action of Hydrazine Hydrate on Heptachloroindolenine.

Hydrazine hydrate (1 m.mole) in water was added dropwise to VIII in dioxan (10 ml.) with stirring at 0°C. The yellow solution was evaporated and the residue (193 mg.) analysed by thin layer chromatography on silica gel (using chloroform and carbon tetrachloride as eluates) showed VIII and three other components close together.

Action of Potassium Hydroxide in Tertiary Butanol on Heptachloroindolenine.

A solution of potassium hydroxide (0·6 g.) in tertiary butanol (30 ml.) was added to VIII (179 mg.) and stirred at 50° for 3 hrs. Water (70 ml.) was added and the mixture made acidic with hydrochloric acid (4 N). The mixture was distilled (using Vigreux column) to 100°, then cooled, extracted with methylene dichloride (3 x 100 ml.) and the extracts dried ($MgSO_4$), evaporated and residue (73 mg.) analysed by thin layer chromatography on silica gel (methylene dichloride and chloroform as eluate) showed numerous components and amount of coloured material.

Action of Sodium Methoxide on Heptachloroindolenine.

Sodium methoxide in methanol (7·6 ml., 0·2 M) was added dropwise with stirring to VIII (543 mg.) in dry methanol (20 ml.). The red solution was heated under reflux for 1 hr., evaporated to dryness and the residue separated by chromatography on silica gel (chloroform as eluate) to give two components. The first component (170 mg.) recrystallised from carbon tetrachloride to give a monomethoxyhexachloroindolenine XIX, m.p. 183-4°C (32% yield). The second, major, component (350 mg.) was not identified. (XII Found: C, 30·63; H, 1·12; Cl, 59·33; N, 3·86%; $M^+$, 351; $C_9H_3Cl_6NO$ requires: C, 30·46; H, 1·14; Cl, 59·95; N, 3·95%; $M^+$, 351). $\lambda_{max}$ 246·5, 238 , and 253·5 nm. [$\epsilon$, 24,400, 21,600, and 22,400 (in cyclohexane)].

The Action of Potassium Isopropoxide on Heptachloroindolenine.

Potassium isopropoxide (0·75 ml., 0·91 M in isopropanol) was added dropwise with stirring to VIII (179 mg.) in dry isopropanol (30 ml.). After 15 mins. the mixture was poured in water (100 ml.), acidified (HCl, 4 N), extracted with ether, and the ether extracts dried ($MgSO_4$), and evaporated.

The residue (195 mg.) was separated by chromatography on silica gel (chloroform-carbon tetrachloride, 50% $^{v}/_{v}$ as eluate). The major component (102 mg.) was decolourised (charcoal in petroleum ether (b.p. 60 - 80°)) and recrystallised from petroleum ether (b.p. 60 - 80°) to give a mono-isopropoxyhexachloroindolenine (XII), m.p. 126·5 - 127·0°C (54% yield). (Found: C, 34·37; H, 2·16; Cl, 55·4; N, 3·67%; $M^+$, 379, $C_{11}H_7Cl_6NO$ requires: C, 34·60; H, 1·85; Cl, 55·70; N, 3·67%; $M^+$, 379). $\lambda_{max}$ 239, 245·5, 253·5 nm [$\epsilon$, 26,800, 31,400 and 27,200 (in cyclohexane)]. $^1H$ n.m.r. in deutero chloroform: ($\delta$ values) methyl proton, 1·57; multiplet ~4·4. Coupling constant of methyl proton ~6·5 Hz.

Attempted Fluorination of Heptachloroindolenine.

A mixture of VIII (0·3 g.) and caesium fluoride (1 g.) was sealed under vacuum in a Carius tube and heated to 150°C for 14 hrs. The contents gave no products other than silicon tetrafluoride (identified by infrared spectroscopy). Thin layer chromatography on silica gel (chloroform as eluate) showed no components other than on the base line.

Action of Thiophenol on Heptachloroindolenine.

A solution of thiophenol (0·0604 g.) in dry tetrahydrofuran (5 ml.) was added dropwise with stirring to VIII (179 mg.) in tetrahydrofuran (20 ml.). After being stirred at room temperature for 3 hrs. the solution was poured into water (200 ml.), made slightly acid with hydrochloric acid (4 N) and extracted with ether (2 x 100 mls.). The extracts were dried ($MgSO_4$), evaporated and separated by chromatography on silica gel (carbon tetrachloride-chloroform 75:25 $^{v}/_{v}$ as eluate). The first components (145 mg.) smelled strongly of thiophenol and the mass spectrum indicated the presence

of diphenyl disulphide and possibly thiophenol. The remaining, major, component (104 mg.) was recrystallised from petroleum ether (b.p. 60-80°) and was identical with authentic 2,3,4,5,6,7-hexachloroindole (XIV), m.p. 189·5 - 190·5°C (64% yield), identified by infrared, mass spectrometry and elemental analysis.

Action of Sodium Thiophenoxide on Heptachloroindolenine.

Excess sodium hydride was added to a solution of thiophenol (0·099 g.) in tetrahydrofuran (19 ml.) and when effervescence had ceased the solution was filtered. The filtrate was added dropwise with stirring to VIII (179 mg.) in dry tetrahydrofuran (10 ml.). After being stirred for 1 hr., the solution was poured into water, made slightly acid with hydrochloric acid (4 N), and extracted with ether. The extracts were dried ($MgSO_4$), evaporated and the residue (383 mg.) was separated by chromatography on silica gel (chloroform-carbon tetrachloride 50:50 $^{v}/_{v}$ as eluate). The first components (54 mg.) smelled of thiophenol and the mass spectrum indicated the presence of diphenyl disulphide and possibly thiophenol. The major component (109 mg.), recrystallised from petroleum ether (b.p. 60 - 80°), XIV, m.p. 189·5 - 190·5° (67% yield) identical to authentic 2,3,4,5,6,7-hexachloroindole, identified by infrared, mass spectrometry and elemental analysis.

Action of Dimethyl Sulphate on the Reaction Mixture of Sodium Thiophenoxide and Heptachloroindolenine.

Excess sodium hydride was added to a solution of thiophenol (0·1512 g.) in dry tetrahydrofuran (10 ml.). When effervescence had ceased the solution was filtered and added with stirring to a solution of VIII (183 mg.) in

dry tetrahydrofuran (20 ml.). After 1 hr. dimethylsulphate (0·5 ml.) was added, and the mixture was stirred for 30 mins., poured into water, acidified with hydrochloric acid (4 N) and extracted into ether (2 x 100 mls.). The combined ether extracts were dried ($MgSO_4$), evaporated and the residue separated by chromatography on silica gel (carbon tetrachloride as eluate) to give the major component (99 mg.). This was recrystallised from petroleum ether (b.p. 60 - 80°) carbon tetrachloride (50:50 v/v) to give XV (65 mg.), m.p. 235-6°C (57% yield) and was identified as 1-methyl-2,3,4,5,6,7-hexachloroindole by infrared and mass spectrometry.

Action of Trimethyl Phosphite on Heptachloroindolenine.

A solution of trimethyl phosphite (0·067 ml.) in dry ether (10 ml.) was added dropwise with stirring to a solution of VIII (200 mg.) in dry ether (30 ml.) at 0°C. The solution was allowed to warm to room temperature with stirring for 1 hr. then poured into water and made slightly acid with hydrochloric acid (4 N). The mixture was extracted with ether and the combined extracts dried ($MgSO_4$), evaporated and the residue (259 mg.) separated by chromatography on silica gel (carbon tetrachloride as eluate). The major component (176 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) to give 1-methyl-2,3,4,5,6,7-hexachloroindole (XV), m.p. 236·5 - 237·0° (93% yield). (Found: C, 32·06; H, 1·19; Cl, 62·46; N, 3·82%; $M^+$, 335, $C_9H_3Cl_6N$ requires: C, 32·00; H, 0·90; Cl, 62·96; N, 4·15%; $M^+$, 335). $\lambda_{max}$ 303 nm. [$\epsilon$, 9500 (in cyclohexane)]. $^1H$ n.m.r. in chloroform ($\delta$ value): methyl protons, 4·10, singlet.

Action of n-Butyl Lithium on Heptachloroindolenine.

VIII (312 mg.) was dissolved in dry tetrahydrofuran (40 ml.) under nitrogen and cooled to -70°C. A solution of n-butyl lithium (0·5 ml. of 1·98 M butyl lithium in hexane) was added dropwise with stirring and the mixture maintained at -70°C for 1 hr. then allowed to warm to -20°C. Water (20 ml.) was added and the mixture was extracted with ether (2 x 100 ml.). The ether extracts were dried ($MgSO_4$), evaporated and the residue (280 mg.) separated by chromatography on silica gel (chloroform as eluate). The major component (277 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) to give XIV, m.p. 187-188° (96% yield) identified as 2,3,4,5,6,7-hexachloroindole by infrared spectroscopy and mass spectrometry.

Action of Dimethyl Sulphate on the Lithio Complex Formed Between n-Butyl Lithium and Heptachloroindolenine.

VIII (214 mg.) was dissolved in dry tetrahydrofuran (30 ml.), the solution cooled to -60°C and n-butyl lithium (0·5 ml. of 1·98 n-butyl lithium in hexane) was added dropwise with stirring. After 1 hr. the mixture warmed to -20°C and dimethyl sulphate (0·5 ml.) added and after being stirred for 1 hr. the mixture was poured into water. The mixture was extracted with ether and the combined extracts dried ($MgSO_4$), evaporated and the residual black liquid was separated by chromatography on silica gel (carbon tetrachloride-chloroform 75:25 v/v as eluate) to give a yellow oil (154 mg.) which slowly crystallised from petroleum ether (b.p. 60-80°). The mass spectrum of the product (35 mg.) showed that it contained mainly hexachloromethylindole and some pentachloromethylindole and tetrachloromethylindole.

Action of Lithium Aluminium Hydride on Heptachloroindolenine.

A dispersion of lithium aluminium hydride (0·04 g.) in dry tetrahydrofuran (20 ml.) was added to a solution of VIII (179 mg.) in tetrahydrofuran (20 ml.) under $N_2$. When effervescence had ceased, wet tetrahydrofuran (50 ml.) was added, the solution was poured into water (100 ml.), made slightly acidic with hydrochloric acid (4 N) and the mixture extracted with ether (2 x 100 mls.) and the ether extracts dried ($MgSO_4$), evaporated and the residue (202 mg.) separated by chromatography on silica gel (chloroform-carbon tetrachloride, 50:50 $^{v}/v$ as eluate). The major component (145 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) carbon tetrachloride (75:25 $^{v}/v$) to give XIV, m.p. 187 - 190°, (90% yield), identified as 2,3,4,5,6,7-hexachloroindole by infrared spectroscopy, mass spectrometry, and elemental analysis.

Attempted Formation of Grignard Compound with Heptachloroindolenine.

A mixture of magnesium turnings (0·5 g.), VIII (358 mg.) and dry tetrahydrofuran (10 ml.) was placed in a baked flask and ethylene dibromide (0·5 ml.) was added. The mixture was warmed slightly, to initiate the reaction stirred at 35 - 40°C for 2 hrs., and finally heated under reflux for 15 mins. then cooled. Water (50 ml.) was added and the mixture extracted with ether and the ether extracts dried ($MgSO_4$), evaporated and the residue (333 mg.) separated by chromatography on silica gel (chloroform as eluate). The major component (267 mg.) was recrystallised from carbon tetrachloride to give 2,3,4,5,6,7-hexachloroindole (XIV), m.p. 189·5 - 190·5° (83% yield). (Found: C, 29·94; H, 0·6; Cl, 66·20; N, 4·59%; $M^+$, 321, $C_8HCl_6N$ requires: C, 29·67; H, 0·311; Cl, 65·69; N, 4·33%; $M^+$, 321). $\lambda_{max}$ 293 nm [$\epsilon$, 10,000 (in cyclohexane)]. The infrared spectrum shows a band at 3400 $cm.^{-1}$ due to N-H stretch.

Action of Dimethyl Sulphate on the Grignard Compound Formed from Heptachloroindolenine.

A mixture of magnesium turnings (0·5 g.), dry tetrahydrofuran (20 ml.) and VIII (176 mg.) was placed in a baked flask and ethylene dibromide (0·5 ml.) added to initiate the reaction. After 1 hr. dry tetrahydrofuran (40 ml.) was added and the solution decanted to another baked flask and dimethyl sulphate (0·5 ml.) added and the mixture was stirred for 1·5 hrs. The mixture was poured into water, made slightly acid with hydrochloric acid (4 N) and extracted with ether (2 x 100 mls.). The combined ether extracts were dried ($MgSO_4$), evaporated and the residue (184 mg.) separated by chromatography on silica gel (carbon tetrachloride as eluate). The major product (78 mg.), m.p. 235 - 235·5°C (49% yield), was identified as 1-methyl-2,3,4,5,6,7-hexachloroindole by infrared spectroscopy and mass spectrometry.

Action of Antimony Pentachloride on Heptachloroindolenine.

A mixture of VIII (190 mg.) and antimony pentachloride (0·5 ml.) was stirred for 30 mins. at 0°C then cooled to -60°C. Dry methanol (40 ml., -60°C) was added slowly and the mixture slowly warmed to room temperature with stirring. The mixture was poured into water (100 ml.) and extracted with ether. The ether extracts were dried ($MgSO_4$), and evaporated and the residue separated by chromatography on silica gel (chloroform as eluate) into three components. The first component (91 mg.) was recrystallised to give IX pentachloroaniline (71 mg.) (yield = 51%), identified by infrared spectroscopy and mass spectrometry. The second component was not identified and the third component was an oil.

Catalytic Hydrogenation of Heptachloroindolenine (VIII).

A mixture of VIII (270·3 mg.), magnesium oxide (460 mg.) and dry tetrahydrofuran (40 ml.) was hydrogenated at 20°C, 1 atm. pressure (uptake 30 ml.). The solution was filtered, evaporated and the residue (215·6 mg.) was separated by chromatography on silica gel (carbon tetrachloride as eluate). The major component (79 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) to give 4,5,6,7-tetrachloroindole, XVI, m.p. 177·0 - 177·5° (21% yield) (Found: C, 37·96; H, 1·37; Cl, 55·89; N, 5·79%; $M^+$, 253, $C_8H_3Cl_4N$ requires: C, 37·69; H, 1·19; Cl, 55·63; N, 5·49%; $M^+$, 253). $\lambda_{max}$ 283, 294·5, 306 nm [$\epsilon$, 8100, 6300, 2900 (in cyclohexane)]. The infrared spectrum showed a single band at 3400 $cm.^{-1}$ due to N-H stretch. $^1H$ n.m.r. in acetone ($\delta$ values): 2, 7·33; 3, 6·61. Coupling data: $J_{1,2}$, ~2·6; $J_{1,3}$, ~2·2; $J_{2,3}$, ~3·2 Hz. $^1H$ n.m.r. in carbon tetrachloride ($\delta$ values): 2, 7·20; 3, 6·63. 1 proton not observed.

Catalytic Hydrogenation of 2,3,4,5,6,7-Hexachloroindole (XIV).

A mixture of XIV (90 mg.), magnesium oxide (0·3 g.), 10% palladium charcoal (40 mg.), and dry tetrahydrofuran (40 ml.) was hydrogenated at 20°C and 1 atm. pressure (uptake = 13 ml.). The solution was filtered, evaporated and the residue separated by chromatography on silica gel (chloroform-carbon tetrachloride 50:50 v/v as eluate). The major product (52·4 mg.) was recrystallised from petroleum ether (b.p. 60 - 80°) to give XVI (27·1 mg.), m.p. 177·0 - 177·5° (24% yield), identified by infrared spectroscopy and mass spectrometry.

Catalytic Hydrogenation of 1-Methyl-2,3,4,5,6,7-Hexachloroindole (XV).

A mixture of XV (119 mg.), 10% palladium charcoal (0·2 g.), magnesium

oxide (0·5 g.), dry tetrahydrofuran (50 ml.) was hydrogenated at 20°C, 1 atm. pressure (uptake, 17 mls.). The solution was filtered, evaporated and the residue (129 mg.) was separated by chromatography on silica gel (chloroform as eluate). The major component was decolourised with charcoal in petroleum ether (b.p. 60 - 80°) and recrystallised from petroleum ether (b.p. 60 - 80°) to give 1-methyl-4,5,6,7-tetrachloroindole (XVII), (75 mg.), m.p. 211·5 - 212·5°C (79% yield). (Found: C, 40·48; H, 1·61; N, 5·12%; $M^+$, 267, $C_9H_5NCl_4$ requires: C, 40·19; H, 1·87; N, 5·21%; $M^+$, 267). $\lambda_{max}$ 292, 312 nm [$\epsilon$, 6500, 4700 (in cyclohexane)]. $^1H$ n.m.r. in deutero chloroform ($CDCl_3$) ($\delta$ values): methyl protons, 4·05; 2, 6·95; 3, 6·45. Coupling data: $J_{2,3}$, ~3·3 Hz.

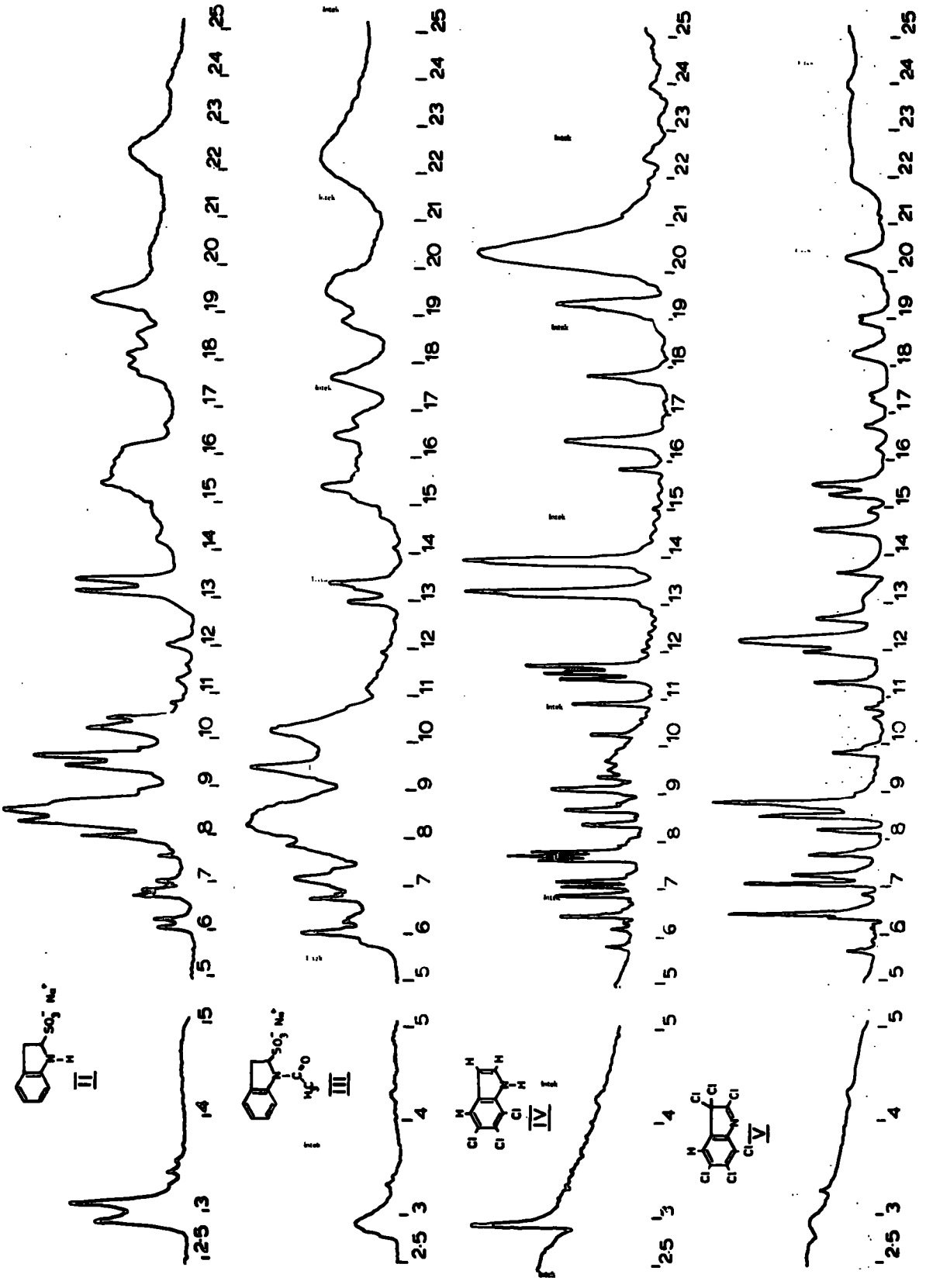
## Appendix 1

### Infrared Spectra.

All samples were solids and were recorded as KBr discs. The scale given is the wavelength in microns. All spectra were recorded on a Grubb-Parsons Spectromaster except for (IX), (X) and (XVII) which were recorded on a Perkin-Elmer 457 Grating Infrared Spectrometer.

### Index.

| Number | Name |
|---|---|
| II | Sodium Indoline-2-sulphonate |
| III | Sodium N-Acetyl Indoline-2-sulphonate |
| IV | 5,6,7-Trichloroindole |
| V | 2,3,3,5,6,7-Hexachloroindolenine |
| VI | 3,5,6,7-Tetrachloroindole |
| VII | 5,7-Dichloroindole |
| VIII | 2,3,3,4,5,6,7-Heptachloroindolenine |
| XI | N-Pentachlorophenyl Trichloroacetimidoyl Chloride |
| XII | 2-Isopropoxy-3,3,4,5,6,7-hexachloroindolenine |
| XIII | 2-Methylamino-3,3,4,5,6,7-hexachloroindolenine |
| XIV | 2,3,4,5,6,7-Hexachloroindole |
| XV | 1-Methyl-2,3,4,5,6,7-hexachloroindole |
| XVI | 4,5,6,7-Tetrachloroindole |
| XVIII | 2-Dimethylamino-3,3,4,5,6,7-hexachloroindolenine |
| XIX | 2-Methoxy-3,3,4,5,6,7-hexachloroindolenine |
| IX | Pentachloroaniline |
| X | 2',2',2',2,3,4,5,6-Octachloroacetanilide |
| XVII | 1-Methyl-4,5,6,7-tetrachloroindole |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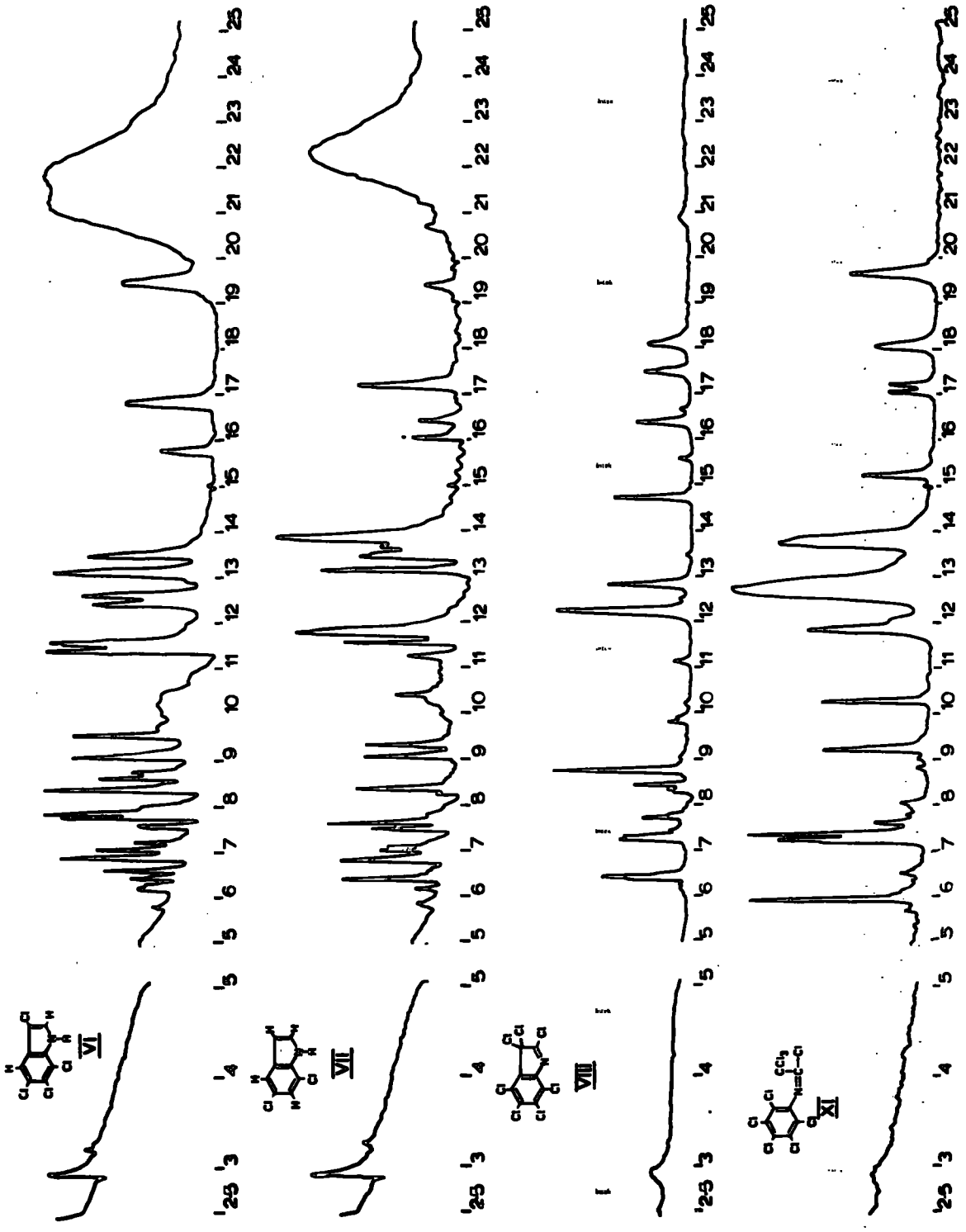
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VII
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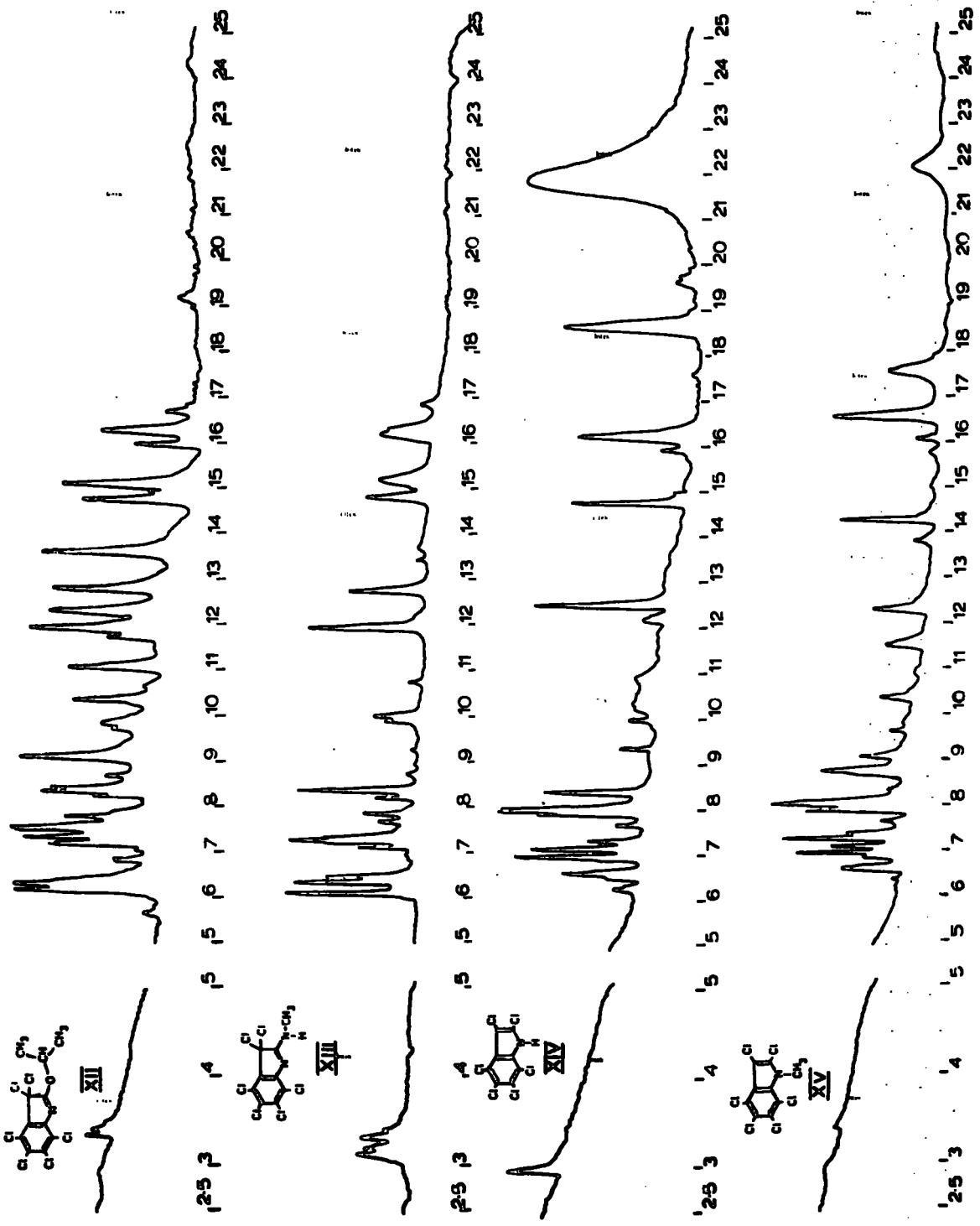
XI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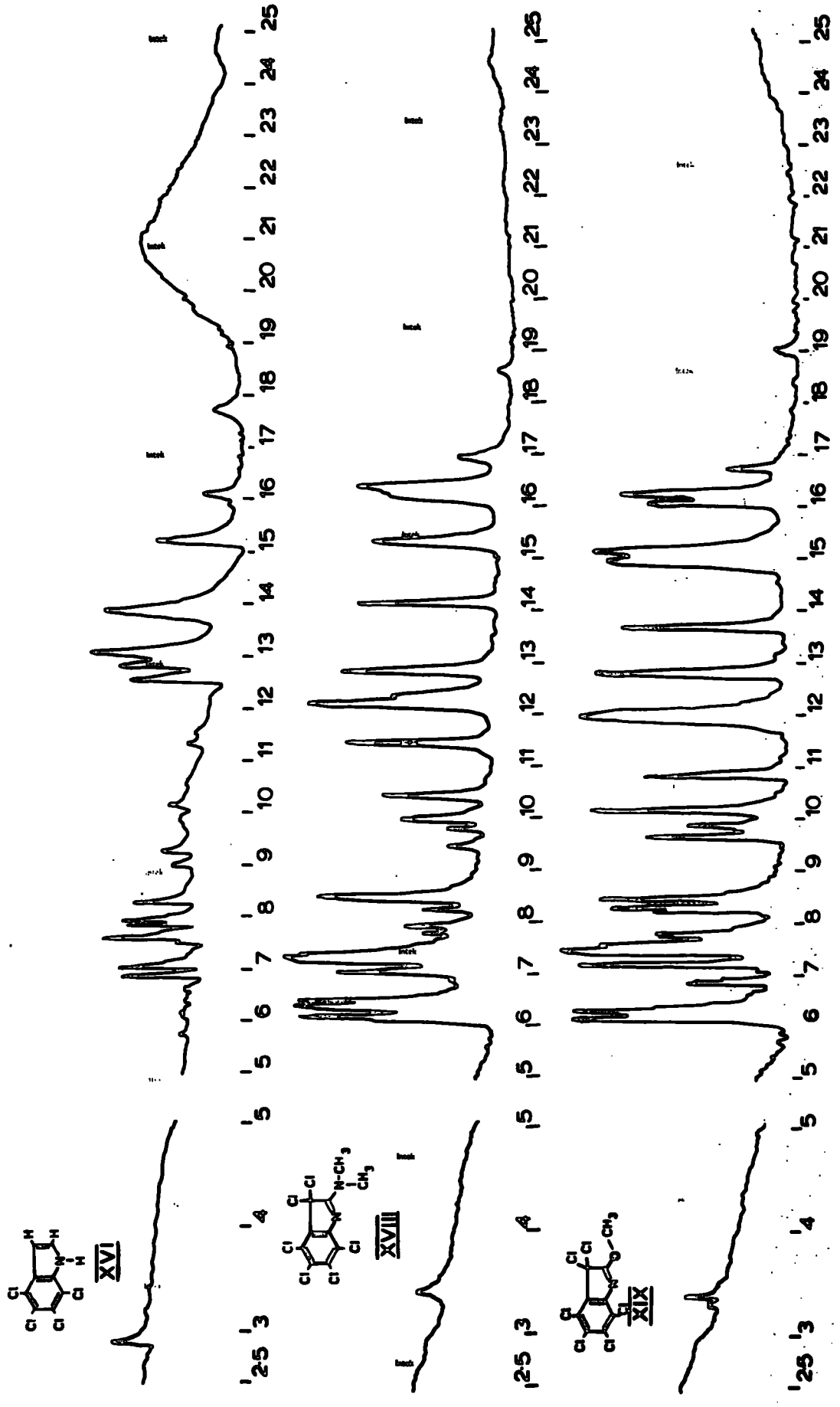
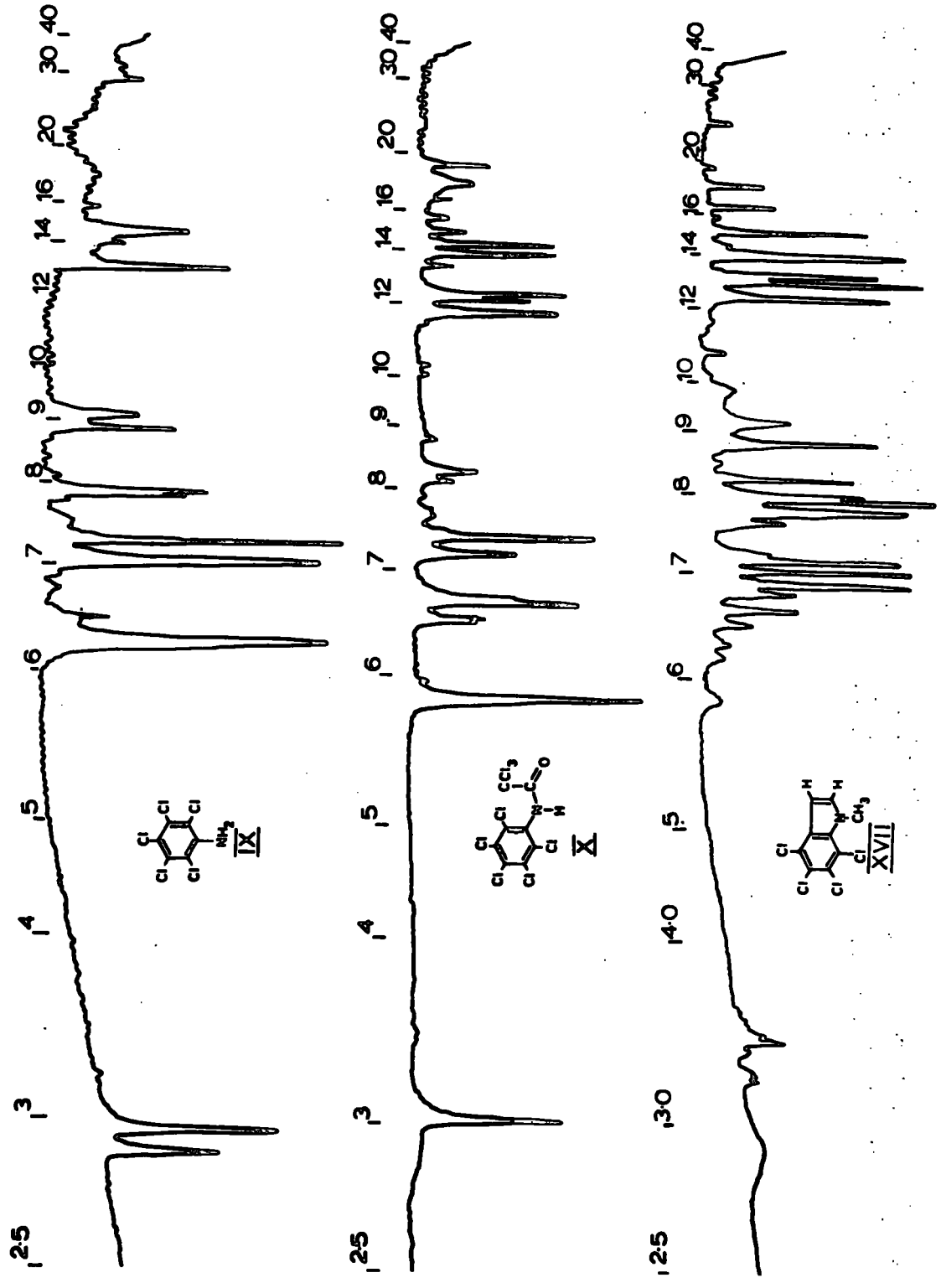
XIII
XIV
XV


XVI
XVIII
XIX


IX
X
XVII

Ultraviolet Spectra.

All samples were recorded in cyclohexane solution by a Unicam SP800 Ultraviolet Spectrometer.

The horizontal scale is wavelength in nanometers and the vertical scale is numbered in thousands of molar extinction coefficient units, (i.e. $cm.^{2}$ $\mu mole^{-1}$).

Index.

| Number | Name |
|---|---|
| IV | 5,6,7-Trichloroindole |
| V | 2,3,3,5,6,7-Hexachloroindolenine |
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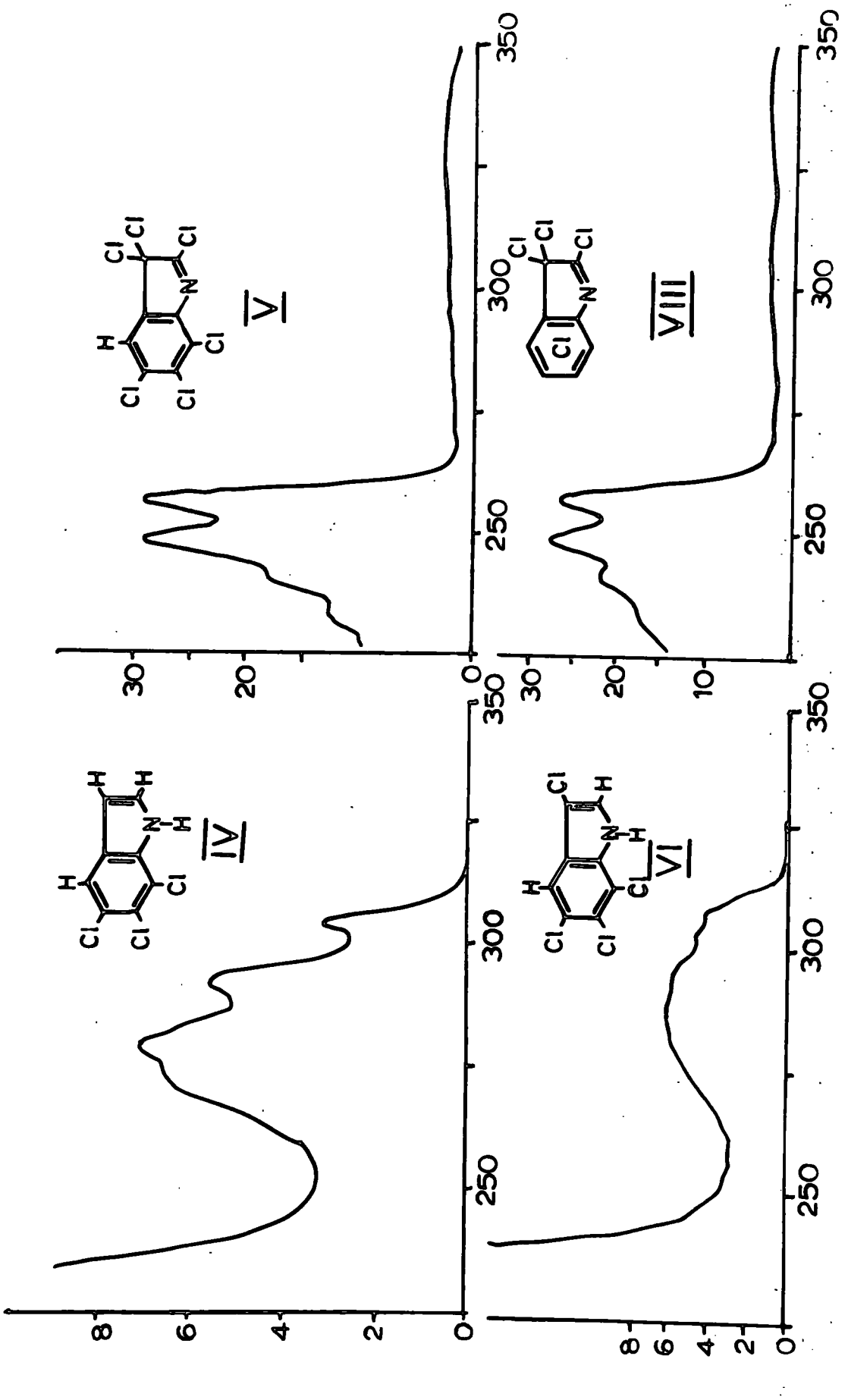
| XVIII | 2-Dimethylamino-3,3,4,5,6,7-hexachloroindolenine |
| XV | 1-Methyl-2,3,4,5,6,7-hexachloroindole |
| XVII | 1-Methyl-4,5,6,7-tetrachloroindole |
| XVI | 4,5,6,7-Tetrachloroindole |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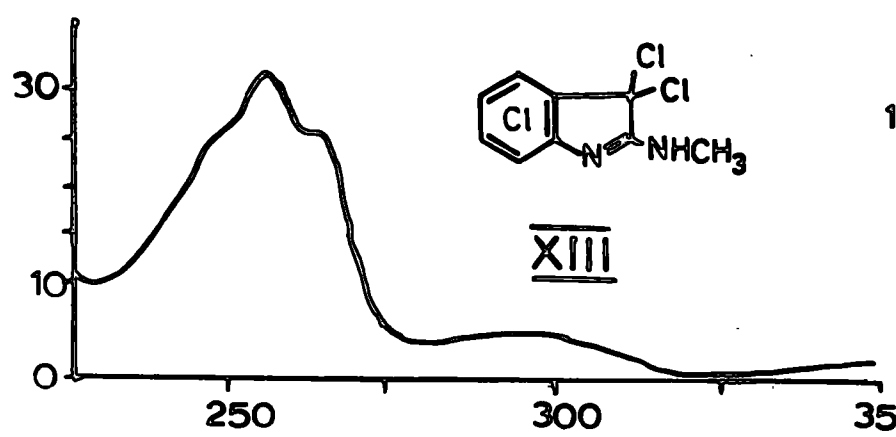


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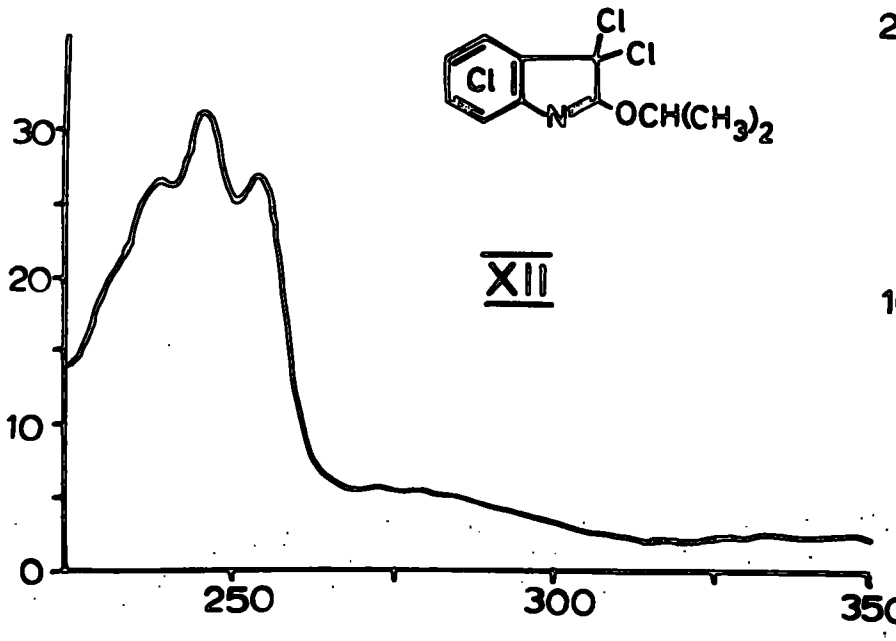


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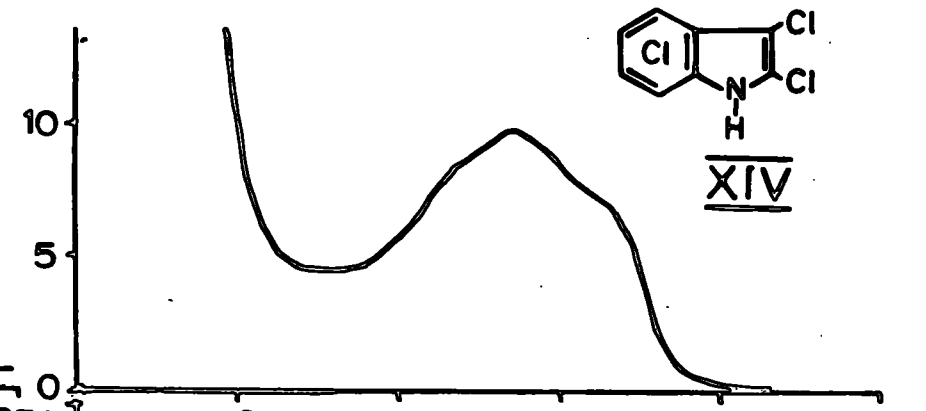


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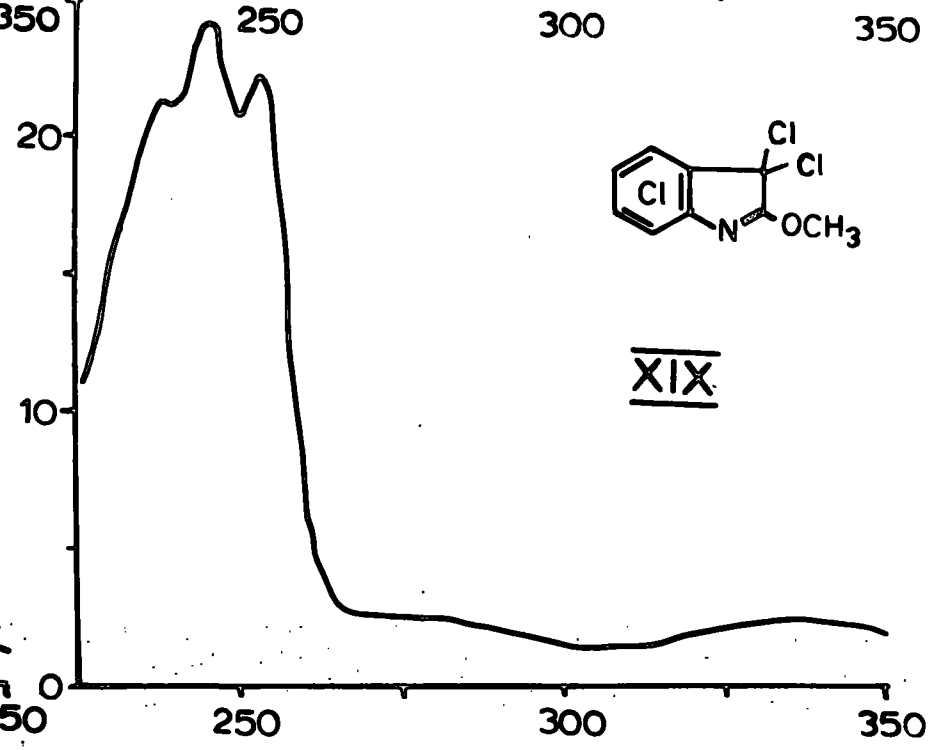


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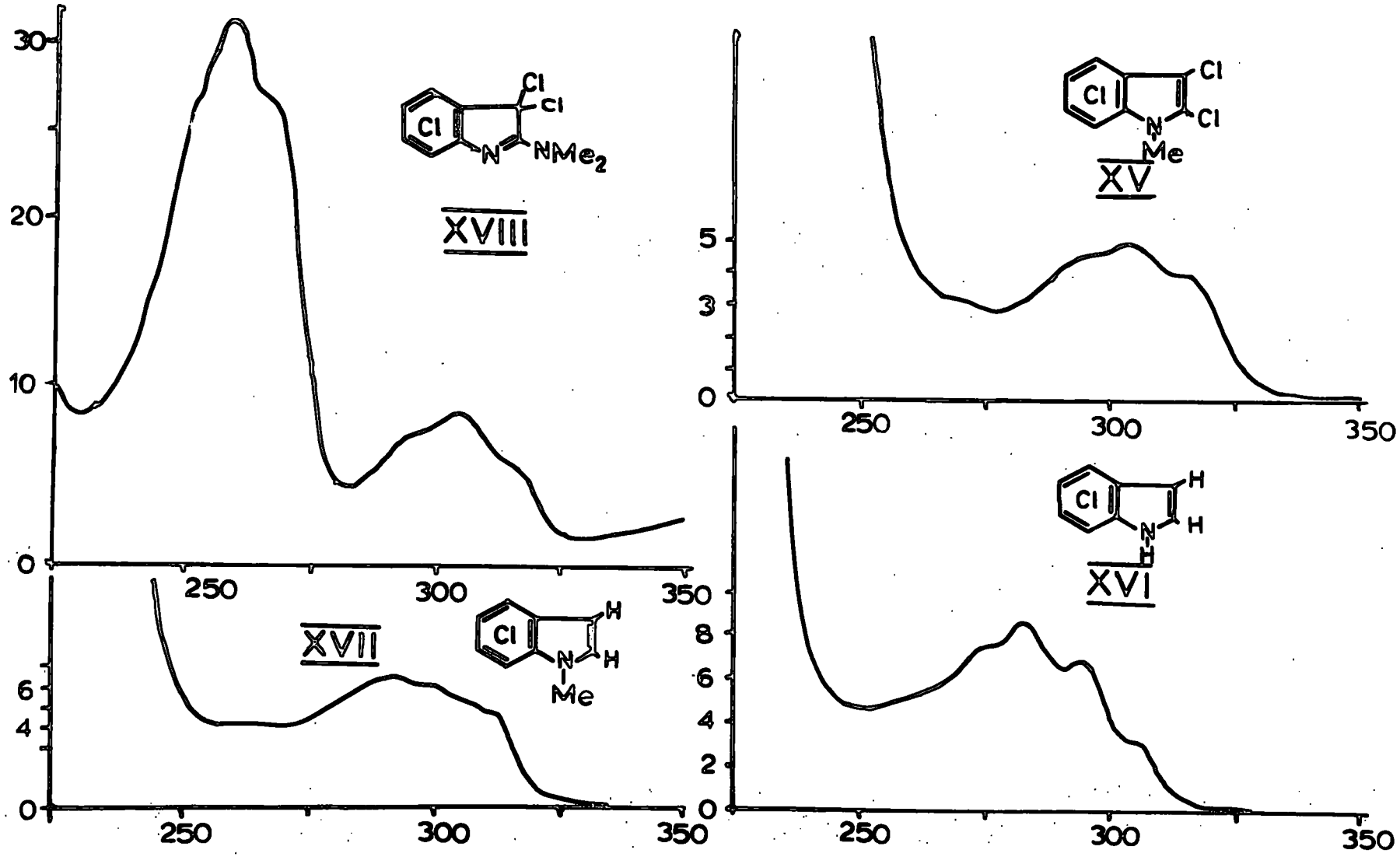
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XVIII
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XVI
8
6
4
2
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XVII
6
4
0
Cl
H
N
H
Me

## Appendix 2

## $^1$H N.M.R. Spectra

$^1$H N.M.R. Spectra were recorded on a Varian HA60D in a) acetone, b) carbon tetrachloride, c) chloroform and d) deuteroform.

The chemical shifts are given in p.p.m. on the δ scale and coupling constants are measured in Hertz.

The compounds listed in Table 5 are:-

| | |
|---|---|
| I | Indole.[161] |
| VII | 5,7-Dichloroindole |
| IV | 5,6,7-Trichloroindole |
| VI | 3,5,6,7-Tetrachloroindole |
| XVI | 4,5,6,7-Tetrachloroindole |
| XVII | 1-Methyl-4,5,6,7-tetrachloroindole |
| XV | 1-Methyl-2,3,4,5,6,7-hexachloroindole |

VII, IV, VI and XVI also appear in Table 6 which deals in detail with the solvent dependence of chemical shift.

## TABLE 5

| Substance | $I^{161}$ | VII | | IV | | VI | | XVI | | XVII | XV |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Solvent | a | a | b | a | b | a | b | a | b | d | c |
| $\delta_1$ | 10·12 | ~10·3 | ~7·9 | ~10·5 | ~8·0 | ~10·9 | ~8·1 | * | * | - | - |
| $\delta_2$ | $7·26_5$ | 7·45 | 6·95 | 7·43 | 7·08 | 7·50 | 7·10 | 7·33 | 7·20 | 6·95 | - |
| $\delta_3$ | $6·44_6$ | 6·56 | 6·32 | 6·50 | 6·36 | - | - | 6·61 | 6·63 | 6·45 | - |
| $\delta_4$ | $7·55_0$ | 7·57 | 7·35 | 7·65 | 7·48 | 7·60 | 7·53 | - | - | - | - |
| $\delta_5$ | $6·99_5$ | - | - | - | - | - | - | - | - | - | - |
| $\delta_6$ | $7·07_9$ | 7·22 | 7·05 | - | - | - | - | - | - | - | - |
| $\delta_7$ | $7·39_9$ | - | - | - | - | - | - | - | - | - | - |
| $\delta_{Me}$ | - | - | - | - | - | - | - | - | - | 4·05 | 4·10 |
| J(1,2) | 2·5 | ~2·5 | ~2·4 | 2·6 | 2·4 | 2·7 | 2·5 | ~2·6 | | - | - |
| J(1,3) | 2·0 | 2·0 | 2·1 | 2·0 | 2·1 | - | - | ~2·2 | | - | - |
| J(1,4) | 0·8 | 0·7 | 0·7 | 0·7 | 0·7 | 0·7 | 0·7 | - | | - | - |
| J(2,3) | 3·1 | 3·2 | 3·1 | 3·1 | 3·1 | - | - | ~3·2 | | ~3·3 | - |
| J(2,6) | - | 0·4 | 0·4 | - | - | - | - | - | | - | - |
| J(3,7) | $0·7_0$ | - | - | - | - | - | - | - | | - | - |
| J(4,5) | $7·8_4$ | - | - | - | - | - | - | - | | - | - |
| J(4,6) | $1·2_3$ | 1·8 | 1·7 | - | - | - | - | - | | - | - |
| J(4,7) | $0·9_4$ | - | - | - | - | - | - | - | | - | - |
| J(5,6) | $7·0_7$ | - | - | - | - | - | - | - | | - | - |
| J(5,7) | $1·2_9$ | - | - | - | - | - | - | - | | - | - |
| J(6,7) | $8·0_7$ | - | - | - | - | - | - | - | | - | - |

* Solution too dilute to observe broad band.

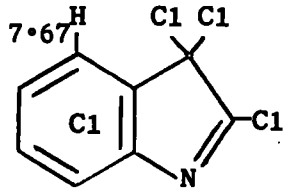
TABLE 6

Solvent Shifts of the Protons in Various Chloroindoles in Carbon Tetrachloride and Acetone (60 MHz)

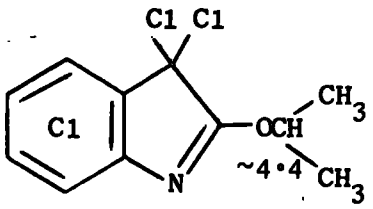
| Compound | Proton | Chemical Shift (Hz) ($CCl_4$) | (Acetone) | Δ(Hz) ($CCl_4$ to acetone) | Δδ |
|---|---|---|---|---|---|
| VII | 1 | ~475 | ~620 | ~145 | ~2·4 |
| | 2 | 417 | 447 | 30 | 0·50 |
| | 3 | 379 | 393 | 14 | 0·23 |
| | 4 | 441 | 454 | 13 | 0·22 |
| | 6 | 423 | 433 | 10 | 0·17 |
| IV | 1 | ~480 | ~630 | ~150 | ~2·5 |
| | 2 | 425 | 446 | 21 | 0·35 |
| | 3 | 382 | 390 | 8 | 0·13 |
| | 4 | 449 | 459 | 10 | 0·17 |
| VI | 1 | ~490 | ~650 | ~160 | ~2·8 |
| | 2 | 426 | 450 | 24 | 0·40 |
| | 4 | 452 | 456 | 4 | 0·07 |
| XVI | 1* | - | - | - | - |
| | 2 | 432 | 452 | 20 | 0·34 |
| | 3 | 397 | 397 | 0 | 0 |

* Solution too dilute to observe broad band.

V 2,3,3,5,6,7-Hexachloroindolenine ($CCl_4$)

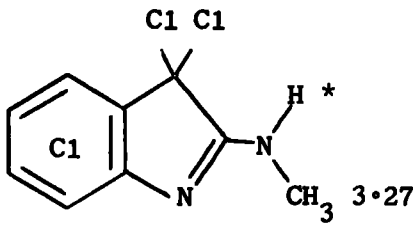


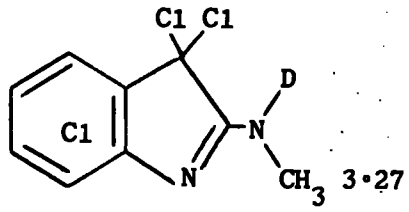

XII 2-Isopropoxy-3,3,4,5,6,7-hexachloroindolenine ($CDCl_3$)




$J_{CH_3-CH}$ = ~6·5 Hz

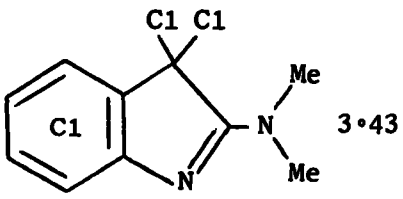
XIII 2-Methylamino-3,3,4,5,6,7-hexachloroindolenine ($CHCl_3$)




$J_{(CH_3-NH)}$ = ~4 Hz

XVIII 2-Dimethylamino-3,3,4,5,6,7-hexachloroindolenine ($CHCl_3$)




* Solution too dilute to observe broad band.

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