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STUDIES IN
CANCER CHEMOTHERAPY

A Thesis Presented to the University of Auckland
for the degree of
Doctor of Philosophy
by
Ian Christopher Dean

CONTENTS.

ABSTRACT

INTRODUCTION 1

DISCUSSION

Amidoximes 45
Imidoyl Chlorides 48
Hydroxyamidines 59
Tests with Metals 74
2-Aminoquinoline-1-oxides 79
Biological Activity 109

EXPERIMENTAL DETAILS 110

Amides 113
Imidoyl Chlorides 124
Hydroxyamidines 136
Metal Chelates 171
2-Aminoquinoline-1-oxides 173
Tests with Metals 188

APPENDICES

1. Classification of Chelating Ligands 190
2. Infrared Spectra of Hydroxyamidines 191
3. Ultraviolet Spectra of Hydroxyamidines 194
APPENDICES contd.

4. Tests with Metals 196
5. Anticancer Testing Results 198

REFERENCES 201

ACKNOWLEDGEMENTS 217

DIAGRAMS 218
ABSTRACT

The role of metals in biological processes has been discussed with particular emphasis on the importance of chelation. Furst\textsuperscript{29} has suggested that many anticancer drugs may owe their activity to their chelating properties. A number of new amidoximes and hydroxyamidines have been made from the appropriate imidoyl chloride and a hydroxylamine. The spectral and chelating properties of these compounds are discussed. All the compounds have been submitted to the anticancer screening programme of the National Cancer Institute. The results available so far are presented and indicate that the compounds are toxic but inactive against experimental tumours.

Sodium sulphide reduces α-phenyl-o-nitro-cinnamonomitrile (106) to 2-amino-3-phenylquinoline-1-oxide (107) in good yield. Extension of the reduction to other o-nitrocinnammonitriles gives very poor results. The spectral properties, configurations and conformations of the o-nitrocinnammonitriles are discussed. The 2-aminoquinoline-1-oxide group is shown to form solid metal complexes. That from 2-amino-3-phenylquinoline-1-oxide (107) with nickel has been prepared. Antitumour screening results are presented for several 2-aminoquinoline derivatives. None of these compounds appears to be active.
INTRODUCTION

Cancer and Research

Cancer has been defined as "a disease of multicellular organisms which is characterised by the seemingly uncontrolled multiplication and spread within the organism of apparently abnormal forms of the organism's own cells." This definition by its use of the words "seemingly" and "apparently" gives some idea of the large gaps in our knowledge of the considerable number of diseases of man collected under the title of cancer. In some way cancer cells depart from the normally well controlled division of cells, but the primary metabolic lesion is as yet unknown and much research is therefore directed towards understanding the basic cell processes. In general cancerous tissue is characterised by the similarity of cells, often to the extent that tumours originating from different tissues are morphologically indistinguishable. The cells generally have an increased nucleic acid content and a great number at any one time are found in some phase of division. The division is often very abnormal. Attempts to define specific exploitable differences between ordinary and cancer cells have in no cases given unequivocal answers.

The methods available for cancer therapy are thus, of necessity, directed at the effect rather than the cause, with the exception of studies directed towards the identification of carcinogens and the avoidance of them. Radiation treatment is severely
limited in its application because it can only be administered at low dose rates over small areas of the body. Surgery can only be used on compact, accessible tumours and only a limited amount of tissue can be removed. Furthermore, manipulation of the tumour mass during surgery may shed cancerous cells into the bloodstream which can cause cancer in other parts of the body.\textsuperscript{5} The patient's own host response seems incapable of dealing with such cells and research is being directed to ways of strengthening the host response, particularly since spontaneous tumour regression is known in some cases.\textsuperscript{6} Combined surgery and chemotherapy seems to be the most powerful method available today and although by no means a cure-all some success is apparent. In leukaemia, which is an overproduction of immature white blood cells, chemotherapy is probably the only method of treatment.

**Cancer Chemotherapy**

The generally accepted criterion for a cancer cure is an absence of any of the symptoms for a minimum of five years.\textsuperscript{7a} The treatment of cancer with drugs is a logical extension of the great success of chemotherapy against such diseases as typhoid, cholera and tuberculosis. Cancer, however, is not due to an invading organism and the exploitable differences between ordinary and cancer cells are largely unknown. This is reflected in the relatively poor returns in terms of useful drugs from the vast expenditure of time and money on the cancer problem.
Whatever mode of action a drug has, specificity for cancer cells is obviously desirable. Unfortunately, most drugs in clinical use are generally cytotoxic rather than specific. Ordinary cells with a slow rate of mitosis may absorb a drug more slowly than a rapidly dividing cancer mass and thus some specificity may arise. However, in areas of normal rapidly dividing cells no specificity may be shown and thus side effects such as depression of bone marrow will occur. Where the drug is a chemically very reactive molecule, much of the drug dose may react in ways unrelated to tumour inhibition and thus have toxic side effects. To overcome such effects, arterial infusion may be used, where the drug is put into the blood stream as near as possible to the site of the tumour's own blood source. The tumour region may be isolated as much as possible and the drug dose repeatedly cycled through it. In this way, higher doses can be given without increased systemic toxicity.

Another approach is to administer a drug which in itself is inactive but which is somehow activated in or near the tumour. The drug becomes available only as fast as it is used up in the tumour. The compound N-phenylpropylcarbamate (1a) is thought to induce the formation of an enzyme in some rat tumours which removes the urethane group. The inactive nitrogen mustard derivative (1b) is then administered and cleavage of the urethane groups activates the drug in situ. Incubation of the inactive drug cytoxan i.e. 2-[bis(2-chloroethyl)amino] tetrahydro-3H-1,3,2-oxazaphosphorine-2-oxide (2)
with liver homogenate causes the drug to become very active. It is thought that in vivo the liver may hydrolyse cytoxan to 2,2'-dichlorodiethylamine\textsuperscript{7c} (3a).

The drug must be able to reach its site of action and thus its solubility in both aqueous and lipid phases is a determining factor. Drugs have been designed where a cytotoxic group is attached to a carrier molecule, usually an analogue of a cell constituent such as an amino acid or peptide.\textsuperscript{10} Such a drug is the highly active melphalan (4) or 3-(p-[bis(2-chloroethyl)amino]phenyl)-L-alanine. Other carrier molecules such as mannitol, steroids, purines, and pyrimidines have been tried with some success.\textsuperscript{7d} Even with such a carrier group, however, access may be difficult. Some experimental tumours are very poorly vascularised\textsuperscript{11} and therefore inaccessible to drug therapy, yet they still contain live cancer cells which can become detached and spread.\textsuperscript{12}

Prolonged treatment with one particular drug frequently gives rise to the phenomenon of drug resistance. The tumour becomes resistant to the drug and another treatment must be used. This may arise from the killing or restraint of sensitive cells whilst a resistant cell is allowed to develop or possibly the drug acts as a mutagen, changing previously sensitive cells into resistant ones.\textsuperscript{13a} Combined drug therapy can overcome this problem to some extent. The so-called VAMP therapy, where vincristine (5a), amethopterin (6a),
6-mercaptopurine (7a) and prednisone (8a) are administered together, overcomes resistance and toxicity to some extent. A lower dose of each drug can be given without lowering the overall cytotoxic activity. Amethopterin (6a) toxicity may be reduced by prior administration of folic acid (7b), the metabolite for which it is an antagonist or by administration of an antidote which presumably alleviates side effects without lowering its cytotoxic activity. Sensitivity to drugs varies throughout the mitotic cycle and thus dosage with drugs when the dividing cancer cells are in their most sensitive phase could result in a higher lethal rate for the normal drug dose. Cell kinetics, even of normal cells are poorly known and those for cancerous cells are being worked on with the above aim in mind.

**Screening of Drugs**

Before any drug can be tried on human beings, it must be tested on some other system and, in the case of cancer, this is usually some sort of mouse or rat tumour. The design of such a screening programme is obviously very important since it should ideally reject all inactive compounds and retain all active ones. This criterion is not met since the existing screening protocols probably select antigrowth rather than specifically anticancer activity. The screening procedures used, apart from those for antilymphoma and antileukemic activity, give little indication of the
sort of human cancer the drug may be useful against and once clinical trials are begun a whole new screening protocol is needed.\textsuperscript{14} It may be that in this way, useful drugs have been passed over because activity against animal cancers and human cancers is not parallel. Knock\textsuperscript{5} has bitterly attacked the present views on clinical testing and called for individual cell culture - drug testing to fit a particular drug regimen to an individual patient. It is unfortunately true that the number of substances able to inhibit experimental tumours is very large and yet the number of clinically useful drugs is very small.

Design of Anticancer Drugs

The design of anticancer drugs is a problem of selective toxicity and at present there is no known metabolic basis for the design of drugs with specific anticancer activity as opposed to general cytotoxicity. It must be true, however, that such specificity as does exist in the available drugs must be due to some difference between cancerous and normal cells. Most of these drugs have been discovered empirically.\textsuperscript{15a}

The screening of natural products for anticancer activity has led to such drugs as actinomycin D (9) L-asparaginase and vincristine (5a).\textsuperscript{15b} The idea that if the utilisation or synthesis of an essential cell metabolite could be prevented\textsuperscript{16} cells could be killed, led to the development of the so called antimetabolites. Folic
acid (7b) is involved in the transfer of one-carbon units and is responsible for the introduction of the C-2 and C-8 carbon atoms of purines and the C-2 atom of histidine (10). Slight structural variants of folic acid such as amethopterin (6a) and aminopterin (6c) interfere with this process, probably by blocking the access of the correct substrate to a specific enzyme site. Both these compounds are powerful antitumour agents.

Knock believes that the -SH or sulphhydryl groups on the protein bound to DNA are very important in the mitotic process. The sulphydryl group from the amino acid cysteine (11a) and its reduced form cystine is a chemically highly reactive one and could readily react with many drug molecules. An active component of the natural cell-growth regulator retine is thought to be pyruvaldehyde (12a) which can react with sulphydryl groups as can actinomycin D (9), mitomycin C (13) and the alkylating agents. Alkylating agents which react via an $S_N$ mechanism should react preferentially with sulphydryl groups since these are the most powerful nucleophiles available. Almost all the excretion products of the drug busulphan (14) can be accounted for by attack at sulphydryl groups.

Swan has proposed a site on the DNA strand as a receptor site for drug molecules. The DNA molecule consists of two polydeoxyribose phosphate chains to which are attached the purine bases adenine (15) and guanine (16) and the pyrimidine bases thymine (17) and cytosine (18). These bases form specific base-pair
hydrogen bonds and the two chains are thus held together in the double helix geometry (Fig. 1).

Fig. 1

Further stabilisation is thought to arise from hydration of the ionic phosphate groups on the outside of the deoxyribose phosphate chains,¹⁹ and charge transfer complexes formed between the bases which are
effectively stacked flat.\textsuperscript{19,20}

The antimalarial drug chloroquine (19) is thought to act by intercalation of the flat molecule between the stacked base layers causing expansion of the whole molecule.\textsuperscript{21} Antibiotics such as actinomycin D (9) interact with DNA possibly through the chromophoric group of the drug with the bases along the inside of the DNA spiral.\textsuperscript{22} The strength of binding is not however, directly proportional to the cytotoxic effect.\textsuperscript{13a}

Swan\textsuperscript{18} has shown that anticancer drugs of the ellipticine (20) type are of the right shape and size to sit on the flat ends of the DNA ribbon. Compounds designed to fit these requirements have been shown to be active.\textsuperscript{23,24} Swan also suggests that many steroid molecules have a suitable shape and size to cap the DNA molecule.

Normal cells respond properly to the homeostatic mechanisms of the body. Obviously cancer cells do not and it has been suggested that the solution to the cancer problems lies not in the use of cytotoxic drugs but in the development of homeostatic regulators.\textsuperscript{25} In plants, the cytokinins\textsuperscript{26} appear to fill this role and it is possible that the discovery of the chalones\textsuperscript{27} in animal systems may lead in this direction. Berglas\textsuperscript{28} believes that cancer is a "runaway healing" attempt and causing cancer cells to divide even more rapidly than they normally do might mean that the tumour would outstrip its food supply and hence die out.
The diversity of the various clinically used anticancer drugs has led Furst to look for a common denominator. He suggests that the metal binding properties of many such drugs might be connected with their anticancer activity. He further suggests that the whole field of cancer might be involved with metal ion participation.

This thesis is concerned with the synthesis of potentially anticancer drugs based on this idea and since much information has come to light since 1963, the next part of this introduction will be concerned with metal binding and the role of metal ions in biochemical processes.

Chelation

In the latter half of the nineteenth century many unusual compounds which consisted either of two metal salts or a metal salt and some other neutral molecule were made. Such compounds seemed to violate the ideas of combining power or valence then in vogue. Werner in his coordination theory rationalised the properties of these compounds, establishing the maximum number of groups (ligands) which could be more or less firmly bound to a particular metal atom and the geometries of such arrangements.

Much is now known about the bonding, coordination numbers, geometry, stereochemistry, optical activity, and reactivity of such compounds, particularly those involving the metals of the first
transition series. Coordination numbers from two to twelve are found with four and six being the most common. Thus plane square, tetrahedral or octahedral arrangements of ligands are usual although large distortions from these ideals are found.

The ligands may be any ion, atom or molecule capable of acting as an electron donor partner in the formation of a coordinate bond. Two or more donor sites may exist on the same ligand which is then called bi-, ter- dentate etc. Polyydentate ligands with structures which permit the attachment of two or more donor sites to the same metal atom are called CHELATE\textsuperscript{31} ligands (khēlē, Gk., a claw). Such ligands are generally organic molecules and the donor atoms N, O, and S are the most common. Examples are given in Fig. 2.

Fig. 2

\begin{align*}
\text{(24)} & \quad \text{M}^n+ \quad \text{bi-} \\
\text{(22)} & \quad \text{M}^n+ \quad \text{ter-} \\
\text{(23)} & \quad \text{M}^n+ \quad \text{tetra-}
\end{align*}
The known chelating systems have been reviewed and classified on the basis of their donor atoms. The result of such attachment is the formation of rings containing the metal atoms. It is observed that such rings are more stable than similar but acyclic compounds (the so-called chelate effect) and that five-membered rings are more stable than six-membered rings (Table 1). The figures also indicate that the formation of further rings including the same metal atom gives added stability. Rings with less than five atoms are energetically unfavourable because of the high degree of strain. Rings with more than six members suffer strain also until the ring is large enough for this to be relieved, but the probability of a donor six or seven atoms away from the metal achieving the configuration needed for bonding is very low.

The Chelate Effect

The added stability due to ring formation may be explained qualitatively in the following way. The equilibrium constant $K$ is a measure of the standard free energy of a reaction:

$$
\Delta F^o = -RT \ln K
$$

and

$$
\Delta F^o = \Delta H^o - T \Delta S^o
$$

The enthalpy change in the formation of a complex of an aquated metal ion is due mainly to the difference in bond energies between the metal-oxygen bonds broken and the metal-ligand bonds formed. Experimental determinations show that this difference is too small to
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ammonia</th>
<th>( \log \beta )</th>
<th>( \text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2 )</th>
<th>( \log \beta )</th>
<th>( \text{H}_2\text{N(CH}_2\text{)}_3\text{NH}_2 )</th>
<th>( \log \beta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>([\text{Cu(NH}_3\text{)}^2]^+)</td>
<td>([\text{Cu(NH}_3\text{)}_2]^2^+)</td>
<td>3.5</td>
<td>([\text{Cu(en)}]^2^+)</td>
<td>10.7</td>
<td>([\text{Cu(tn)}]^2^+)</td>
<td>10.0&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>([\text{Cu(NH}_3\text{)}_3]^2^+)</td>
<td>([\text{Cu(NH}_3\text{)}_4]^2^+)</td>
<td>2.9</td>
<td>([\text{Cu(en)}_2]^2^+)</td>
<td>9.3</td>
<td>([\text{Cu(tn)}_2]^2^+)</td>
<td>7.2&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>([\text{Cu(NH}_3\text{)}_4]^2^+)</td>
<td>([\text{Ni(NH}_3\text{)}]^2^+)</td>
<td>2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>([\text{Ni(NH}_3\text{)}_2]^2^+)</td>
<td>([\text{Ni(en)}]^2^+)</td>
<td>2.2</td>
<td>([\text{Ni(tn)}]^2^+)</td>
<td>7.7</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>([\text{Ni(NH}_3\text{)}_3]^2^+)</td>
<td>([\text{Ni(NH}_3\text{)}_4]^2^+)</td>
<td>1.7</td>
<td>([\text{Ni(en)}_2]^2^+)</td>
<td>6.5</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>([\text{Ni(NH}_3\text{)}_5]^2^+)</td>
<td>([\text{Ni(en)}_3]^2^+)</td>
<td>0.7</td>
<td>([\text{Ni(tn)}_2]^2^+)</td>
<td>5.1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>([\text{Ni(NH}_3\text{)}_6]^2^+)</td>
<td></td>
<td></td>
<td>([\text{Ni(tn)}_3]^2^+)</td>
<td>11.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{Table 1} \]
account for the chelate effect. In a chelating system each ligand which binds to the metal displaces two or more water molecules, resulting in an increase of freedom for the system. Each non-chelating ligand bound displaces only one water molecule and the nett freedom of the system stays the same. Thus in the chelating system there may be a large entropy increase, particularly if the ligand is charged and hence solvated. Thus "K" (the formation constant) will be larger in the chelating case. The overall stability constant β is the product of all the stepwise formation constants and hence it too will be larger in the chelating case (Table 1).

The properties of a metal ion or the system containing it may be radically altered by chelate formation.

**Solubility**

Replacement of water molecules in the aquation sphere of a metal ion with organic chelating ligands enables the metal to be extracted into organic solution. It may make the metal totally insoluble in water or cause it to be distributed in both phases. Suitable choice of ligands makes this very useful in analytical and industrial processes.\(^{35}\)

**pH Effect**

In binding to the ligand, the metal is usually in competition with protons and thus, formation of a chelate complex usually involves a change in pH. Such complexes are therefore more stable at neutral or
high pH than in acid solution. Adjusting the pH may result in preferential decomposition of the complex of one metal enabling this technique to be used for metal separations. Metals can be titrated with suitable ligands and the end point found by pH measurements. The concentration of a metal ion in solution can be accurately controlled by chelation and pH adjustment. The conductivity of metal ion solutions will also obviously alter with chelation.

**Oxidation Potential**

The different oxidation states of a metal may form chelate complexes of widely different stabilities with the same ligand. This will be reflected in the measurable e.m.f. of cells consisting of two oxidation states of the metal and the chelating ligand.\(^{36}\)

\[
\begin{align*}
\text{Fe}^{2+} & \rightarrow \text{Fe}^{3+} + e^- \quad E^0 = -0.771 \text{v} \\
[\text{Fe(CN)}_6]^4^- & \rightarrow [\text{Fe(CN)}_6]^3^- + e^- = -0.36 \text{v} \\
[\text{Fe o-phen}_3]^{2+} & \rightarrow [\text{Fe o-phen}_3]^{3+} + e^- = -1.06 \text{v}
\end{align*}
\]

(\text{o-phen} is o-phenanthroline (24))

Surrounding a metal ion with suitable chelated ligands may lower the rate of a redox reaction to the point where the metal is effectively inert. This effect is used in the technique of metal sequestration.

The uses of chelating agents in industry and analysis have been reviewed by Smith.\(^{35}\)
Metal Catalysis

Martell\textsuperscript{37} has reviewed the unique properties of chelate formation in the catalysis of reactions and suggests that metal ions promote nucleophilic attack on a chelated ligand due to the ligand being made more positive by the metal atom. Conversely, if chelate formation involves the displacement of protons by the metal, the ligand is made more negative and hence electrophilic attack is promoted. Unusual oxidation states of a metal may act as intermediates in electron transfer reactions and such unusual states may be much more readily obtainable when the metal is chelated. The metal ion can act as a bridge for electron transfer between the oxidant and reductant in a reaction. Metal ion catalysed reactions often occur in dilute solutions. Formation of a metal chelate with the substrate, greatly increases the amount of reactive intermediate in solution. Chelating ligands may act as carriers for metal ions in conditions of high pH where the metal ion alone would not exist. If only some of the coordination positions of the metal are used it may retain Lewis acid properties and enhance the reactivity of a substrate towards a base by binding to it. Under such pH conditions, proton and simple metal ion catalysis could not occur. Such properties become of great interest in view of the biochemical role of chelation.

Chelation in Biochemistry

Many of the simple building blocks of large biologically important molecules have marked chelating properties. The stabilities
and properties of chelates of transition metal ions with amino acids, pteridines (25), the purines adenine (15) and guanine (16a), and riboflavin (26) have been determined.\textsuperscript{38,39} Over recent years many models for complex biochemical systems have been investigated. Such models involve chelation with metal ions.\textsuperscript{37,40} Amino acid esters are more rapidly hydrolysed in the presence of metal ions than by base alone.\textsuperscript{41,42} The hydrolysis of the ethyl ester of phenylalanine has a metal catalysed rate constant one million times larger than the base catalysed rate constant.\textsuperscript{42} Kroll\textsuperscript{43} has made similar postulates and has shown that the metal chelates are stronger Lewis acids than the uncomplexed ligand and thus hydroxyl ion attack is more favourable. The product of such attack is unstable and rapidly decomposes to give the acid (Scheme 1).

\textit{Scheme 1}

\[
\begin{align*}
M^{++} + H_2N\cdot CH\cdot CO_2R' & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot CO_2R' \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

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\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
\begin{bmatrix}
R \\
CH\cdot C\cdot OR' \\
NH_2 \\
M^{++}
\end{bmatrix} & \iff \begin{bmatrix}
R \\
CH\cdot C\cdot OH \\
NH_2 \\
M^{++}
\end{bmatrix} \\
\end{align*}
\]
He has also been able to correlate the increase in rates for different metals with the increasing ability of the metals to take part in chelation – the Irving-Williams order.\textsuperscript{44}

Probably the best known model is that for the catalysis by pyridoxal phosphate type enzymes of transamination, decarboxylation, racemisation, and elimination reactions of amino acids. The catalytic properties of the enzymes are almost entirely due to the prosthetic group and the model of Metzler et al.\textsuperscript{45} incorporating metal chelation (Scheme 2) has recently received powerful support from n.m.r. studies.\textsuperscript{46} Pyridoxamine has been shown to prefer chelating with copper and this is the superior catalyst.\textsuperscript{47} A model for the selective hydrolysis of N-terminal peptide bonds involving chelation with cobalt has also been investigated.\textsuperscript{48}

The evidence for metal involvement in actual biological systems is slowly being brought to light. Many enzymes have been discovered which require a fixed amount of the right metal to operate properly.\textsuperscript{49-53} Removal of the metal from many of these enzymes by dialysis or the use of chelating agents, deactivates them. Rabin\textsuperscript{54} has suggested that the coordination sites found in aqueous solution experiments with simple peptides are identical with binding sites \textit{in vivo}. On this suggestion, the models discussed before should be lifelike and make reasonable prediction about enzyme systems. Williams\textsuperscript{55} has investigated some enzymes with a molybdenum
Scheme 2

\[
\begin{align*}
R-C-CO_2^- + NH_3^+ + M^{+++} & \rightarrow R-C-CO_2^- + H^+ \\
& \rightarrow R-C-CO_2^- + HOH_2C-CH_2NH_2^- + R-C-CO_2^- + M^{+++}
\end{align*}
\]

TRANSAMINATION
requirement. Binding of a metal like molybdenum demands unusual geometry and the binding site must therefore have certain properties. Replacement of one metal in an enzyme with another more suited to spectrophotometry has also given some idea of the binding sites.\textsuperscript{53,55,56}

The first reasonably complete picture of the binding site of a metallo-enzyme has recently been published\textsuperscript{57} for bovine carboxypeptidase A (CPA) which cleaves peptides at the carboxyl group end. This enzyme requires 1 atom of zinc in a molecule of 307 amino acid residues. The ligands bound to the zinc atom and the groove for the substrate have been found and the picture completed by another study with a peptide substrate bound in place (Scheme 3). The C-terminal residue of the substrate inserts into a pocket in CPA displacing several water molecules. The C-terminal carboxyl group forms a salt link with the guanidinium group of arginine-145, and the carbonyl oxygen of the susceptible substrate peptide link replaces a water molecule as the fourth ligand to zinc. The molecule undergoes conformational changes when the substrate is bound. The guanidinium group of arginine-145 moves approximately 2\textdegree. The carboxyl group of glutamic acid-270 moves away from the zinc atom by the same amount. The phenolic hydroxyl group of tyrosine-248 moves 12\textdegree, to within 3\textdegree of the susceptible peptide bond. The movement of arginine-145 and tyrosine-248 is coordinated and involves the breaking of four hydrogen bonds between them. The protein of the enzyme thus adapts to the substrate. It is thought that tyrosine-248 is the proton donor and glutamic acid-270 promotes the attack of a lone
Scheme 3

![Chemical structure diagram](image-url)
pair of electrons from water on the susceptible carbonyl group carbon. In the binding of larger peptide substrates other residues not near enough to take part in catalysis, act as recognition sites.

The porphyrin ring\(^{58}\) (27) forms the basis of such biologically important molecules as haem where the central metal atom is usually iron and the cytochromes which use iron or copper. Vitamin \(\text{B}_{12}\) (28) requires cobalt for its activity.

**The Role of Metal Atoms**

It is well known that the human body has a small but definite requirement for some of the transition elements. Copper, iron, manganese, cobalt, molybdenum, and zinc are all necessary but only in trace amounts. Often, the presence of metal in the ratio of only one atom per 200,000 units of molecular weight is needed for an enzyme to be active. The previous evidence indicates that the active site of the enzyme is intimately concerned with the metal ion.

Gillard\(^ {59}\) has surveyed the studies of complexes of metals with amino acids, and peptides and showed that chelation with metal could be the explanation for naturally occurring asymmetry. Certainly stereoselectivity can be a feature of chelation. The copper chelating drug penicillamine (22) is the best drug for treating Wilson's disease which is a copper abnormality. Only the D-penicillamine isomer is active. Haldane\(^ {60}\) suggested that coordination
with a metal ion may activate a bond in the substrate by causing strain in the protein–enzyme–substrate complex. This is strikingly illustrated in model compounds by the activation of methylene protons in α-amino acid chelate rings to deuterium exchange. The in-plane protons are more activated than those out of the plane of the metal atom, i.e., $K_1$ is greater than $K_2$ \(^6\) (Scheme 4).

Scheme 4

![Diagram of a metal complex with labeled protons]

Protons in circles exchanged with deuterium
Protons underlined exchanged with deuterium.
The out of plane rings are virtually strain free whilst the in-plane rings have considerable bond angle distortion. Asymmetry and ring strain are a consequence of the geometry requirements of the central metal atom.\textsuperscript{53} This is particularly marked where the donor atoms are sulphur.\textsuperscript{55} Coordination of a metal with the apo-protein may cause a certain "lock" geometry of the overall binding site so that only certain substrates can become attached. The substrate itself may be forced into a certain "key" geometry to fit the "lock" of the apo-protein specifically. Elements of both "lock" and "key" can be seen in the carboxypeptidase example discussed earlier. The metal may actually be responsible for binding the enzyme and the substrate together or for binding a coenzyme to a protein to form the effective enzyme. In haemoglobin, the protein, coenzyme, and substrate are bound together by the iron atoms. A similar role is postulated in some other metallo-enzymes.\textsuperscript{62}

In haem and the cytochromes, chelation is thought to modify and stabilise the oxidation potentials of the metal ions involved. In haemoglobin this enables reversible oxygen binding to occur and in the cytochromes, electron transfers from one member of the chain to the next.\textsuperscript{63,64} The metal may stabilise some intermediate in a reaction chain such as the semiquinones in metallo-flavoprotein reactions.\textsuperscript{65}
Origins of Selectivity in Metal Binding

The roles postulated for metal binding in the preceding discussion imply that there is specificity in the metal requirement of the various biologically important ligands. In the case of carboxypeptidase for example replacement of the zinc atom with cobalt(II), nickel(II), manganese(II) or iron(II) gives enzymes with at least some peptidase activity. Substitution with copper(II) or removal of zinc, completely deactivates the enzyme. Mercury(II) or Cadmium(II) replacement of zinc gives an enzyme with no peptidase activity but some esterase activity.54

The most common chelating ligands such as ethylenediaminetetraacetic acid (EDTA) (23) show no selectivity (Fig. 3).66 Increasing the number of chelate rings and hence the stability, likewise does not give selectivity. The order of catalytic activity of the metals in biological chelates is not the same as that for ordinary systems.56 The answer must lie in the nature of the binding groups.

Williams has rationalised the metals found in biological systems on the basis of natural abundance.67 For the common chelating agents, the order of metal affinity (Table 2)68 and chelate stability was predicted by Irving and Williams44 and closely parallels the strengths of the metal ions as Lewis acids.
Table 2

Greatest avidity

Fe$^{3+}$  Hg$^{2+}$
Cu$^{2+}$  R$^{3+}$
Ni$^{2+}$  Pb$^{2+}$
Co$^{2+}$  Zn$^{2+}$
Fe$^{2+}$  Ca$^{2+}$
Mn$^{2+}$
Mg$^{2+}$
Ca$^{2+}$

Least avidity

Plotting the stability constants of chelates of the above metals with several diverse ligands shows some interesting results (Fig. 3).

Fig. 3

![Graph showing the stability constants of chelates for different metals with various ligands.](image)
It can be seen that the different chelates of the same metal have widely different stability constants. For metals to the right of iron in Fig. 3 nitrogen donor ligands are preferred. Metals to the left of iron prefer oxygen donors. Iron is unique in that all its complexes have roughly the same stability. The ligands with mixed donor atoms show a variety of stabilities. The oxygen ligands have a relatively flat curve and this is general for ligands of this type such as phosphate. The greatest stability determining factor in phosphate chelates is the number of groups bound and this explains why phosphates are such universal ligands. The reasons for such selectivity may be given in terms of Pearson's theory of hard and soft acids and bases. In Fig. 3 the hardness of the metals as Lewis acids decreases from left to right. The hardness of the donor atoms as Lewis bases decreases in the order oxygen, nitrogen, and sulphur. The metals of groups one and two of the periodic table will prefer hard oxygen donors such as those of phosphate ligands. Metals to the right-hand side in Fig. 3 should be preferentially bound by the soft sulphur donors such as cysteine (11). The imidazole nitrogen is a borderline case and the borderline metals, i.e. those immediately to the right of iron in Fig. 3 should prefer the imidazole amino acids and bases.

Most chelate ligands are also proton bases. At the physiological pH of 7 most metal chelates with phosphates have approximately the same stability, as do the imidazole and carboxylate
complexes of magnesium, manganese, iron, and zinc. Thus minor changes in pH could dictate which binding site is used or which metal is bound. The sulphhydryl group has a high pKa and will only form complexes with metals at the top of Table 2, because of strong proton competition. Thus in the case of cysteine (11) low pH favours chelation with the nitrogen and oxygen donors, whereas high pH favours the use of sulphur and nitrogen donors (Fig. 4).

Fig. 4

\begin{align*}
\text{low pH} & \quad \text{high pH} \\
\text{low pH} & \quad \text{high pH}
\end{align*}
Similarly for histidine (10) low pH favours the imidazole and amino nitrogen donors and high pH favours the amino nitrogen and carboxylate oxygen donors.

In proteins, such amino acids probably have great importance because after the amino and carboxylate groups have been used in forming peptide bonds the third binding site remains. In amino acids such as cysteine (11) and histidine (10) (Fig. 4) such binding sites are strong whereas for serine (29a) and threonine (30) which have as the third site a hydroxyl group, they are likely to be weak. Both groups can be strong enough to create a specific structure and such structures will be of low symmetry. Ability to enter such low symmetry sites is a notable feature of cobalt and zinc.53,55

Differentiation between two metal ions of different sizes is shown by several ligands because their structure does not allow the donor atoms to approach closely enough to bind a small ion. This is shown by tartaric acid which will bind calcium but not magnesium.

Metals and DNA

The evidence for metal involvement with nucleic acids has accumulated since Wacker and Vallee71 found that preparations of RNA from diverse sources contained a significant concentration of Chromium(III), nickel(II), and manganese(II) and that this concentration appeared to be constant. Such metal was only removed with
difficulty and must therefore have been strongly bound. They suggested that the metals helped to maintain the configuration of RNA by bonding to the purine and/or pyrimidine bases either through nitrogen donors or via the \( \pi \) electrons of the bases. A similar report by Fuwa and co-workers\(^72\) added zinc to the list of strongly bound metals and suggested much the same role for the metal. Dove and Davidson\(^73\) found that magnesium and cobalt could bind strongly and in definite proportions to DNA causing alterations to its physical properties. They presumed that the binding involved phosphate groups. DNA was found to be able to compete with protein for cobalt, zinc, magnesium, calcium, and manganese at neutral pH.\(^74\). Eichhorn\(^75\) has found that magnesium ions stabilise DNA in aqueous solution probably by binding to the phosphate groups and neutralising negative charges. Denaturation of DNA by heating in aqueous solution was reversible in the presence of the metal. It was suggested that the metal holds the chains in close proximity so that hydrogen bonds can reform on cooling. Calcium, barium, manganese, cobalt, nickel, and zinc had the same effect. Copper, on the other hand, was thought to bind to the nitrogen bases of the denatured strands and prevent the re-formation of the hydrogen bonds. Mercuric and zinc ions have been found to unwind reversibly, double stranded polynucleotides.\(^76,77,78\) Evidence was found that mercury was bound across the base pairs for ratios of base to mercury of less than 2:1. When the metal concentration rose above this, the helix began to unwind (Fig. 5).
Fig. 5

CHAIN - BASE - N - Hg - N - BASE - CHAIN < 2:1

CHAIN - BASE - N - Hg Hg - N - BASE - CHAIN > 2:1

Nucleic acids offer a diversity of electron donor sites for metals. Zinc, nickel, manganese, and lanthanum can bind to phosphate oxygen or nitrogen. When bound to phosphate they are thought to stabilise the hydrogen bonded structure of the nucleic acids. Such phosphate binding has been demonstrated for manganese by n.m.r. relaxation techniques.\textsuperscript{79} Metals such as copper, silver, and mercury are thought to bind to the nitrogen bases through the sites used for hydrogen bonding.\textsuperscript{75} For copper at least, this has been demonstrated by infrared spectral studies\textsuperscript{80} which showed that copper could bind to guanine (16a) and cytosine (18).

Hueper and Conway\textsuperscript{3b} have reviewed the suggestions for the role of metals in carcinogenesis. Chelation with protein has received some attention and it has also been suggested that the carcinogenic metal may replace a biologically normal metal resulting in the synthesis of an abnormal growth regulator. However in the light of the effects discussed above, the role of some metals as carcinogens\textsuperscript{3a} may perhaps be explained on the basis of their interaction with DNA. Even though some of the metals are required by the body, an excess in the wrong place may be damaging. The present concern with permissible mercury levels is surely not overdue in view of its effects on DNA.
The ferricinium (31) and bis [benzene] chromium (32) cations have been found recently to bind to DNA by both charge transfer and covalent bonding. This is interesting because of the well known carcinogenic effects of polynuclear aromatic hydrocarbons.

**Chelating Drugs**

The use of chelating agents in medicine has been reviewed by Albert and Schubert. Dimercaprol (33) is used as an antidote for gold, arsenic, antimony, and mercury poisoning and penicillamine (22) for chronic copper poisoning. Cysteamine (34), one of the few radiation protection drugs, is thought to chelate copper and thus break a metal catalysed oxidative reaction causing tissue destruction.

The idea of chelation as a mechanism of drug action rather than just as an antidote for metal poisoning arises from the work of Albert on 8-hydroxyquinoline (oxine) (35). Oxine was thought to be a very powerful bactericide and fungicide but Albert showed that it required small amounts of iron or copper to be active. He showed that it is the 1:1 oxine to iron (or copper) chelate which is the active compound. A large excess of oxine causes the formation of the 2:1 oxine to iron chelate, which is inactive. The N-oxide of 2-mercaptopuridine (36) is a powerful disinfectant and is very similar to oxine in its requirements and mode of action.
Albert has shown that the antitubercular drug isoniazid (37) can chelate metals and it is thought that the drug in the form of its iron chelate, penetrates the human tubercle organism. The isatin thiosemicarbazones (38) are used against poliomyelitis and smallpox and are chelating agents but their mode of action is uncertain. The tetracycline drugs, terramycin (39a) and aureomycin (39b) have high affinities for metals. Biallylamicol (40), used against amoebic dysentery, and hydrallazine (41), used for lowering blood pressure are both good chelating ligands. The latter is thought to chelate metals which are co-factors for the decarboxylating enzymes responsible for producing pressor substances.

The common drug aspirin (42) is believed in some cases, to chelate copper and return it to the cells from which it came. Bulk removal of the copper from the system is ineffective. Many of the effects of aspirin can be duplicated by the administration of suitable copper compounds.

**Chelation in Cancer**

Metal participation and metal chelation seem to be widespread biochemical phenomena. Furst speculated that cancer might be intimately concerned with the role of metals. An abnormal metal may allow a wrong substrate to be bound or cause an enzyme to act abnormally. The binding of an abnormal metal to an enzyme or substrate may alter the kinetics of a process beyond the stage where
normal cell control mechanisms could deal with the problem. Cancer may just be a problem of altered kinetics.

The direct evidence of metal involvement with cancer is small. The metals which can cause cancer have been reviewed and there are a few reports of abnormal metal levels in some cancerous tissues. The question of what is a significant abnormality remains unanswered, however, and to a large extent even normal metal levels in tissue are not known with accuracy.

Furst surveyed many of the anticancer drugs and found that a considerable proportion of them were chelating agents or could easily be metabolized into chelating agents. Chemotherapy of this sort may prevent wrong metals from achieving the concentrations necessary for interference in a metal dependent biochemical system. It has been suggested that since various enzymes are known to be involved in biosynthesis, the design of enzyme inhibitors might be a useful cytotoxic principle. If such enzymes required metal ions for their activity, inhibition could conceivably be brought about by chelating agents. If the cancer effect was due to the wrong metal activating an enzyme the possibility of selective inhibition by chelation arises. The chelating agent may bind to and deactivate carcinogenic metals or serve to carry metal ions through cell walls by increasing their lipid solubility. Chelation chemotherapy could possibly prevent metal-nucleic acid interactions.
Cytotoxic ability and in some cases clinical usefulness has been demonstrated for selenium derivatives of cysteine\textsuperscript{13c} (11b,c), the chelate of 8-azaguanine (40) with cobalt,\textsuperscript{88} "oxime" (43),\textsuperscript{89} with copper, hematoporphyrin with mercury,\textsuperscript{90} and lead, cadmium, and copper chelates of dithio-oxalic acid (44).\textsuperscript{91} The platinum, and palladium chelates of 6-mercaptopurine (7a)\textsuperscript{92} and the platinum compounds cisdiaminoplatinum (IV) chloride (45a), cisdiaminoplatinum (II) chloride (45b), ethylenediamineplatinum (IV) chloride (45c) and ethylenediamineplatinum (II) chloride (45d)\textsuperscript{93} have shown strong anti-tumour activity. The compound 2,5-bis(iodomercurimethyl)-p-dioxan\textsuperscript{94} (46) has also shown cytotoxic activity.

There have been a few attempts to make anti-cancer chelating agents or pre-formed chelates. Creighton et. al.\textsuperscript{95} have prepared derivatives of ethylenediaminetetraacetic acid (25) which is a powerful chelating agent for divalent metals but which has no anti-cancer activity. EDTA is a very polar molecule and would not be expected to penetrate to intracellular sites. Less polar derivatives which might be expected to penetrate such as 1,2-bis(3,5-dioxopiperazin-1-yl)ethane (47a) were made and found to be active. Methyl substitution of the central carbon atoms (47 b,c) also gave active compounds but ethyl substitution (47 a, R\textsuperscript{1}=CH\textsubscript{2}CH\textsubscript{3}) did not. The authors conclude from this that the mode of action is not chelation but an interaction with a cell component with very specific geometry. This is a surprising statement because although chelation would still
be expected for the ethyl compound \((47 \ a, \ R^1=\text{CH}_2\text{CH}_3)\), the stability of its metal complexes or its lipophilicity might be altered sufficiently to cause its inactivity. Albert,\(^9^6\) for example, has shown that substituents in the 2-position of oxine (35) can lower its biological activity without altering its chelating ability.

The \textit{bis} (thiosemicarbazone) of 2-keto-3-ethoxy-butyraldehyde (48) as its copper chelate has antitumour activity and this activity is greater than that of the compound on its own or as a chelate with any other transition metal.\(^9^7\) The copper chelate was able to inhibit DNA synthesis by 82%, RNA synthesis by 54% and protein synthesis by 62% in test cells. The copper content of cells treated with the chelate increased fifteen times. The chelation of the copper enhances its lipid solubility and presumably enables it to be transported into cells. It is not known whether copper or the ligand or the chelate is the active principle. A similar compound, pyruvaldehyde \textit{bis}(thiosemicarbazone) (12b) has tumour inhibiting properties which are enhanced if copper is administered concurrently. Greater activity is shown by the preformed \textit{bis}-copper chelate.\(^9^8\) Pyruvaldehyde itself (12a), which is thought to be an active component of the cell growth regulator retine,\(^1^7\) can chelate with metals.

\textbf{Chelating Cytotoxic Drugs}

There have been many reviews of the useful anticancer drugs and each has attempted to classify them in some logical way.\(^4^a,5,7a,13,9^9\)
The chemical structures of the drugs are incredibly diverse and if all the compounds with cytotoxic activity are included, the picture becomes even more complex. Furst's chelation hypothesis is the only one which offers some explanation for the mode of action of some of the most important drugs on the basis of one theory. Such drugs will now be reviewed in the light of Furst's suggestions.

**Biological Alkylating Agents**

These drugs are thought to act by alkylating electron deficient centres on nucleic acid molecules. Alkylation of the 7-nitrogen atom of guanine (16a) and the 3-nitrogen atom of adenine (15) is thought to alter the rate or the products of DNA replication, affect the base pairing or cause deletion of the bases as their alkylated derivatives. Many agents with alkylating ability have been made and most of them contain the nitrogen mustard or 2,2'-dichlorodiethylamine (3a) moiety. Such variants as HN2 or 2,2'-dichloro-N-methyldiethylamine (3b), cytoxan(2), melphalan (4), chlorambucil (49), thioTEPA (50), triethylenemelamine (51), the bis-epoxides e.g. (52), and sulphonic acid esters such as busulfan (14), have all been employed clinically.

These compounds are not of themselves chelating agents. They can alkylate groups by two possible mechanisms.
\[ S_N^1 \]
\[ R - X \xrightarrow{\text{Slow}} R^+ + X^- \]
\[ R^+ + Y^- \xrightarrow{\text{Fast}} RY \]

The rate of the reaction is dependent only on the concentration of the alkylating agent.

\[ S_N^2 \]
\[ RX + Y^- \rightarrow RY + X^- \]

The rate of the reaction depends on the concentration (and structure) of \( Y^- \) and the concentration of the alkylating agent.

Combinations of these mechanisms are found. Aliphatic nitrogen mustards, after the ionisation step, readily form a cyclic ethlenimmonium ion (Fig. 6)

**Fig. 6**

\[ \text{(a)} \quad \text{R} - \text{N} - \begin{array}{c} \text{CH}_2 \\ \text{Cl-CH}_2\text{CH}_2 \end{array} \]

\[ \text{(b)} \quad \text{R} - \text{N} - \begin{array}{c} \text{CH}_2\text{CH}_2\text{Cl} \\ \text{CH}_2\text{CH}_2^+ \end{array} \]

\[ \text{(c)} \quad \text{Cl-CH}_2\text{CH}_2 - \text{N} - \begin{array}{c} \text{CH}_2\text{CH}_2\text{N} \\ \text{R} \end{array} \]}

and this ion then reacts with the substrate by a bimolecular nucleophilic mechanism. In aromatic nitrogen mustards, the nitrogen atom may not be basic enough to form such an ion and thus they react
through an intermediate such as (b Fig. 6) by a unimolecular nucleophilic mechanism. Whichever reaction path is followed, the initial alkylation product should look like (c Fig. 5) and this is a chelating ligand with two nitrogen donors. An unstable reactive carbonium ion can also be postulated for the bis-epoxides, ethyleneimines and sulphonates (fig. 7)

![Fig. 7]

Of these only the sulphonates will not give a chelating ligand after alkylating DNA. However busulfan (14) is known to form derivatives with cysteine (11) which could chelate (Fig. 8).

![Fig. 8]

busulfan $n = 2$
In this case it seems unlikely that both sulphur atoms bind to the same metal, since this would give a seven-membered ring and activity is found in the sulphonates (14) for all values of "n" between two and ten.

**Antimetabolites**

Numerous structural variants of known metabolites have been evaluated for antitumour activity.\(^{13f}\) The folic acid (6b) antagonists amethopterin (6a) and aminopterin (6c) have been discussed and both are chelating agents. Many analogues of the DNA purine bases adenine (15) and guanine (16a) have been found clinically useful. Such drugs as 6-mercaptopurine (7a) and its riboside (7b), 6-thioguanine (16b) and 8-azaguanine (16c) are the best of these and all are chelating agents. Ribosidation in some cases increases antitumour activity, which could possibly be explained by ribose being able to chelate metals. The pyrimidine antagonists are in general not as effective as the purine ones. However 5-fluorouracil (53) which may be able to chelate metals via the phenolic oxygen and the fluorine atom, and 6-azauridine (54) which could bind metals via the sugar group are two examples of highly cytotoxic pyrimidine antagonists.

Some amino acid antagonists such as ethionine (55), betazine (56), betamine (57), N-dichloroacetyl-DL-serine (58) and β-2- and -3-thienylalanine (59 a,b) have all shown some antitumour activity,\(^{13f}\) albeit small and all are chelating agents.
Administration of acid hydrazides (60a), hydrazino acids (60b) or aminoxy acids (60c) coupled with a diet deficient in the B₆ vitamins (themselves chelating agents, see Scheme 2, p. 19), has shown antitumour effects.⁷f

**Antibiotics**

Actinomycin D (9) and many of its close relatives, mitomycin C (13), azaserine (29b), 6-diazo-5-oxo-L-norleucine (or DON) (61), puromycin (62), streptonigrin (63) and psicofuranine (64) are all cytotoxic¹₃d and many are chelating agents. It is of interest that the binding of actinomycin D (9) to DNA which is thought to block RNA synthesis, is strongly inhibited by calcium, magnesium or manganese ions.¹⁰¹ Daunomycin¹⁰² (65) also interferes with nucleic acid metabolism and is a chelating agent.

Various random examples of chelating agents with cytotoxic activity include the steroids prednisone (8a), cortisone (8b) and cortisol (8c). These are the only steroids which could chelate out of a large number of steroids with cytotoxic properties.¹₃g Hydroxyurea (66) is cytotoxic and salicylhydroxamic acid (67), a compound with the same chelating moiety, can selectively inhibit DNA synthesis in some cancer cells in vitro.¹⁰⁴ Hydroxamic acids are well known chelating agents. Methylglyoxal big (guanylhydrazone) (68) was suggested for testing by Furst²⁹ because of his chelation hypothesis and has been found to be very active against a leukemia.¹⁰⁴
Isoquinoline-1-aldehyde thiosemicarbazones which can chelate through the ring nitrogen and the side-chain are quite cytotoxic and the nature of the side-chain has been found to be vital for this activity.\textsuperscript{105} A very similar compound pyridine-2-aldehyde thiosemicarbazone (69) is also active whereas the 3-isomer which cannot incorporate the ring nitrogen atom in a chelate is inactive.\textsuperscript{29,106} Several of the compounds which Swan\textsuperscript{18} suggests could cap the DNA molecule are also chelating agents, \textit{e.g.} the polyporic acid derivatives\textsuperscript{23} (70).

Rao\textsuperscript{99} has listed the drugs which are capable of giving remarkable remissions of human cancers and of these, Furst\textsuperscript{29} would classify cytoxan (2), nitrogen mustard (3a), melphalan (4), vincristine (5a), vinblastine (5b), amethopterin (6a), 6-mercaptopurine (7a), prednisone (8a), cortisone (8b), cortisol (8c) actinomycin D (9), busulfan (14), chlorambucil (49), thiotePA (50), triethylenemelamine (51), 5-fluorouracil (53) and its riboside and methylglyoxal \textit{bis} (guanylhydrazone) (68) as chelating agents a total of eighteen out of twenty eight. In prednisone (8a) cortisone (8b) cortisol (8c) actinomycin D (9) vincristine (5a) and vinblastine (5b) however, the chelating part is such a minor section of the whole molecule that the significance of chelation as a mode of action is suspect. It is possible that a chelating group may be needed to bind the drug to a particular site or to cause a particular orientation of the rest of the molecule. Chelation alone as a mode of action is difficult to envisage for the steroidal hormone drugs (other than those
given above), the very promising antileukaemic drugs of Cain et al.\textsuperscript{107} (\textsuperscript{71}) and many of the recently discovered, naturally occurring cytotoxic drugs (\textsuperscript{71-74}).\textsuperscript{108-110}

Furst\textsuperscript{29} speculates that metabolic changes may convert a non-chelating drug into a chelating one. The fate of an administered drug is most uncertain and no real evidence exists to support this idea. There are certainly other factors besides the ultimate site of action of a drug which determine whether it is active or not. The drug has to penetrate to the site and to do this it has to pass many biological barriers. An orally administered drug may have to pass from the gut into the bloodstream and from there into the cells. This demands a fine aqueous-lipid phase solubility distribution. The drug may be deactivated by a metabolic transformation or it may react before reaching the site. Certainly steric factors play an important part in determining whether a drug is active or not. The DNA capping drugs of Swan\textsuperscript{18} and the whole principle of antimetabolites are evidence of this. Because the active site of a drug is usually unknown, such factors can only be allowed for by trial and error.

In the light of the evidence of the profound importance of metals to biological systems the chelation hypothesis is attractive as a starting point for drug synthesis but it is certainly not the only factor in the activity of the drugs previously discussed. If
chelation is vital, there remains the problem of selectivity for a particular metal. Little is known about the chelating properties of the drugs used against cancer.

The present study was undertaken to see if a known chelating system could be modified to give cytotoxic compounds.
DISCUSSION

The Amidoximes

The amidoxime function (Fig. 9(a)) was first recognised by Tiemann\(^{111}\) who was able to show the simultaneous presence of the oxime and amino groups in the compound benzamidoxime (Fig. 9, \(R=\text{Ph}\)) made from benzonitrile and hydroxylamine.\(^{111a}\) Many compounds of this type are now known and their chemistry and that of their alkylated and acylated derivatives has been reviewed.\(^{112}\) Tautomerism is possible between two forms (Fig. 9(a) and (b)). The hydroxylamine form has not been found to predominate in any amidoxime so far studied although for formamidoxime (Fig. 9 \(R=\text{H}\)) a mixture of the two tautomers is thought to be present.\(^{113}\) The amino-oxime form has been demonstrated by infrared\(^{114-118}\) and n.m.r. spectroscopy\(^{118}\) for a variety of aliphatic and aromatic amidoximes in both the solid state and in solution.

Amidoximes form coloured crystalline compounds with a variety of metal atoms\(^{119c}\) and Werner\(^{120}\) showed these to be of the chelate type (Fig. 10).
Pearse\textsuperscript{121} has investigated the properties of some of these compounds.

Ley\textsuperscript{119} was the first to prepare an amidoxime with substituents on both nitrogen atoms and on the central carbon atom\textsuperscript{+} (Fig. 11).

He proved that compounds (a) and (b) made by two different routes (Scheme 5) were not identical\textsuperscript{119b} and thus there could be no tautomerism. The double bond in each case must therefore be fixed.

\textsuperscript{+} These trisubstituted amidoximes are probably better named as hydroxy derivatives of amidines with the azomethine nitrogen atom labelled $N'$. This nomenclature is consistent with that used by the Cancer Chemotherapy National Service Centre.
These compounds also formed metal derivatives of the same type as the unsubstituted amidoximes (Fig. 10).\textsuperscript{119c}

This chelating system has been almost totally neglected since Ley's work and does not appear in the review of the amidoximes by Eloy and Lenaers\textsuperscript{112} or in the classifications of Diehl,\textsuperscript{122} and Haendler\textsuperscript{32} (Appendix 1). In Haendler's classification Ley's amidoximes would be written as C,C=N, N-OH.

The Hydroxyamidines as Potentially Cytotoxic Drugs

There have been a few reports of biological activity in the amidoxime series. Antitubercular activity has been demonstrated for some halogen substituted derivatives,\textsuperscript{123} isonicotinamidoxime,\textsuperscript{124} and some diphenylsulphide and diphenylsulphone amidoximes.\textsuperscript{125} Some
aliphatic heterocyclic amidoximes have antihypertensive activity. All of these compounds are of the type depicted in Fig. 9. The amidines, which are closely related to the amidoximes, show a wide range of antibacterial action. No reports on biological activity have been published for the hydroxyamidines.

The hydroxyamidines are chelating agents with an oxygen and a nitrogen donor atom and should, therefore, form their most stable chelates with iron, copper, and nickel (see p. 27). The ligands are easily made from simple precursors which lend themselves to easy modification of the substituent groups. Their solubility, size, and the electronic distribution about the chelating centre can thus be easily modified. Hydroxyamidines appear, for these reasons to be an eminently suitable system for testing for cytotoxic activity in view of Furst's chelation hypothesis.

The Imidoyl Chlorides

There are several synthetic routes to the amidoximes, the most general being that due to Tiemann involving the reaction of a nitrile with hydroxylamine. Such a method is not applicable to the synthesis of the hydroxyamidines. The two methods reported as successful are both due to Ley and involve the reaction of a substituted hydroxylamine with an imidoyl chloride (Scheme 5) or an imido ether. In general, imidoyl chlorides are easier to make than the corresponding imido ethers.
Imidoyl chlorides are made from secondary amides by reaction with carbonyl chloride, thionyl chloride or phosphorus pentachloride depending on the nature of the amide. In a series of papers, von Braun et al.\textsuperscript{128} have investigated the factors responsible for the stability or otherwise of imidoyl chlorides. They conclude that where both substituents are aromatic the compounds are quite stable in the absence of moisture but if the substituent attached to the nitrogen atom is aliphatic the compounds are less stable. If the carbon substituent is aliphatic and the nitrogen substituent is aromatic; the compounds are reasonably stable as long as there is no $\alpha$-hydrogen atom on the carbon substituent. If there is such an $\alpha$-hydrogen atom, rearrangement followed by condensation can occur as soon as some imidoyl chloride is formed (Fig. 12(a)). A large

(a) \[ \begin{align*} \text{R}_2\text{C} & \rightarrow \text{R}_2\text{C} \text{NH-R} \\ \text{Cl} & \rightarrow \text{R}_2\text{C} \text{N-C=Cl} \end{align*} \]

(b) \[ \begin{align*} 2\text{R-C=Cl} & \rightarrow 2\text{R-C=N-R'} \\ \text{Cl} & \rightarrow 2\text{R-C=N-R'} \end{align*} \]

(c) \[ \begin{align*} 2\text{R-CH-C=Cl} & \rightarrow 2\text{R-CH-C=N-R'} \\ \text{Cl} & \rightarrow 2\text{R-CH-C-N-R'} \end{align*} \]
group in the ortho position of the aromatic group attached to the nitrogen atom reduces or prevents this condensation possibly because of steric hindrance. Condensation without rearrangement would seem possible (Fig. 12(b) and (c)), although there are no clear-cut examples in the literature. Step[en][129] suggests a slightly different scheme to explain the production of amidines from the Beckmann transformation of ketoximes (Scheme 6).

\[
\begin{align*}
R_2\text{C}=\text{NOH} & \rightarrow R-\overset{1}{C}=\text{N-R} & \rightarrow R-\overset{1}{C}\text{Cl}_2-\text{NH-R} \\
\text{Cl} & \quad \text{I} & \quad \text{II} \\
\text{I} + \text{II} & \rightarrow R-\overset{1}{C}=\text{N-R} & \rightarrow R-\overset{1}{C}=\text{N-R} + R-\text{CO}_2\text{H} \\
R-\overset{1}{N-C}\text{Cl}_2\text{R} & \quad \text{HN-R} + 2 \text{HCl}
\end{align*}
\]

Where the α-hydrogen atom is a tertiary one the imidoyl chlorides are more stable than if it is secondary possibly due to the lower reactivity of the tertiary hydrogen atom.

Aromatic imidoyl chlorides are generally best prepared with phosphorus pentachloride or thionyl chloride and aliphatic ones with carbonyl chloride or, in some cases, thionyl chloride. In some aliphatic examples, however, sulphur containing compounds are formed. In the present study, attention has been concentrated on those hydroxyamidines from aromatic or, at least, stable aliphatic imidoyl chlorides. Phosphorus pentachloride was chosen because in preliminary experiments, thionyl chloride gave very dark products with
a very strong odour, even after distillation.

In a typical procedure, the thoroughly dried amide was dissolved or suspended in dry benzene and an equimolar quantity of fresh, powdered phosphorus pentachloride was added. The mixture was then heated gently under reflux. Complete solution nearly always took place after one hour but hydrogen chloride was evolved for a further five hours. The solvent and phosphorus oxychloride were rapidly removed under vacuum and the product distilled at high vacuum. The melting points of the compounds which crystallised agreed with those in the literature. The agreement of the boiling points was generally not so good since in previous reports the imidoyl halides were distilled at higher pressures. No imidoyl chloride could be isolated from the reaction of \( N,N' \)-dibenzoyl-\( \varepsilon \)-phenylenediamine with two moles of phosphorus pentachloride.

Imidoyl chlorides can be decomposed by heating, generally into a nitrile and an alkyl halide (Fig. 13). This forms the basis of the von Braun degradation\(^{130}\) of amides.

**Fig 13**

\[
\begin{align*}
R-\overset{\text{Cl}^-}{\underset{0}{C-N-R_2}} & \rightarrow R-\overset{\text{Cl}}{\underset{\text{Cl}}{C=N-R_2'}} & \rightarrow R-\overset{\text{Cl}}{\underset{\text{Cl}+R'-\text{Cl}}{C=N-R'}} \\
R-\underset{\text{Cl}+R'-\text{Cl}}{C=N} & + R'-\text{Cl}
\end{align*}
\]
Distillation of the imidoyl chlorides may thus cause decomposition and in some cases the infrared spectra showed a trace of a nitrile impurity. Purification by crystallisation is however complicated by the anhydrous conditions required to prevent hydrolysis. Since the melting points of the solid imidoyl chlorides were in agreement with reported values and were not raised by crystallisation, all the imidoyl halides were used after one distillation.

The mechanism of formation of imidoyl chlorides from secondary amides and phosphorus pentachloride is not known. Lapidot and Samuel have shown, however, that the reaction of primary amides to give a nitrile, most probably proceeds via the route shown in Scheme 7(a). It is difficult to see how this could apply to secondary amides unless the initial attack was on the oxygen atom by an electrophile such as \( ^{+} \text{PCl}_4 \). Katritzky has concluded that amides are protonated on the oxygen atoms. Thus a similar path to that of Scheme 7(b) would give an imidoyl chloride.

Scheme 7

\[
\begin{align*}
R-C-NH_2 + PCl_5 & \rightarrow R-C-NH-PCl_4 \rightarrow R-C-N=PCl_3 \\
& \quad + HCl \\
R-CN & \rightarrow R-CN + POCl_3 \\
R-C-N-R' + PCl_5 & \rightarrow R-C-N-R' \\
& \quad + PCl_4 \\
& \quad + HCl
\end{align*}
\]
Infrared Spectra

Very few infrared spectra have been published on imidoyl halides. Ugi\textsuperscript{133} has reported values between 1680 and 1710 cm\textsuperscript{-1} for the double bond stretching frequency of some wholly aliphatic ones and Bosshard\textsuperscript{134} has recorded 1672 cm\textsuperscript{-1} for \textit{N}-phenylbenzimidoyl chloride. In the present work, the infrared spectra of a series of thirty-five imidoyl chlorides in chloroform have been determined. Those with aromatic substituents at both ends of the azomethine bridge have a prominent band in the range 1650-1690 cm\textsuperscript{-1}, the majority very near 1660 cm\textsuperscript{-1}. \textit{N}-methyl, (75a) \textit{N}-ethyl, \textit{N}-isopropyl, \textit{N}-benzyl, \textit{N}-cyclohexyl- and \textit{N}-cyclohexyl-2-nitro benzimidoyl chloride also have a strong band in this region. This band is generally the strongest in the spectrum and is attributed to the carbon-nitrogen double bond stretching mode. In \textit{N}-phenylcyclohexanecarbonimidoyl chloride, \textit{N}-2-nitrophenylacetimidoyl chloride, \textit{N}-cyclohexylcyclohexane-carbonimidoyl chloride and \textit{N}-2,4,6-tribromophenylacetimidoyl chloride, the bands are at 1700, 1710, 1715, and 1723 cm\textsuperscript{-1} respectively. In these compounds the carbon-nitrogen double bond is not conjugated with a phenyl group and the frequency is raised in agreement with the similar rise in frequency for aliphatic as compared with aromatic carbonyl groups. The frequencies of all the imidoyl chlorides are higher than those for solutions of similarly substituted benzyldeneanilines. Margerum\textsuperscript{135} has found the carbon-nitrogen double bond stretching frequency near 1630 cm\textsuperscript{-1} for these compounds. This
is in agreement with the fact that acid chlorides show a carbonyl absorption at higher frequencies than the corresponding aldehydes.\textsuperscript{136}

Ugi\textsuperscript{133} has interpreted the bonding of the halogen and the double bond as being spontaneously and reversibly converted into an ion-pair to explain the reactivity of imidoyl chlorides (Fig. 14) and draws a parallel with the structure and reactivity of t-alkyl halides even though the low melting points and solubilities in non-polar solvents of the imidoyl halides strongly suggest covalent bonding.

All the infrared spectra have unexpected, weak absorption in the 3300–2400 cm\(^{-1}\) region. This is very similar to the absorption expected for an amine or imine salt. This is probably due to hydrogen chloride being carried over during the distillation or hydrochloric acid generated from minor decomposition of the imidoyl chloride by water vapour during handling. Imidoyl chlorides are known to form adducts with hydrogen chloride (Fig. 15) which have infrared absorption bands in the same region as those recorded above.\textsuperscript{137} The concentration of such compounds must be small since the melting points of the imidoyl chlorides are close to those reported. The hydrogen
chloride adducts mentioned above react in the same way as the imidoyl chlorides.\textsuperscript{137}

Ugi\textsuperscript{133} has investigated the hydrolysis of various imidoyl chlorides in aqueous acetone and has found that electronic effects far outweigh steric effects. The hydrolysis is interpreted as a unimolecular nucleophilic substitution reaction but some deviations are found due to inhibition by chloride ion. Fully alkyl imidoyl chlorides were found to react much faster than aromatic ones and electron withdrawing substituents strongly retarded the reaction whereas electron donating ones accelerated it. This may explain why N-$p$-anisyl-$p$-anisimidoyl chloride was so unstable.

The reaction of excess phosphorus pentachloride with secondary amides having an aliphatic carbon substituent and an aromatic nitrogen substituent is known to give chlorinated imidoyl chlorides.\textsuperscript{128b} The reaction of two moles of phosphorus pentachloride with one mole of isopropionanilide gave N-phenyl-2-chloro-2-methylpropionimidoyl chloride which on hydrolysis gave 2-chloro-2-methylpropionanilide. Acetanilide with three moles of phosphorus pentachloride gave a mixture of imidoyl chlorides. The product was hydrolysed and the composition of the resulting amide mixture estimated from the integrals of the signals in the n.m.r. spectrum as 3.5\% acetanilide, 13.5\% chloroacetanilide, 42.5\% dichloroacetanilide, and 40.1\% trichloroacetanilide. The reaction of acetanilide with four moles of phosphorus pentachloride following the same procedure, was
estimated to give 31% of dichloroacetanilide and 69% of trichloroacetanilide. This is interesting because phosphorus pentachloride did not react with trichloroacetanilide. Propionanilide with three moles of phosphorus pentachloride followed by hydrolysis of the product gave a high yield of 2,2-dichloropropionanilide.\(^{128b}\)

**Preparation of N-Phenylhydroxylamine.**

The only general method of making substituted hydroxylamines is by the reduction of nitro compounds. For the present work a hydroxylamine was required which could be readily made and easily handled. Hydroxylamines can be stored in bulk as their hydrochlorides but liberation of the free base would add an extra step each time. N-Phenylhydroxylamine was chosen because its synthesis has received a great deal of attention. The reduction of nitrobenzene with sodium sulphide\(^{141}\) was most unsatisfactory, giving a very low yield of a highly coloured product. Marvel and Kamm\(^{142}\) have surveyed the various methods which use zinc dust in a neutral medium. Most of the early reports of this method claim impossible yields because apparently dry N-phenylhydroxylamine contains appreciable amounts of water. Following Marvel and Kamm's\(^{143}\) method proved difficult because an emulsion of nitrobenzene in water was difficult to maintain and the zinc dust tended to agglomerate and lose efficiency. The addition of "Teepol"\(^{144}\) and vigorous manual shaking of the reaction flask followed by the work-up procedure described in the experimental section gave a reproducible yield of greater than
47% of dry, colourless material. If stored in the dark under nitrogen the compound remained colourless for several weeks. Material which has decomposed on storage is practically impossible to purify.

Reaction of Imidoyl Chlorides with Nucleophiles.

Imidoyl chlorides react readily with nucleophiles which substitute for the chlorine atom. Thus reaction with water, alcohols or phenols, amines, and hydroxylamines, gives the corresponding amides,133 imidates,138 amidines139 and amidoximes140 or hydroxyamidines119 respectively. Aniline, hydroxylamine, and N-phenylhydroxylamine have been condensed with imidoyl chlorides in the present work. Dry ether was used as the solvent to avoid interference from moisture.

Hydroxylamine was prepared from its hydrochloride by solution in the minimum volume of ethanol and treatment with the calculated amount of sodium ethoxide. The solution was filtered and added to a solution of the appropriate imidoyl chloride. The product was a substituted amidoxime (95-97) obtained as the free base.

N,N'-Diphenylbenzamidine (100) was prepared by adding a solution of aniline in dry ether to a solution of N-phenylbenzimidoyl chloride also in dry ether. The product was obtained as the hydrochloride which was converted to the free base.
A series of hydroxyamidines (77-93) was prepared by adding a solution of dry \( N \)-phenylhydroxylamine in dry, peroxide-free ether to a solution of the imidoyl chloride also in dry peroxide-free ether. The hydroxyamidines were obtained as their hydrochlorides and were converted to the free bases. The use of old ether as a solvent in the condensation gave coloured by-products which were difficult to remove. Rapid mixing of the two solutions often gave the product as a gum which had to be triturated with acetone before it became solid. Slow mixing of the solution and rapid stirring, in general, gave a crystalline product.

Both \( N \)-2,4,6-tribromophenylbenzimidoyl chloride and \( N \)-2,4,6-tribromophenylacetimidoyl chloride failed to react with \( N \)-phenylhydroxylamine. In contrast, hydroxylamine reacted readily with the former compound. The negative inductive effect of three bromine atoms will tend to make the imidoyl chlorides unreactive and the two ortho bromine atoms will severely obstruct the approach of \( N \)-phenylhydroxylamine. Hydroxylamine is a stronger nucleophile and a smaller molecule than \( N \)-phenylhydroxylamine and thus can react with the imidoyl chloride.

\( N \)-p-anisyl-p-anisimidoyl chloride was only sparingly soluble in ether and rapidly decomposed. A hydroxyamidine could not be prepared from this compound.

Harvill et al.\(^{145}\) have prepared imidoyl chlorides at low temperatures and used them without isolation or purification. By a
reaction with hydrazoic acid, an unstable imidoyl chloride could be utilised to prepare a tetrazole. Reaction with $N$-phenylhydroxylamine was investigated for $N$-cyclohexylcyclohexanecarbonimidoyl chloride, prepared using Harvill's method. The product was a brown tar which gave a low yield (20%) of the required hydroxyamidine hydrochloride (93). The low yield could be due to the fact that $N$-phenylhydroxylamine appeared to react with phosphorus oxychloride as shown by a separate experiment. Benzene may not be as good a solvent as ether for ionisation of the carbon-chlorine bond.

The Hydroxyamidines.

The hydrochlorides are colourless solids which, with the exception of the nitro substituted compounds (86-89), can be recrystallised from organic solvents without decomposition. They all decompose at the melting point and all become coloured blue or green on keeping for several months. The nitro substituted compounds (86-89) were readily converted to the coloured free bases on exposure to air or in solution in damp solvents. The free bases were obtained from all the other hydrochlorides by solution in hot aqueous ethanol and addition of excess ammonium hydroxide solution. Where no precipitate was obtained, the free base was extracted with chloroform. The free bases were easily crystallised from organic solvents to give pale yellow or, in the case of the nitro compounds (86-89) orange or red solids which do not decompose on melting. The solid free bases
appear to be indefinitely stable. Several of the free bases obtained by chloroform extraction could not be crystallised. These were in general those with ortho substituents on one or both the rings attached to the carbon-nitrogen double bond. Three other compounds also failed to give crystalline free bases i.e. \( \text{N-hydroxy-N-phenyl-N'-cyclohexylcyclohexanecarbonamidine} \) (93), \( \text{N-hydroxy-N-phenyl-N'-phenylcyclohexanecarbonamidine} \) (90), and \( \text{N-hydroxy-N-phenyl-N'-phenyl-2-chloro-2-methylpropionamidine} \) (92). The spectra of these free bases are similar to those of the crystalline free bases and hence decomposition is not the explanation. The most probable reason is the inability of these bulky unsymmetrical molecules to pack together efficiently.

The hydroxyamidine hydrochlorides are slightly soluble in water, the aliphatic ones more so than the aromatic ones. In the case of the nitro derivatives (86-89) however, the compounds slowly precipitate as the coloured free bases. The hydrochlorides are moderately soluble in alcohol, benzene, and chloroform and insoluble in acetone, ether, and light petroleum. The free bases are insoluble in water, light petroleum, and ether, slightly soluble in acetone and soluble in alcohol, chloroform, benzene, and ethyl acetate. The \( \alpha \)-naphthyl (78b) and nitro substituted (86-89) hydroxyamidines are the least soluble of all.
The Spectra of the Amidoximes.

The infrared spectra of amidoximes of the type

\[ R-C\equiv NOH \]

\[ \text{NH}_2 \]

have been reported\(^{114-118}\) and favour the oxime tautomer. Mollin and Kašpárek\(^{116}\) report the following frequencies and assignments for \(N\)-phenylbenzamidoxime in benzene solution.

<table>
<thead>
<tr>
<th>Cpd. No.</th>
<th>OH</th>
<th>NH</th>
<th>Assoc.</th>
<th>C-N</th>
<th>NH</th>
<th>C-NH</th>
<th>Ar-NH</th>
<th>N-O cm(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>95a(^{116}) C(_6)H(_6)</td>
<td>3575</td>
<td>3390</td>
<td>1610</td>
<td>1510</td>
<td>1370</td>
<td>1320</td>
<td>950</td>
<td>910</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>3590</td>
<td>3395</td>
<td>3210</td>
<td>1630</td>
<td>1508</td>
<td>1390</td>
<td>1320</td>
<td>950</td>
</tr>
<tr>
<td>KBr</td>
<td>3398</td>
<td>3165</td>
<td>1643</td>
<td>1508</td>
<td>1398</td>
<td>1320</td>
<td>959</td>
<td>924</td>
</tr>
<tr>
<td>95b CHCl(_3)</td>
<td>3590</td>
<td>3395</td>
<td>3210</td>
<td>1643</td>
<td>1500</td>
<td>1350</td>
<td>950</td>
<td>921</td>
</tr>
<tr>
<td>95c KBr</td>
<td>3320</td>
<td>3125</td>
<td>1653</td>
<td>1504</td>
<td>1389</td>
<td>963,950</td>
<td>921</td>
<td></td>
</tr>
<tr>
<td>95d CHCl(_3)</td>
<td>3590</td>
<td>3395</td>
<td>3220</td>
<td>1643</td>
<td>1503</td>
<td>1387</td>
<td>1322</td>
<td>942</td>
</tr>
<tr>
<td>96 CHCl(_3)</td>
<td>3590</td>
<td>3390</td>
<td>3210</td>
<td>1646</td>
<td>1480</td>
<td>1391</td>
<td>1318</td>
<td>940</td>
</tr>
<tr>
<td>97 CHCl(_3)</td>
<td>3580</td>
<td>3410</td>
<td>3270</td>
<td>1685</td>
<td>1498</td>
<td>1378</td>
<td>1299</td>
<td></td>
</tr>
</tbody>
</table>

The values obtained in the present work for the substituted amidoximes (95-97) are recorded in Table 3. The hydroxyl band at approximately 3590 cm\(^{-1}\) is very close to that recorded above and is close to the absorption frequency of a free hydroxyl group.\(^{136}\) The band due to NH stretching near 3390 cm\(^{-1}\) is quite sharp and is close
to that for a free secondary amide. It is not shifted when the solid state spectrum is recorded. The nitro compound (95 c) is an exception to this. The value in the solid state is 3320 cm\(^{-1}\) and is probably explained by hydrogen bonding of the amine hydrogen to the ortho nitro group. The compounds have a band near 3210 cm\(^{-1}\) which moves to a lower frequency in the solid state. This band is close to that recorded in ben zamidoxime by Bell\(^{118}\) as an intermolecular association band and is also present in the spectrum published by Mollin and Kašpárek.\(^{116}\) The strong broad nature of the band in compounds in the present work, its movement to lower frequency in the solid state and its decrease in intensity relative to the 3390 cm\(^{-1}\) band when the solution is diluted support its assignment as an intermolecular association band. All the compounds have one or more strong bands in the range 1630–1660 cm\(^{-1}\) with the exception of the tribromo compound (97) which has a strong band at 1685 cm\(^{-1}\) These bands are attributed to the carbon–nitrogen double bond stretching mode. The occasional complex nature of the band is possibly a reflection of the strong intermolecular associations taking place. In the solid state, the two bands of N-phenylbenzamidoxime (95a) at 1639 and 1630 cm\(^{-1}\) are shifted to 1643 and 1620 cm\(^{-1}\) supporting this conclusion. The equivalent band recorded by Mollin and Kašpárek\(^{116}\) as a single frequency appears from the published spectrum to be broad and have at least one shoulder. Mollin and Kašpárek\(^{116}\) conclude from the similarity of the spectrum of N-phenylbenzamidoxime to that of N,N-diethylbenzamidoxime where no tautom erism can occur,
that the oxime form is correct. The spectra of the present compounds fully support this conclusion. The other assignments given by Mollin and Kaspárek\textsuperscript{116} for the carbon-nitrogen bonds, and the nitrogen-oxygen bond are also supported by the present work.

The n.m.r. spectra of these amidoximes all have a very broad peak between $\delta$ 8 and 9 p.p.m. which integrates for two protons. The peak completely disappears when deuterium oxide is added to the sample. Bell \textit{et al.}\textsuperscript{118} have recorded the oxime proton at $\delta$ 9.80 p.p.m. and the amino protons at $\delta$ 5.18 p.p.m. for benzamidoxime. Both signals disappeared on addition of deuterium oxide. In the present compounds, the two protons probably have similar chemical shifts, since aromatic secondary amides have a broad peak, due to the amide hydrogen, near $\delta$ 8 p.p.m. The oxime and the NH protons are therefore not resolved.

Pearse and Pflaum\textsuperscript{121} have recorded the ultraviolet spectrum of benzamidoxime and found a maximum at 250 nm with an extinction coefficient of 5,400. The present compounds, with the exception of N-o-anisylbenzamidoxime (95 d), have a band between 260 and 270 nm with extinction coefficients of 5000-6000. In N-o-anisylbenzamidoxime (95 d) this band is found at 295 nm with an extinction coefficient of 6650. These bands are in similar positions but weaker than the bands found in the spectra of the corresponding amides. This result is expected if these amidoximes exist as the oxime rather than the
hydroxylamine tautomer.

Fig. 16

\[
\begin{align*}
\text{not} & \quad \text{OH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Partridge and Turner\textsuperscript{146} found that the treatment of amidoximes such as \(N_m\text{-tolylbenzamidoxime}\) with benzenesulphonyl chloride in aqueous base gave a carbodiimide which was hydrolysed to the corresponding urea. Garapon\textsuperscript{147} et al. found that \(N\text{-phenylbenzamidoxime (95(a))}\) when treated with phosphorus pentoxide or polyphosphoric acid gave a mixture of the corresponding carbodiimide and substituted urea. By analogy with the Beckmann rearrangement of oximes, these experiments suggest that the amidoximes of this type exist in the \textit{syn} configuration with respect to the carbon substituent i.e. Fig. 17

Fig. 17

\[
\begin{align*}
\text{OH} & \quad \text{OH}
\end{align*}
\]

The Spectra of the Hydroxyamidines.

The important bands in the infrared spectra of these compounds are tabulated in appendix 2. In nearly all the spectra of the free bases in solution, there is a weak band near 3650 cm\(^{-1}\) which
is attributed to the stretching mode of the free hydroxyl group. There are, generally, two broad, weak bands between 3400 cm$^{-1}$ and 3100 cm$^{-1}$ which are due to the various forms of association possible between the molecules. These are at lower frequencies in the compounds with one or more aliphatic substituents compared with those where all substituents are aromatic. This is probably because the latter are the weaker bases. When the spectra of the free bases are recorded in the solid state all these bands are shifted to lower frequencies as expected for intermolecular association modes. Most of the spectra recorded in chloroform have a broad weak band near 2450 cm$^{-1}$, which is absent in the solid state spectra. Similar bands in other compounds have been explained by the reaction of hydrogen chloride from the solvent chloroform with the bases.$^{148a}$

The hydrochlorides of these compounds have quite different spectra in this region. The free hydroxyl stretching frequency is again found near 3560 cm$^{-1}$ and, usually, two bands due to association are found between 3400 cm$^{-1}$ and 3100 cm$^{-1}$. These latter bands, however, are superimposed on a broad, weak absorption which extends over the range 3400-2300 cm$^{-1}$ and has a maximum near 2450 cm$^{-1}$. Witkop$^{148a,b}$ has found this absorption to be characteristic of the hydrochlorides of organic bases and he attributes it to the cation.

\[
\begin{align*}
\text{C} & \equiv \text{N}^+ \\
\text{H} 
\end{align*}
\]
The solution spectra of the free bases have a strong band between 1600 cm.⁻¹ and 1610 cm.⁻¹ which is attributed to the carbon-nitrogen double bond stretching mode. The partially aliphatic hydroxyamidines absorb at the high frequency end of this range and the aromatic ones at the low frequency end. These frequencies are consistently lower than those reported by Margerum for a series of similarly substituted benzylideneanilines (1624-1633 cm.⁻¹) and those recorded for the amidine (100) in the present work (1630 and 1640 cm.⁻¹) and must reflect the effect of the hydroxylamino substituent. Recording the spectra in the solid state shifts the absorptions an average of 20 cm.⁻¹ to higher frequencies.

The hydrochlorides all show a similar strong band in solution spectra in the range 1620-1640 cm.⁻¹. Witkop finds that this also is characteristic of hydrochlorides from organic bases. Recording the spectra in the solid state alters the frequency only slightly.

All the hydroxyamidine spectra recorded in the present work, with the exception of the nitro compounds, have one or more bands in the range 1300-1380 cm.⁻¹ which are attributed to the nitrogen-ring bonds. The compounds containing a nitro group have only one strong broad band in this region due to the symmetrical bond stretching mode of the nitro group and this may obscure the weaker nitrogen-ring absorption. All the spectra possess one or more bands in the range 900-1000 cm.⁻¹ which are absent in the spectrum of the
amidine (100). These bands are, therefore, attributed to the stretching mode of the nitrogen-oxygen bond. \[16\]

**N.M.R. Spectra of Hydroxyamidines.**

The signals due to the hydroxyl protons of the free bases occur as broad peaks at low field positions. The centre points of these peaks occur between \(\delta 8.0\) and \(\delta 9.5\) p.p.m. and this wide range is probably partly due to the errors in determining the true chemical shifts. Direct evidence for the site of the hydrochloride proton comes from the spectra of the \(N'\)-alkyl compounds (77(a-c)). The signals for the protons on the carbon atom joined to the \(N'\)-nitrogen atom are normal in the free bases but have greater multiplicity in the spectra of the hydrochlorides. This must be due to coupling with a proton on the \(N'\)-nitrogen atom which must therefore be the site of basicity in the molecule. The proton on this nitrogen atom must also have a slow rate of internal exchange with respect to the n.m.r. time scale. Further evidence for this is the occurrence of separate signals for the hydroxyl hydrogen and the \(N'\)-hydrogen in the spectra of these compounds and that of the \(N'\)-cyclohexyl (77 d) hydrochloride. This does not occur in the spectra of any of the other hydrochlorides where one broad peak occurs which integrates for two protons. The position of this peak is presumably an average of the true chemical shifts of the two protons involved.
Ultraviolet Spectra of Hydroxyamidines.

The ultraviolet spectral data are tabulated in appendix 3. The ultraviolet spectrum of \textit{N}-methylbenzimidoyl chloride (75a) is identical with the spectrum \textit{N}-benzylidene-methylamine (75b) and very similar to those of benzaldehyde and styrene.\textsuperscript{151}. The spectrum of \textit{N}-phenylbenzimidoyl chloride (98c) is however significantly different from that of benzylideneaniline \textsuperscript{151} (98a) in both the band positions and their intensities. The substituent on the α-carbon atom thus reduces the intensity of the longer wavelength peak and causes a blue shift in the shorter wavelength peak. Smith\textsuperscript{152} attributes a similar effect in α-methylbenzylideneaniline (98b) to steric interaction between the aniline ring and the methyl substituent.

The ultraviolet spectrum of benzylideneaniline (98a) is markedly different from those of both the \textit{cis} and \textit{trans} forms of the apparently analogous compounds stilbene and azobenzene.\textsuperscript{153, 158} The generally accepted explanation is that the benzylideneaniline molecule is non-planar, although Houlden\textsuperscript{157} claims to have accounted for the differences without this assumption.

An X-ray study\textsuperscript{158} has shown that the molecule has a \textit{trans} geometry with the aniline ring at an angle of 55°.
to the plane of the azomethine bridge. The carbon substituent ring is $10^\circ$ out of the plane in the opposite sense. The orbital containing the lone pair of electrons on the bridge nitrogen atom will be in the plane of the bridge. The tendency of these unshared electrons to conjugate with the aniline ring will thus cause this ring to twist out of the plane of the bridge.

This lack of planarity has been used as an explanation of the unexpectedly low intensity of the long wavelength band in the spectrum of benzylideneaniline compared with that of stilbene. 151-156 Brocklehurst 153 has suggested that the two main bands in the spectrum of benzylideneaniline are due to the benzal part (260nm) and to weak conjugation over the whole molecule. On the other hand El-Aasser et al. 151 believe that the molecule acts as two separate chromophores - the benzal part and the aniline part - and attribute the long wavelength absorption to a local excitation of the latter. The correct band assignments are thus still uncertain.

The spectra of the fully aromatic hydroxyamidines in the present work have two bands in positions similar to those of benzylideneaniline (98a). The long wavelength band near 315 nm is similar in intensity to the
corresponding band of benzylideneaniline (98a) but the short wavelength band near 260 nm is much less intense.

The 260 nm band in benzylideneaniline is thought to be a charge transfer transition where the carbon substituent ring donates electrons to the azomethine bridge. In the hydroxyamidines, the carbon atom of the bridge now has the $\text{N-}$phenylhydroxylamine group attached. This substituent could give rise to two effects. It may withdraw electrons from the azomethine bridge and it may by virtue of its size force the carbon substituent ring further out of the plane of the bridge. Both these effects would be expected to lower the intensity of the band at 260 nm. Thus the fully aromatic hydroxyamidines are expected to be similar in configuration and conformation to benzylideneaniline i.e. a trans geometry about the double bond with both the attached rings being twisted out of the bond plane.

If the longer wavelength band in the hydroxyamidine spectra is due to limited conjugation of both end rings with the bridge, then protonation of the bridge nitrogen atom should localise the lone pair of electrons and enable greater conjugation to take place, thus enhancing the intensity of this band. Addition of acid to the sample
however causes the disappearance of the band, leaving the 260 nm band virtually unaffected. This supports the assignment of the 315 nm band to a local excitation involving the aniline end of the molecule since a similar effect is noted in aniline itself. This explanation implies that protonation of the nitrogen still does not restore planarity to the system. This may well be because the _N_-phenylhydroxylamine substituent is too bulky to permit a planar geometry of the bridge and the two end rings.

The effects of substituents directly attached to the benzene rings at each end of the bridge are too irregular to allow any general trends to be discerned. An ortho or para nitro substituent gives rise to an expected weak band near 370 nm, accounting for the colours of these compounds.

Compounds with an aliphatic substituent at the nitrogen end of the azomethine bridge (77a–e) have only a single band in the spectrum, _λ_ max. 300 nm, with an extinction coefficient of ca. 6000. This band is at too long a wavelength to be due to the benzal end of the molecule. Addition of acid causes the band at 301 nm in _N_-hydroxy- _N_-phenyl- _N'_'-methylbenzamidine (77a) to shift to 260 nm, the position expected for the benzal chromophore alone. The band near 300 nm in these compounds is
tentatively explained as being due to an entirely different chromophore (Fig. 18).

\[
\text{Fig. 18}
\]

These compounds (77a–e) are likely to be stronger bases than the fully aromatic hydroxyamidines and the stabilisation afforded by hydrogen bonding may be sufficient to stabilise the cis form with respect to the trans isomer.

**2-Hydroxylaminopyridine**

This compound is formally a hydroxyamidine (Fig. 19)

\[
\text{Fig. 19}
\]

and it was of interest to compare it with the previous hydroxyamidines. The compound was prepared from 2-aminopyridine by oxidation to 2-nitropyridine followed by controlled hydrogenation to 2-hydroxylaminopyridine. The
compound is very unstable, decomposing in a matter of days, but stable for several months in the absence of air.

The infrared spectrum (appendix 2) is very similar to those of the amidoximes and hydroxyamidines but shows greater association. The ultraviolet spectrum (appendix 3) is very similar to that of \( N \)-phenylhydroxylamine, but much more intense as would be expected for a pyridine derivative. The similarity of the spectra shows that 2-hydroxylaminopyridine must exist as tautomer (a) and not (b) (Fig. 20).

![Fig. 20](image)

The n.m.r. spectrum has a broad singlet at \( \delta 8.67 \) p.p.m. which integrates for two protons and which vanishes when deuterium oxide is added to the sample. This peak is attributed to the \( NH \) and \( OH \) protons. Its downfield position with respect to that of \( N \)-phenylhydroxylamine (\( \delta 6.73 \) p.p.m.) reflects the electron withdrawal power of the ring nitrogen atom. The remainder of the n.m.r. spectrum is very similar to those of other 2-pyridyl compounds.
Tests with Metal Ions.

All the amidoximes and hydroxamidines made in the present work have been tested with a series of metal ion solutions for signs of chelation. A series of solutions of metal salts (0.5%) were made up in aqueous ethanol and added to aqueous ethanolic solutions (0.5%) of the compounds. Any changes were noted. The results are tabulated in appendix 4. It can be seen that the colour change is dependent on the metal alone and that the colours which develop are similar to those noted by Ley. Precipitates were generally obtained with the metals mercury (II), copper, nickel, cobalt and iron (II). A deep blue colour always occurred with iron (III) but no precipitate was obtained. Faint colour changes were noted for cadmium and manganese. Lead and zinc, in general, gave no colour change or precipitate.

The amidoximes prepared in the present work only gave a definite colour change with solutions of iron (II), and (III), and copper. In only two cases (both with copper) were coloured precipitates obtained. Addition of base to the solutions precipitated the metal hydroxides. Thus under the above conditions only N-phenylbenzamidoxime (95a) and N-p-tolylbenzamidoxime (95b) appear to form metal chelate compounds and these only with copper.

A colour change was obtained with 2-hydroxylamino—
pyridine with all the metals except lead. The colours were not taken up into chloroform solution, implying the formation of a charged complex. Addition of base to the aqueous solutions precipitated the metals as their hydroxides. Thus 2-hydroxylaminopyridine does not appear to form stable metal chelates under the above conditions.

Metal Chelates of Hydroxyamidines.

Ley prepared metal chelates of several hydroxyamidines. He found that there were two ligand molecules bound to each metal atom and that the colours were characteristic of the metal atom. Thus iron gave typically blue, copper red-brown, nickel green, manganese green, cobalt red-brown and mercury dark yellow colours with the various ligands. The chelates of $N$-hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a) $N$-hydroxy-$N$-phenyl-$N'$-1-naphthyl-benzamidine (78b) and $N$-hydroxy-$N$-phenyl-$N'$-mesityl-benzamidine (94c) with the metals iron, copper, nickel, palladium, cobalt and manganese have previously been prepared and characterised in this department. They are all found to have two ligand molecules per metal atom.

In the present work several of the metal derivatives have been re-prepared and their infrared spectra recorded (appendix 2).

The copper and nickel chelates of $N$-hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a) and the nickel chelate of
N-hydroxy-N-phenyl-N'-1-naphthyl-benzamidine (78b) were prepared by carefully neutralising a solution of the metal salt and the hydroxyamidine hydrochloride. The precipitated chelates were crystallised from chloroform or benzene. The chelates are sparingly soluble in chloroform, alcohol and benzene and insoluble in the other common organic solvents.

The infrared spectra of the chelates in the solid state are little different from the spectra of the free ligands except that there is now no strong band near 1600 cm\(^{-1}\) but a strong band near 1510 cm\(^{-1}\). This new band is probably still due to the carbon-nitrogen double bond, modified now by its participation in the chelate ring.

The geometry about the carbon-nitrogen double bond for the fully aromatic hydroxyamidines is expected to be trans from a consideration of the similarity of their ultraviolet spectra with that of benzylideneaniline (see p.70). If the configuration is rigidly trans, the molecule cannot chelate because the two donor sites i.e. the hydroxylamine oxygen atom and the orbital of the lone pair electrons of the bridge nitrogen atom are on opposite sides of the double bond (Fig.21a). To make chelation possible therefore, there must be a rotation about the double bond of the ligand to give a cis arrangement of the donor sites (Fig. 21b).
The ultraviolet spectra of chloroform solutions of the two nickel chelates (appendix 3) support this conclusion. The spectra of the chelated ligands are different from those of the free ligands below 350 nm. Above 350 nm each spectrum has a band due to chelate formation. The spectrum of the copper chelate is also different but here the difference is not as clear because the band due to chelate formation is at 340 nm and is very intense thus partially masking the absorption due to the ligand. Addition of acid to each of the three chelates causes the spectrum to become like that of the free ligand in acid solution. The chelates therefore decompose in the face of strong competition by protons for the donor sites.

Models show that two hydroxyamidine ligands can be accommodated in a square planar or tetrahedral geometry about a metal atom but that the central site is far too crowded to admit a third such ligand. Iron (III) does not give a precipitate with the various ligands. If only two ligands
can be accommodated about the metal atom which normally has a coordination number of six, a charged complex may result which might be soluble in aqueous medium.

The suggested structure for the nickel complex of \( \text{N-hydroxy-N-phenyl-N'-phenylbenzamidine} \) (78a) is (Fig. 22).—

Fig. 22
2-Aminoquinoline-1-oxides.

In Pschorr's classical phenanthrene synthesis\textsuperscript{162} the first step is the formation of $\alpha$-phenyl-$\alpha$-nitrocinnamic acid (101) from the condensation of $\alpha$-nitrobenzaldehyde with sodium phenylacetate. This is then reduced with tin and hydrochloric acid and the resulting amine diazotised. Decomposition of the diazonium compound with copper powder gives phenanthrene-$\alpha$-carboxylic acid (102). The condensation step does not give high yields and Pschorr turned to the condensation of $\alpha$-nitrobenzaldehyde with benzyl cyanide which gives a high yield of $\alpha$-phenyl-$\alpha$-nitrocinnamonic acid (106). Reduction of this with tin and hydrochloric acid gave not the required amine but 2-amino-3-phenylquinoline\textsuperscript{163} (107).

Dingley\textsuperscript{164} considered that the condensation gave the cinnamonic acid in the cis configuration (Fig. 23) and that strong acid converted it to the trans isomer (Fig. 23) thus facilitating the formation of the quinoline. In an effort to avoid this he used mild alkaline conditions. Reduction of the cinnamonic acid with sodium sulphide however, gave a high yield of an oxygenated product.
which he formulated as.

Odell,\textsuperscript{165} showed that Dingley's product was, in fact, identical with that obtained by Bauer\textsuperscript{166} from the catalytic reduction of the cinnamonic acid. Bauer could not distinguish between the two possible tautomers of his compound (Fig. 24).

Seelye is reported\textsuperscript{167} to have prepared a metal chelate of the compound which was used as evidence in support of the hydroxy-imino (Fig. 24(b)) form since it was thought that the N-oxide-amino form (Fig. 24(a)) would not chelate. This need not be so (see later).

Although there are no previous reports on the tautomerism of the 2-aminoquinoline-1-oxide (Fig. 24), the preferred tautomer in the analogous 2-aminopyridine-1-oxide compounds has been the subject of controversy.\textsuperscript{168} Katritzky has shown beyond doubt that in this case
the preferred tautomer by a factor of at least $10^8$ is the amine-oxyde form (Fig. 25(a)).

![Fig. 25](image)

The reactions of 2-aminopyridine-1-oxide are not those expected for a hydroxyamidine. Alkylation and acylation take place on the nitrogen atom. Katritzky\textsuperscript{169} has also shown that oxidation of the acyl and alkyl derivatives of 2-aminopyridine gives products identical with those from acylation and alkylation of 2-aminopyridine-1-oxide.

For this reason the preferred tautomer in the equivalent quinoline compounds should be the 1-oxide form (Fig. 24(a)). There are several reports of the reduction of α-nitro substituted compounds to heteroaromatic 2-amino-1-oxides. Heller and Wunderlich\textsuperscript{170} prepared 2-aminquinoline-1-oxide-3-carboxylic acid (112) by reducing α-cyano-α-nitrocinnamic (103) acid with zinc and acetic acid. Hansen and Petrow\textsuperscript{171} prepared 10-aminodiazaphenanthrene-9-oxides (104) by the reduction of suitable nitro compounds with zinc and ethanol. The examples prepared by Bauer\textsuperscript{166} have already been mentioned and those of Lund and Feoktistov\textsuperscript{172} will be mentioned later.
In many cases, it appears that the 2-amino-1-oxide compound was formed but was further reduced to the 2-amino compound.\textsuperscript{173-176}

The use of sulphides for the reduction of nitro groups is well known and one method for the synthesis of phenylhydroxylamine involves the reduction of nitrobenzene with sodium sulphide.\textsuperscript{144} Coutts\textsuperscript{175} used sodium dithionite for reductive cyclisations of nitro groups and Friedlander\textsuperscript{177} used alcoholic ammonium sulphide to reduce ethyl-\textsubscript{o}-nitrocinnamate to N-hydroxyquinolone (105). Dingley's use of sodium sulphide\textsuperscript{164} for reductive cyclisation, seems to remain an isolated case.

In view of the present work on hydroxyamidines and the chelation hypothesis, it seemed worthwhile to investigate the scope of the sodium sulphide reduction and the production of new chelating agents.

The Present Investigation

Vanillin (114) was first acetylated and this was then nitrated following Butenandt's method.\textsuperscript{178} Hydrolysis of the acetyl derivative gave an overall yield of 60% of 2-nitrovanillin (115). Nitration of 2,3-dimethoxybenzaldehyde (118) according to Perkin and Robinson's procedure\textsuperscript{179} gave a mixture of the 5- and 6-nitro isomers as found by the previous authors, which could not be separated by crystallisation but which were separated by column chromatography in poor yield.
Frost's procedure was followed for the condensation of o-nitrobenzaldehyde with benzyl cyanide to give α-phenyl-o-nitrocinnamonicnitrile (106). When applied to 2-nitrovanillin (115), at least one mole of sodium ethoxide per mole of 2-nitrovanillin was necessary for a good yield of α-phenyl-4-hydroxy-3-methoxy-2-nitrocinnamonitrile (117). Presumably the first mole of base reacts with the phenol group since this is more acidic than the methylene group of benzyl cyanide. Benzyl cyanide was also condensed with o-nitrobenzaldehyde using a few drops of potassium hydroxide solution as catalyst but the yield was only 20%. Both the 5- and 6-nitro derivatives of 2,3-dimethoxybenzaldehyde were condensed with benzyl cyanide in high yield with aqueous base as a catalyst to give α-phenyl-2,3-dimethoxy-5 (and-6)-nitrocinnamonicnitrile (123,124). Ethyl cyanoacetate could be condensed with o-nitrobenzaldehyde to give ethyl-α-cyano-o-nitrocinnamate (109) with 2-nitrovanillin to give ethyl-α-cyano-4-hydroxy-3-methoxy-2-nitrocinnamate (116) and with the 5- and 6-nitro isomers of 2,3-dimethoxybenzaldehyde to give ethyl-α-cyano-2,3-dimethoxy-5 (and-6)-nitrocinnamate (121,122) all in high yield, using aqueous base or piperidine as a catalyst.

Perkin and Robinson were able to separate the 5- and 6-nitro isomers of 2,3-dimethoxybenzaldehyde (119, 120) by first forming the respective benzylidene derivatives with p-toluidine. They found that the 6-nitro derivative was the more soluble in ethanol and was separable by careful fractional crystallisation. In the present work, the condensation products of ethyl cyanoacetate and benzyl cyanide
with the 6-nitro isomer were more soluble in ethanol than the corresponding 5-nitro products. By condensing the compounds in large volumes of ethanol, most of the 5-nitro product precipitated. The reaction mixture was then neutralised and concentrated. Fractional crystallisation from ethanol effected reasonable separation of the required 6-nitro product. The content of each crop of crystals was best estimated from the integrals of the signals for the prominent aromatic doublets in the n.m.r. spectrum.

The composition of the crude product from the nitration of 2,3-dimethoxybenzaldehyde was found to be a 1:1 ratio of the 5- and 6-nitro isomers by the same technique. Perkin and Robinson\textsuperscript{181} obtained approximately the same ratio.

The Stereochemistry of the Condensation Products.

Zabicky\textsuperscript{182} studied the stereochemistry of the products of carbonyl-methylene condensations (Fig. 26).

\[ Z\cdot C_6H_4\cdot CHO + X\cdot CH_2\cdot Y \rightarrow Z\cdot C_6H_4\cdot CH\equiv C\cdot Y \]

\[ X or Y = -CN, -CO_2Et, -CO\cdot NH_2. \]

\[ Z = m\text{-NO}_2, -O\cdot CH_3, X^- \]

From a consideration of the positions of the infrared absorption bands due to the nitrile and carbonyl groups, he concluded that the \underline{trans} configuration is the preferred one for compounds where \( X = C\equiv N \) and \( Y = CO_2CH_2CH_3 \). In this case, the nitrile group and the benzene
ring are cis to each other and the whole molecule is planar and in full conjugation. (Fig. 27).

Fig. 27

In compounds where Y is a benzene ring, the trans configuration may also be expected, since there would be much less steric pressure than if the two benzene rings were in the cis relationship. The trans compounds will also be planar and fully conjugated. Lohaus has found that a mixture of the cis and trans isomers of ethyl-α-cyano-cinnamate is spontaneously converted to one of the isomers which Zabicky later showed to be the trans isomer.

The analogous compounds in the present work i.e. those where X is a nitrile group and Y is a benzene ring or a carbethoxy group, with two exceptions have a nitro group in a position ortho to the side chain. Models show that this effectively blocks free rotation about the bond joining the side-chain to the ring and further, the large sizes and electronegativities of the nitrile and nitro groups will cause them to be remote from each other. Thus for compounds (106, 109, 116, 117) the situation will be as in Fig. 28.

Fig 28

\[ Y = -\emptyset \text{ or } -\text{CO}_2\text{Et} \]
The mechanism of carbonyl-methylene condensations has been investigated by Patai et al.\textsuperscript{184} They find that the reactions bear the characteristics of a dissociation governed reaction. Thus they propose the first step as an ionic dissociation of the active methylene compound. This is consistent with their observation of partial or complete retardation of the condensation by the addition of acid. The reaction is then envisaged as proceeding by attack of the resulting carbonion on the carbon of the carbonyl group followed by protonation and elimination of an hydroxide ion (Scheme 8).

Scheme 8

\[
\begin{align*}
\text{Ph-C} & \quad \xrightleftharpoons{\text{CH(CN)CO}_2\text{Et}} \quad \text{Ph-CH-C} \\
& \quad \text{H}^+ \quad \text{Ph-CH-C} \\
& \quad \text{Ph-CH=C} \\
& \quad +\text{H}^+ \quad \text{Ph-CH=C} \\
& \quad +\text{OH}^\text{-} \quad \text{Ph-CH=C}
\end{align*}
\]

The requirement for more than one mole of sodium ethoxide in the condensation of benzyl cyanide with 2-nitrovanillin probably arises from the retardation of the condensation caused by the acidic phenolic group.
This is supported by the large deshielding of the C₆ proton in the n.m.r. spectra of these compounds (Table 5, p. 90).

In compounds where the side-chain is attached between the nitro group and a methoxyl group (122, 124), the situation is even more crowded. It is thus unlikely that the side chain double bond can be coplanar with the ring. The nitrile group is still expected to be as far away from the nitro group as possible. In the case of the 5-nitro derivatives (121, 123), free rotation about the bond joining the ring to the side-chain is possible and the ring and the side-chain can be coplanar and in conjugation. These conclusions are supported by the large differences in the ultraviolet spectra (Table 4) of the isomers.

Thus in α-phenyl-α-nitrocinnamoniitrile (106) which was reduced by Pschorr,¹⁶² Bauer,¹⁶⁶ and Dingley,¹⁶⁴ the ring bearing the nitro group, and the nitrile group are cis to each other and the nitro and nitrile groups are remote from each other.
### TABLE 4

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$\lambda_{\text{max}}$ (EtOH) nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>106</td>
<td>273 ($\varepsilon$ 10,300)</td>
</tr>
<tr>
<td>109</td>
<td>253($\varepsilon$9,200) 273(infl.) (7,200) 303(infl.) ($\varepsilon$4,600)</td>
</tr>
<tr>
<td>117</td>
<td>239($\varepsilon$11,700)</td>
</tr>
<tr>
<td>116</td>
<td>246($\varepsilon$ 8,700)</td>
</tr>
<tr>
<td>124</td>
<td>281($\varepsilon$ 13,300)</td>
</tr>
<tr>
<td>123</td>
<td>312($\varepsilon$ 21,400)</td>
</tr>
<tr>
<td>122</td>
<td>236($\varepsilon$ 12,700) 264($\varepsilon$ 10,000) 325($\varepsilon$7,160)</td>
</tr>
<tr>
<td>121</td>
<td>299($\varepsilon$ 14,200)</td>
</tr>
</tbody>
</table>

For diagrams of these compounds see p. 90–91.
Stereospecificity, i.e., the production of the trans isomer is explained by the preferred configuration of the second carbanion (Fig. 29).

![Fig. 29](image)

For the OH group to separate and the double bond to form from the free electron pair the groups X and Y must be in staggered conformation between the aromatic ring and the hydroxyl group and between the hydroxyl group and the hydrogen. The most stable conformation would be that where the smaller of the two groups X and Y is staggered between the ring and the hydroxyl group. In the present work this would give trans products i.e. those with the nitrile group cis to the aromatic ring.

**N.M.R. Spectra of the Condensation Products.**

The assignment of protons in the nitrated aldehydes (Table 5) was made using the table of shifts caused by substituents given by Mathieson. Application of these values to the positions of attachment of the methoxyl groups predicts that the C₂ methoxyl group in both the dimethoxyaldehydes and their derivatives will be the most deshielded.
<table>
<thead>
<tr>
<th>Compound</th>
<th>δ C&lt;sub&gt;3&lt;/sub&gt;·OMe</th>
<th>δ C&lt;sub&gt;2&lt;/sub&gt;·OMe</th>
<th>δ C&lt;sub&gt;4&lt;/sub&gt;·H</th>
<th>δ C&lt;sub&gt;5&lt;/sub&gt;·H</th>
<th>δ C&lt;sub&gt;6&lt;/sub&gt;·H</th>
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</thead>
<tbody>
<tr>
<td>(106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.22 p.p.m.</td>
</tr>
<tr>
<td>(109)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.25</td>
</tr>
<tr>
<td>(115)</td>
<td>3.99 p.p.m.</td>
<td></td>
<td></td>
<td></td>
<td>7.21 p.p.m.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.67</td>
</tr>
<tr>
<td>(117)</td>
<td>4.12</td>
<td></td>
<td></td>
<td></td>
<td>7.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.10</td>
</tr>
<tr>
<td>(116)</td>
<td>3.87</td>
<td></td>
<td></td>
<td></td>
<td>7.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.08</td>
</tr>
<tr>
<td>(123)</td>
<td>3.98</td>
<td>4.03 p.p.m.</td>
<td>7.84 p.p.m.</td>
<td></td>
<td>8.61</td>
</tr>
<tr>
<td>(119)</td>
<td>4.04</td>
<td>4.17</td>
<td>7.95</td>
<td></td>
<td>8.24</td>
</tr>
<tr>
<td>(121)</td>
<td>4.02</td>
<td>4.08</td>
<td>7.94</td>
<td></td>
<td>8.72</td>
</tr>
</tbody>
</table>
The side chains have little effect on the positions of the proton signals in the n.m.r. spectra for protons meta or para to them (Table 5). The electron withdrawing power of the side chains must therefore roughly parallel that of the aldehyde group. There is a large deshielding effect on the C₆ protons of compounds 106, 109, 116, 117, 121 and 123, compared with the C₆ protons in the respective aldehydes (Table 5). Such an effect would be expected if the substituted aromatic ring and the nitrile group are cis to each other and with the nitrile group close to the C₆ proton in each case, thus deshielding it. The deshielding is especially strong in the 5-nitro derivatives because of the adjacent nitro group. In contrast, in the
6-nitro derivatives (122, 124) where the side chains are not adjacent to an aromatic proton, these protons are little shifted from their positions in the aldehyde.

**Reduction with Sodium Sulphide.**

The reduction of α-phenyl-α-nitrocinnamonic acid (106) with sodium sulphide in a dioxan-ethanol mixture following Dingley's method\(^1\) gave 89% of 2-amino-3-phenylquinoline-1-oxide (107).

Admixture with a sample prepared by Odell\(^2\) caused no depression in the melting point. Further reduction with iron powder in acetic acid according to Bauer's procedure\(^3\) gave 2-amino-3-phenylquinoline (108) in low yield. Phosphorus trichloride in chloroform\(^4\) gave an 86% yield while zinc in acetic acid gave a quantitative yield.

Direct reduction of α-phenyl-α-nitrocinnamonic acid (106) with zinc dust in refluxing acetic acid also gave a high yield of the aminoquinoline. Reduction with zinc at progressively lower temperatures gave decreasing yields of the aminoquinoline and increasing yields of the aminoquinoline-1-oxide.

The sodium sulphide reduction of ethyl-α-cyano-α-nitrocinnamate (109) gave a mixture of products from which 2-amino-3-carbethoxyquinoline-1-oxide (110) and 2-amino-3-carbethoxyquinoline (111) could be isolated by preparative t.l.c. in low yield. Repeating the reduction at lower temperatures gave similar results. Bauer\(^5\) obtained the same products by catalytic reduction of ethyl-α-cyano-α-nitrocinnamate (109).
Reduction of 2-amino-3-carbethoxyquinoline-1-oxide (110) with zinc dust in refluxing acetic acid gave a high yield of the aminquinoline (111). Direct reduction of ethyl-α-cyano-α-nitrocinnamate (109) with zinc dust in refluxing acetic acid gave a high yield of 2-amino-3-carbethoxyquinoline (111). Reduction at 80° gave a 30% yield of both the 1-oxide (110) and the aminquinoline (111) and reduction at 20° gave only a 10% yield of the 1-oxide (110).

Reduction of the other α-nitrocinnammonitriles (117, 124) and ethyl-α-cyanonitrocinnamates (116, 122) with both sodium sulphide and zinc and acetic acid was unsuccessful. After reaction for 21 hr., considerable amounts of starting material were present in each case. T.l.c. of the total reaction mixture in each case showed the presence of two components visible in ultraviolet light which could represent the desired 1-oxide and aminquinoline products but these are present in small amounts. At least four other components were present in each case. Reduction with zinc in refluxing acetic acid of the compounds (116, 117, 122, 124) was continued until t.l.c. showed the absence of starting material. The chromatograms were similar to those for the sodium sulphide reductions in each case. The same two spots were visible in ultraviolet light but the total reaction mixtures now contained an additional four components which have no counterparts in the chromatograms of the sodium sulphide reduction mixtures.
Ethanolic potassium hydroxide converted both 2-amino-3-carbethoxyquinoline-1-oxide (110) and 2-amino-3-carbethoxyquinoline (111) into the free acids (112, 113) as reported by Bauer and Taylor.

The Spectra of the Reduction Products.

The n.m.r. spectra of the aminquinoline-1-oxides and aminquinolines are consistent with structure (Table 6).

Table 6

<table>
<thead>
<tr>
<th></th>
<th>δ NH₂ p.p.m.</th>
<th>δ C₆H p.p.m.</th>
<th>δ C₄H p.p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(108)</td>
<td>5.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(107)</td>
<td>6.64</td>
<td>8.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>J₇,₈ = 9 Hz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(111)</td>
<td>6.76</td>
<td></td>
<td>8.65</td>
</tr>
<tr>
<td>(110)</td>
<td>ca. 7.6</td>
<td>8.52</td>
<td>8.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>J₇,₈ = 8.5 Hz</td>
<td></td>
</tr>
</tbody>
</table>
The signal for the amino protons in the spectrum of 2-aminoo-3-carbethoxyquinoline-1-oxide (110) is obscured by the aromatic signals but the change in the spectrum on adding deuterium oxide to the sample indicates it to be at ca. δ 7.6 p.p.m. In both the 1-oxide spectra there is a prominent, low field, one proton doublet with somewhat irregular arms. This is attributed in each case to the C₉ proton with the splitting caused by coupling to the C₇ proton and the irregularity caused by further coupling to the C₆ proton. The low field position of this doublet is due to the powerful deshielding influence of the 1-oxide oxygen atom. An extra feature in the spectra of both the carbethoxyquinoline compounds is a singlet at low field values. This singlet is attributed to the C₄ proton in each case. The low field position is due to deshielding by the adjacent carbethoxy group. The lesser degree of deshielding experienced by the C₄ proton in 2-aminoo-3-carbethoxyquinoline-1-oxide (110) is a reflection of the electron donation by the oxygen atom to the C₄ position.

The infrared spectra of the aminoquinoline-1-oxides and the aminoquinolines are tabulated in Table 7. The asymmetric and symmetric stretching frequencies of the amino group in 2-aminoo-3-phenylquinoline-1-oxide (107) are similar to those of 2-aminopyridine-1-oxide. Application of Bellamy's empirical relationship predicts a value of 3414 cm⁻¹ for the symmetric stretching band of the amino group in 2-aminoo-3-phenylquinoline-1-oxide. The difference between this and the actual value indicates strong asymmetric hydrogen bonding
between the amino group and the 1-oxide function. In contrast the predicted value for 2-amino-3-phenylquinoline (108) of 3425 cm$^{-1}$ is much closer to the actual value. For 2-amino-3-carbethoxyquinoline-1-oxide (110) the predicted value of 3365 cm$^{-1}$ for the symmetric stretching mode of the amino group is also much closer to the actual value. Strong hydrogen bonding must still occur but it is now more symmetric. Apart from hydrogen bonding to the 1-oxide function, the amino group appears to be hydrogen bonding to the carbonyl group of the side-chain. The lowered position of the asymmetric mode supports this idea, as does a comparison of the predicted symmetric stretching frequency for 2-amino-3-carbethoxyquinoline (111) of 3419 cm$^{-1}$ with the actual value.

The solid state spectra of both the 1-oxides show a general lowering of the frequency of bands due to the amino group and the appearance of new bands due to intermolecular association. The solid state spectra of the acids derived from the carbethoxy compounds have a series of bands between 3400 and 1900 cm$^{-1}$ typical of zwitter ion species. 136

A broad peak is always present near 1630 cm$^{-1}$ in the spectra of all the above compounds. This band is presumably due to carbon-carbon and carbon-nitrogen double bond stretching modes and to the amino group bending mode but specific assignment is not possible.
<table>
<thead>
<tr>
<th>Compound</th>
<th>NH cm.(^{-1})</th>
<th>C=N, C=C cm.(^{-1})</th>
<th>N-O cm.(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl(_3)</td>
<td>3503</td>
<td>3345</td>
<td>1627</td>
</tr>
<tr>
<td>107</td>
<td>3360, 3250, 3200</td>
<td></td>
<td>1623</td>
</tr>
<tr>
<td>KBr</td>
<td>2935</td>
<td></td>
<td>1155</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>3463</td>
<td>3335</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>3450, 3390, 3320</td>
<td>1630</td>
<td></td>
</tr>
<tr>
<td>KBr</td>
<td>3410, 3270, 2920</td>
<td>1642</td>
<td>1620</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>3505</td>
<td>3402</td>
<td>1625</td>
</tr>
<tr>
<td>108</td>
<td>3460, 330, 3120</td>
<td></td>
<td>1627</td>
</tr>
<tr>
<td>KBr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>3500</td>
<td>3380</td>
<td>1612</td>
</tr>
<tr>
<td>111</td>
<td>3420, 3280, 3120</td>
<td>1628</td>
<td></td>
</tr>
<tr>
<td>KBr</td>
<td>3440, 3245, 2930</td>
<td>1630</td>
<td></td>
</tr>
<tr>
<td>113</td>
<td>2740, 2600-2440</td>
<td>1940</td>
<td></td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>3500</td>
<td>3360</td>
<td>1640</td>
</tr>
<tr>
<td>2-Aminopyridine-1-oxide</td>
<td>3400, 2800, 3250</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2940</td>
</tr>
</tbody>
</table>

ref: 168 Nujol
The aromatic N-oxide group usually has a strong absorption at 1200-1300 cm\(^{-1}\).\(^{190,191}\) An amino substituent nearby lowers the frequency, as does strong hydrogen bonding. An electron donating substituent on the ring lowers the frequency by favouring the tautomeric form (a) over (b) (Fig. 30).

![Fig. 30](https://example.com/image.png)

Thus in 2-amino-3-phenylquinoline-1-oxide a prominent band at 1163 cm\(^{-1}\) is assigned to the N-O stretching mode. In the carbethoxy and the acid analogues, the assignment is uncertain because there are no prominent bands in the 1150-1300 cm\(^{-1}\) region unique to the 1-oxides. The carbethoxy and the acid substituents are both electron withdrawing and should raise the N-O frequency somewhat by favouring tautomer (Fig. 30(b)).\(^{190}\)

The ultraviolet spectra of the aminoquinoline-1-oxides and the aminoquinolines are tabulated in Table 8. The spectra of the aminoquinolines are comparable with the spectrum of 2-aminoquinoline\(^{192}\) with the longer wavelength peaks having been shifted to the red. The 1-oxide function in each case causes a further red shift and a great
intensification of the peaks between 250 and 265 nm. This is expected by analogy with the difference found in the spectra of pyridine and pyridine-N-oxide.

Addition of base to the samples has a negligible effect on the spectra but the spectra of the acidified aminoquinolines are nearly identical with those of the corresponding 1-oxide compounds when acidified. It is likely that the 1-oxides are protonated at the oxygen atom since it has been shown that this is the case with 2-aminopyridine-1-oxide.\textsuperscript{168} Steck and Ewing\textsuperscript{192} have shown that aminoquinolines are protonated at the ring nitrogen atom. These protonated forms (Fig. 31)

![Fig. 31](image)

which both involve a quaternary nitrogen atom would be expected to have similar ultraviolet spectra. The influence of the electron donation of the 1-oxide group has been effectively removed and the hydrogen bonding will be very reduced.
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>$\lambda_{max.}$ (EtOH) nm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>253 (ε 50,000)</td>
<td>304 (ε 5,170)</td>
</tr>
<tr>
<td>252 +H⁺</td>
<td>248</td>
</tr>
<tr>
<td>241 (ε 22,000)</td>
<td>279 (η infl.) (ε 3,650)</td>
</tr>
<tr>
<td>264 (ε 52,200)</td>
<td>307 (ε 4,650)</td>
</tr>
<tr>
<td>253 (ε 43,000)</td>
<td>292 (ε 4,300)</td>
</tr>
<tr>
<td>245 +H⁺</td>
<td>254 (η infl.)</td>
</tr>
<tr>
<td>264 (ε 36,700)</td>
<td>308 (ε 3,700)</td>
</tr>
<tr>
<td>245 +H⁺</td>
<td>256</td>
</tr>
<tr>
<td>245 (ε 12,400)</td>
<td>293 (ε 3,000)</td>
</tr>
<tr>
<td>13 +H⁺</td>
<td>244</td>
</tr>
<tr>
<td>230 (η infl.) (ε 16,000)</td>
<td>315 (ε 5,000)</td>
</tr>
<tr>
<td>240 (η infl.) (ε 6,500)</td>
<td></td>
</tr>
<tr>
<td>192 +H⁺</td>
<td>230</td>
</tr>
<tr>
<td>227 (ε 25,000)</td>
<td>231</td>
</tr>
<tr>
<td>169 +H⁺</td>
<td>231</td>
</tr>
</tbody>
</table>
The Mechanism of the Reduction

Taylor and Bartulin\textsuperscript{193} have shown that anthranil reacts with a variety of active methylene compounds to give substituted quinoline-1-oxides in high yield (Scheme 9). Hydroxylamines are suggested as intermediates in an intramolecular addition reaction.

Scheme 9

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{X} \\
\text{C} & \quad \text{C=N} \\
\text{OH} & \quad \text{CH} \\
\text{CHO} & \quad \text{NH} \\
\text{NHOH} & \quad \text{X} \\
\end{align*}
\]

\[\begin{align*}
\text{X} &= \text{-CN; -CONH}_2; \text{-SO}_2 \text{O}
\end{align*}\]

Lund and Peokistov\textsuperscript{172} have studied the controlled potential reduction of some ortho-substituted nitro compounds in hydrochloric acid solution to give the 1-oxides of substituted quinolines. They conclude from polarographic measurements that there is a four electron reduction of the nitro group which corresponds to the formation of a hydroxylamine group. The final product is then formed by an intramolecular addition of the hydroxylamine to an atom of the ortho side-chain. Thus the
reduction of ethyl α-cyano-α-nitrocinnamate (109) in hydrochloric acid was formulated as Scheme 10.

Scheme 10

The reduction of the nitro group to a hydroxylamine group as an intermediate step in the cyclisations of α-nitro substituted compounds is postulated for many other examples which have been reviewed by Loudon and Tennant.\(^\text{194}\) Cyclic products are often obtained, apparently without any reducing species present, merely by the action of warm aqueous base. With the exception of a report by Loudon and Tennant,\(^\text{195}\) however, the formation of 2-aminoquinoline-1-oxides seems to require reduction of the nitro group for cyclisation to take place.

The reduction of aromatic nitro groups is still the subject of much controversy. In general, stopping a reduction at the hydroxylamine stage is difficult and yields are usually far from quantitative. In the case of α-phenyl-α-nitrocinnamomitrile (106) sodium sulphide seems an ideal reductant, giving a yield of 89% of the cyclised product. The correlation of ease of reduction, with the electronic effects of any substituents near the nitro group is virtually impossible on the basis of normal ideas. The nitro group seems to be able to exert an effect through space\(^\text{194}\) and thus the precise spatial
orientation of the neighbouring groups is important. The environment of the nitro group in each of the compounds for which a reductive cyclisation was attempted is very different and a special reagent or set of conditions may be needed for each compound. When the nitro group has been reduced, the steric and electrostatic restrictions responsible for the nitro and nitrile groups being remote are considerably altered and a different conformer may be possible in which the reduced nitro group and the nitrile group can approach each other.

Thus although the reduction of $\alpha$-phenyl-$\alpha$-nitrocinnamnonitrile (106) with sodium sulphide gives an excellent yield of the aminquinoline-1-oxide (107) it appears to be specific for this compound and does not extend to other related compounds. Zinc in acetic acid also does not seem to be a general reagent for the production of 2-aminquinoline-1-oxides.

2-Aminoquinoline-1-oxides as Ligands.

Heterocyclic N-oxides are now well known as ligands binding to metals such as the first transition series, the alkaline earths, and the lanthanides. The strong ligand pyridine-$\overline{N}$-oxide is frequently used in this way.\textsuperscript{196-198} In all compounds it has been shown to coordinate through the lone pair orbital on the oxygen atom.\textsuperscript{198} The di ($\overline{N}$-oxide) of 2,2'-bipyridine forms seven membered ring chelate
compounds. Quinoline-N-oxide and its derivatives are also known as ligands, bonded through the oxygen atom. In several cases compounds have been obtained containing molecules of chloroform.

Investigations of 2-aminopyridine-1-oxide show that at low or neutral pH it is a monodentate ligand binding via the oxygen group. At high pH at least Cu(II) and Fe(III) do form chelate compounds and both the oxygen and amino groups are involved (Fig. 32(a)). Adenosine-1-oxide (Fig. 32(b)) also seems to act as a bidentate ligand in basic solution toward metals of the first transition series. Such chelation is thought to involve the oxygen and the amino groups. Adenine-1-oxide (Fig. 32(c)) behaves differently and it has been shown that here, the donor groups are the amino group and a ring nitrogen atom.

Fig. 32

(a)  
(b)  
(c)  

It is thus apparent that the 2-amino-1-oxide grouping does form metal chelates and hence 2-amino-3-phenylquinoline-1-oxide (107) should be able to chelate as either of its tautomeric forms (p. 80) and the correct tautomer cannot be determined from this property.
The results of qualitative tests of the aminoquinoline-1-oxides with solutions of metal ions are tabulated in appendix 5. Both 2-amino-3-phenylquinoline-1-oxide (107) and 2-amino-3-carbethoxyquinoline-1-oxide formed coloured precipitates with copper and nickel under basic conditions. Iron (III) gave a deep blue coloured solution but no precipitate. Addition of base precipitated ferric hydroxide. The solubility of 2-aminoquinoline-1-oxide-3-carboxylic acid (112) was too low to permit testing.

The Nickel Chelate of 2-Amino-3-phenylquinoline-1-oxide (107).

A nickel complex of 2-amino-3-phenylquinoline-1-oxide (107) was prepared by adding dilute ammonia to a solution of nickel chloride and the quinoline-1-oxide. The product crystallised most readily from chloroform–light petroleum to give dark green plates which melted at 288–289° with decomposition. The complex is moderately soluble in chloroform, benzene, and alcohol. Elemental analysis indicates two molecules of 2-amino-3-phenylquinoline-1-oxide and 1 molecule of chloroform per nickel atom. Reanalysis after drying at 100° in vacuum gives the same results. The mass spectrum of the complex, dried under the latter conditions, gives a molecular ion value of 528.1087 compared with the calculated value for C_{30}H_{22}N_4O_2^{58}Ni of 528.1096. There is no trace of chloroform in the mass spectrum. This anomaly may arise because of a time lag between the injection of the sample and the recording of the spectrum. There are several examples in the literature of complexes which crystallise
with a molecule of chloroform present. They appear to be less stable than the one obtained in the present work however, because they generally decompose on simple heating.

The n.m.r. spectrum of the dry complex has a broad singlet at δ 3.87 p.p.m. which integrates for two protons and which vanishes when deuterium oxide is added to the sample. This signal represents two NH groups and hence a proton must be lost from the amino group of the ligand for chelation to take place explaining the need for basic conditions for the formation of the complexes. A two proton doublet at lower field than the aromatic signals is assigned to the C₈ proton in the two ligands. The low field position is due to deshielding by the oxygen atom on the quinoline ring nitrogen atom. There is also a strong singlet in the right position for a chloroform proton (δ 7.25 p.p.m.). This is due to chloroform from the complex, because a spectrum of the deuterio chloroform solvent showed it to contain very little undeuterated chloroform.

A model of the nickel complex shows that the two ligands can surround the nickel atom in a typical square planar configuration (Fig. 33).
The site of the metal atom is, however, too crowded to allow the approach of a third ligand. This may explain why iron (III) does not form solid complexes (appendix 4), since octahedral coordination is impossible. Iron (III) gives a deep blue colour with a solution of the ligand, possibly by formation of a charged complex consisting of ligands bonded to the metal solely via the oxygen atom. Addition of base to the deep blue solution gives a precipitate of ferric hydroxide.

The infrared spectrum of the complex in both chloroform solution and the solid state has a sharp band at 3415 cm$^{-1}$ in the right position for a secondary amine NH stretching mode. The remainder of the spectrum is very similar to that of the free ligand except for a strong peak at 1530 cm$^{-1}$ which is probably due to the secondary amine NH bending mode.
The nitrogen-oxygen bond stretching mode is assigned to a prominent peak at 1186 cm\(^{-1}\) compared with 1163 cm\(^{-1}\) for the free ligand and ca. 1190 found by Sigel\(^{204b}\) for the copper chelate of 2-aminopyridine-1-oxide.

The ultraviolet spectrum of the complex is similar to that of the free ligand (Table 8) except for the appearance of a weak peak at 434 nm (\(\epsilon\ 1,980\)) which is presumably responsible for the green colour of the complex. Acidification of the complex results in a spectrum nearly identical with that of the acidified ligand. The complex must therefore be decomposed by the competition of protons for the binding sites. Addition of base to the complex has no effect on the spectrum.
Biological Tests

Most of the hydroxyamidines and several of the aminoquinoline compounds have been submitted to the Cancer Chemotherapy National Service Centre for testing against experimental tumours. The compounds are in general inactive against cancer although several are highly toxic. The data from these tests are tabulated in appendix 5.

A selection of the hydroxyamidines and 2-hydroxylaminopyridine have been submitted to Ayerst Research Laboratories, Montreal, for general biological testing. N-Hydroxy N-Phenyl-N'-p-tolylbenzamidine (80a) hydrochloride has marked hypotensive activity but is also very toxic and has serious side-effects. The compounds were found to have no uterotrophic or antiueterotrophic, antiovulation, antifertilisation, anorexiant or antiulcer activity.
Microanlyses were carried out by Dr. A. D. Campbell and his associates, University of Otago. Melting points were determined on a Reichert "Kofler" block and are uncorrected.

Unless otherwise stated, infrared spectra were recorded for chloroform solutions on a Perkin-Elmer 237 Spectrophotometer. The peaks are described as b., broad; w., weak; m., medium; s., strong; sh., shoulder. Ultraviolet spectra were recorded for ethanol (95%) solutions on an Unicam SP.800 spectrophotometer. Nuclear magnetic resonance spectra were recorded for deuterio chloroform solutions on either a Varian A 60 or T 60 spectrometer. The peak positions are expressed as the down-field shift in parts per million (p.p.m.) from tetramethylsilane as the internal reference. The spectra are described in the order: peak position, proton integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J Hz), peak width at half height (W½ Hz) and assignment.

"Exchangeable" implies that the peak vanished when deuterium oxide was added to the sample.

Thin layer chromatography (t.l.c.) was carried out on Silica Gel DG (Riedel de-Häen) layers and the spots developed with iodine vapour. Preparative t.l.c. was carried out on Kieselgel PF 254 (E. Merck) layers, 1mm. in thickness and the bands viewed in ultraviolet light.
The benzene used in the preparation of imidoyl chlorides was dried over sodium. The ether (diethylether) used in the preparations of amidoximes and hydroxyamidines was washed successively with ferrous sulphate solution, dilute sulphuric acid, and water and dried first over calcium chloride and then sodium.

Light petroleum refers to the fraction boiling between 50 and 60°.

Organic solutions were dried over magnesium sulphate.
N-Phenylhydroxylamine.-- A solution of ammonium chloride (25 g., 0.47 mole) in water (700 ml.), nitrobenzene (50 g., 0.44 mole) and Teepol (3 ml.) were thoroughly emulsified by shaking. Zinc dust (50 g.) was added in one portion and vigorous shaking continued for 5 min. A further portion of zinc dust (15 g., total 65 g., 1 mole) was added and the mixture again shaken vigorously when a rise in temperature to 55-57° occurred. The mixture was then shaken at intervals for a further 20 min. The solid material was filtered off and washed with hot water (100 ml.). The washings were combined with the filtrate which was saturated with sodium chloride and kept below 0° for several hours. The resultant pale yellow crystalline material was filtered off, taken up in chloroform (300 ml.), the solution dried and concentrated to 200 ml. Light petroleum was added to the hot solution until turbidity resulted. The solution was kept below 0° for several hours and the resulting creamy-coloured solid was filtered off, washed with light petroleum until colourless and dried in vacuo over silica-gel to give N-phenylhydroxylamine (21 g., 47%) as colourless needles, m.p. 83-84° (lit. 207 80.5-81°).

\( \nu_{\text{max.}} 3570 \text{ (OH)}, 3305 \text{ (NH)} \text{ cm}^{-1} \)

\( \lambda_{\text{max.}} 239 (\varepsilon 11,400), 282 \text{ nm (}\varepsilon 1885); \lambda_{\text{max.}} \text{ (EtOH-NH}_4\text{OH)} 220 (\varepsilon 5,750), 243 (\varepsilon 3,960), 283 (\varepsilon 8,910), 304 \text{ nm} (\varepsilon 5,950). \)

\( \delta 6.73 (2 \text{ H, s W}_2 10 \text{ Hz, NH and OH, exchangeable}) \text{ p.p.m.} \)
N-Methylbenzamide. — Benzoyl chloride (66 g., 0.47 mole) was added dropwise over 1 hr. to a vigorously stirred solution of methylamine (40 ml., 33% w/v aqueous solution, 0.43 mole) in sodium hydroxide solution (190 ml., 10%, 0.47 mole) kept below 10°, and stirring continued for 2 hr. The chloroform extract (2 x 75 ml.), after washing and drying was concentrated to half volume and light petroleum added to the hot solution until turbidity resulted. After recrystallisation of the product from the same solvent mixture N-methylbenzamide (54.7 g., 94%) was obtained as colourless rods, m.p. 79-80° (lit., 208° 78°).

\[ \nu_{\text{max}} \approx 3465 \text{ and } 3350 \text{ (NH), } 1660 \text{ (amide CO) cm}^{-1} \]

\[ \delta 2.92 \text{ (3 H, d, J } 4.8 \text{ Hz, NMe) p.p.m. NH not visible.} \]

N-Ethylbenzamide. — The same procedure as for N-methylbenzamide gave N-ethylbenzamide (92%) as colourless rods, m.p. 69-70° (lit., 209° 71°).

\[ \nu_{\text{max}} \approx 3450 \text{ and } 3340 \text{ (NH), } 1653 \text{ (amide CO) cm}^{-1} \]

\[ \delta 1.18 \text{ (3 H, t, J } 7 \text{ Hz, N-CH}_{2}\text{-CH}_3\text{), } 3.43 \text{ (2 H, m, N-CH}_{2}\text{-CH}_3\text{), 7.01 (1 H, s W } \frac{1}{2} \text{ 16.5 Hz, NHCO) p.p.m.} \]

N-isopropylbenzamide. — The same procedure as for N-methylbenzamide gave N-isopropylbenzamide (91%) as colourless cubes, m.p. 99-100° (lit., 210° 104-104.5°).

\[ \nu_{\text{max}} \approx 3440 \text{ and } 3330 \text{ (NH), } 1650 \text{ (amide CO) cm}^{-1} \]
δ 1.22 (6 H, d, J 6.4 Hz, N·CH₂(CH₃)₂), 4.26 (1 H, m, N·CH₂(CH₃)₂), 6.55 (1 H, s W₁ 15 Hz, NH·CO) p.p.m.

**Acetanalide.**— A sample of acetanalide was made by the usual procedure and after recrystallisation from dilute methanol had m.p. 114-115⁰ (lit., 211 113-114⁰).

\[ \nu_{\text{max.}} 3430 \text{ and } 3310 \text{ (NH), } 1685 \text{ (amide CO) cm}^{-1} \]

δ 2.10 (3 H, s, CO·CH₃), 8.50 (1 H, s W₂ 8 Hz, NH·CO) p.p.m.

**Propionanilide.**— The same procedure as for acetanalide gave propionanilide (67%) as colourless plates, m.p. 106-107⁰ (lit., 212 103-104⁰).

\[ \nu_{\text{max.}} 3430 \text{ and } 3320 \text{ (NH), } 1685 \text{ (amide CO) cm}^{-1} \]

δ 1.18 (3 H, t, J 7 Hz, CO·CH₂·CH₃), 2.35 (2 H, q, J 7 Hz, CO·CH₂·CH₃), 8.19 (1 H, s W₁ 10 Hz, NH·CO) p.p.m.

**IsoButyranilide.**— The same procedure as for acetanalide gave isobutyranilide (62%) as colourless plates, m.p. 104-105⁰ (lit., 105⁰).

\[ \nu_{\text{max.}} 3430 \text{ and } 3320 \text{ (NH), } 1685 \text{ (amide CO) cm}^{-1} \]

δ 1.18 (6 H, d, J 6 Hz, CO·CH·(CH₃)₂), 2.47 (1 H, m, J 6 Hz, CO·CH·(CH₃)₂) p.p.m.

**Benzanilide.**— Benzoyl chloride (66 g., 0.47 mole) was added dropwise to a vigorously stirred mixture of aniline (40 g., 0.43
mole) and sodium hydroxide solution (190 ml., 10%, 0.47 mole). Stirring was continued for 2 hr. The solid product was broken up, filtered off, washed with successively, dilute sodium hydroxide solution and water and recrystallised from methanol to give benzanilide (78 g., 93%) as colourless laths, m.p. 162-163° (lit., 214-163°).

\[ \nu_{\text{max.}} \text{(KBr)} \ 3350 \ (\text{NH}), \ 1655 \ (\text{amide CO}) \ \text{cm}^{-1} \]

The same procedure as for benzanilide was used to prepare the following amides:

\[ \text{N-Cyclohexylbenzamide} \]  The product was recrystallised from chloroform-light petroleum to give \( \text{N-cyclohexylbenzamide} \) (80%) as colourless cubes, m.p. 148-149° (lit., 215-147°).

\[ \nu_{\text{max.}} \ 3430 \ (\text{NH}), \ 1695 \ (\text{amide CO}) \ \text{cm}^{-1} \]

\( \delta \ 0.92-2.2 \ (10 \text{ H}, \text{ methylene envelope}), \ 3.95 \ (1 \text{ H}, \text{ m, NH-CH}), \ 6.42 \ (1 \text{ H}, \text{ d, J 4 Hz, NH-CO}) \ p.p.m. \)

\[ \text{N-Benzylbenzamide} \]  The product was recrystallised from chloroform-light petroleum to give \( \text{N-benzylbenzamide} \) (90%) as colourless rods, m.p. 103.5-105° (lit., 216-105°).

\[ \nu_{\text{max.}} \ 3445 \ and \ 3345 \ (\text{NH}), \ 1660 \ (\text{amide CO}) \ \text{cm}^{-1} \]

\( \delta \ 4.45 \ (2 \text{ H}, \text{ d, J 1.4 Hz, NH-CH}_2), \ 6.75 \ (1 \text{ H}, \text{ s W}_2 14 \text{ Hz, NH-CO}) \ p.p.m. \)
Benz-o-toluidide.— The product was recrystallised from chloroform-light petroleum to give benz-o-toluidide (91%) as colourless needles, m.p. 142-143.5° (lit., 217 145-146°).

\[ \nu_{\text{max.}} = 3430 \text{ and } 3320 \text{ (NH), } 1675 \text{ (amide CO) cm}^{-1} \]

\[ \delta 2.27 \text{ (3 H, s, CH}_3\text{) p.p.m. NH not visible.} \]

Benz-o-anisidide.— The product was recrystallised from chloroform-light petroleum to give benz-o-anisidide (75%) as colourless plates, m.p. 65-66° (lit., 218 59.8°).

\[ \nu_{\text{max.}} = 3430 \text{ (NH), } 2840 \text{ (OCH}_3\text{), } 1675 \text{ (amide CO) cm}^{-1} \]

\[ \delta 3.90 \text{ (3 H, s, O.CH}_3\text{) p.p.m. NH not visible.} \]

Benz-p-toluidide.— The product was recrystallised from chloroform-light petroleum to give benz-p-toluidide (97%) as colourless rhombs, m.p. 157-158° (lit., 219 158°).

\[ \nu_{\text{max.}} = 3430 \text{ and } 3310 \text{ (NH), } 1675 \text{ (amide CO) cm}^{-1} \]

\[ \delta 2.30 \text{ (3 H, s, CH}_3\text{), } 8.10 \text{ (1 H, s W}_1\text{ }^{1/2} \text{ Hz, NH.CO) p.p.m.} \]

Benz-p-anisidide.— The product was recrystallised from chloroform-light petroleum to give benz-p-anisidide (76%) as colourless laths, m.p. 157-158° (lit., 220 156°).

\[ \nu_{\text{max.}} = 3430 \text{ and } 3310 \text{ (NH), } 2830 \text{ (OCH}_3\text{), } 1670 \text{ (amide CO) cm}^{-1} \]

\[ \delta 3.77 \text{ (3 H, s, O.CH}_3\text{) p.p.m. NH not visible.} \]
o-Tolarnilide.— The product was recrystallised from chloroform-light petroleum to give o-tolarnilide (94%) as colourless needles, m.p. 126–127° (lit., 121°).

$\nu_{\text{max.}}$ 3420 and 3290 (NH), 1675 (amide CO) cm$^{-1}$

$\delta$ 2.40 (3 H, s, CH$_3$), 7.86 (1 H, s W$_2$ 10 Hz, NH.CO) p.p.m.

o-Anisanilide.— The product was recrystallised from aqueous ethanol to give o-anisanilide (85%) as colourless plates, m.p. 61–62° (lit., 62°).

$\nu_{\text{max.}}$ 3360 (NH), 2840 (OCH$_3$), 1665 (amide CO) cm$^{-1}$

$\delta$ 3.98 (3 H, s, O.CH$_3$), 9.67 (1 H, s W$_2$ 6 Hz, NH.CO) p.p.m.

p-Tolarnilide.— Recrystallisation of the product from chloroform-light petroleum gave p-tolarnilide (95%) as colourless needles, m.p. 144–145° (lit., 139°).

$\nu_{\text{max.}}$ 3440 and 3300 (NH), 1670 (amide CO) cm$^{-1}$

$\delta$ 2.37 (3 H, s, CH$_3$), 8.06 (1 H, s W$_2$ 10 Hz, NH.CO) p.p.m.

p-Anisanilide.— The product was recrystallised from ethanol to give p-anisanilide (84%) as colourless plates, m.p. 171–172° (lit., 168–169°).

$\nu_{\text{max.}}$ 3440 (NH), 2830 (OCH$_3$), 1665 (amide CO) cm$^{-1}$

$\delta$ 3.87 (3 H, s, O.CH$_3$) p.p.m. NH not visible.
o-Tolyl-o-toluidide.— The product was recrystallised from chloroform-light petroleum to give o-tolyl-o-toluidide (85%) as colourless rods, m.p. 143-144° (lit., 224 145°).

\[ \nu_{\text{max}} = 3420 \text{ and } 3290 \text{ (NH), } 1675 \text{ (amide CO) cm}^{-1} \]
\[ \delta = 2.27 (3 \text{ H, s, } C_2' \text{CH}_3), 2.48 (3 \text{ H, s, } C_2 \text{CH}_3), 7.89 (1 \text{ H, s } W \frac{1}{2} 14 \text{ Hz, NH CO}) \text{ p.p.m.} \]

p-Tolyl-p-toluidide.— The product was recrystallised from chloroform-light petroleum to give p-tolyl-p-toluidide (60%) as colourless rods, m.p. 161-161.5° (lit., 225 160°).

\[ \nu_{\text{max}} = 3440 \text{ and } 3310 \text{ (NH), } 1670 \text{ (amide CO) cm}^{-1} \]
\[ \delta = 2.30 (3 \text{ H, s, } C_4' \text{CH}_3), 2.37 (3 \text{ H, s, } C_4 \text{CH}_3), 8.05 (1 \text{ H, s, } W \frac{1}{2} 6 \text{ Hz, NH CO}) \text{ p.p.m.} \]

o-Anisyl-o-anisidide.— The product was recrystallised from ethanol to give o-anisyl-o-anisidide (86%) as colourless rods, m.p. 99-100° (lit., 226 100°).

\[ \nu_{\text{max}} = 3340 \text{ (N-H), } 2845 \text{ (OCH}_3\text{), } 1660 \text{ (amide CO) cm}^{-1} \]
\[ \delta = 3.89 (3 \text{ H, s, } C_2' \text{O.CH}_3), 3.97 (3 \text{ H, s, } C_2 \text{O.CH}_3), 10.45 (1 \text{ H, s, } W \frac{1}{2} 8 \text{ Hz, NH.CO}) \text{ p.p.m.} \]

p-Anisyl-p-anisidide.— The product was recrystallised from ethanol to give p-anisyl-p-anisidide (95%) as colourless plates, m.p. 201-203° (lit., 227 202°).
\( \nu_{\text{max.}} \) (KBr) 3340 (NH), 2840 (OCH\textsubscript{3}), 1650 (amide CO) cm\textsuperscript{-1}

\( \alpha \)-Chlorobenzanilide.-- The product was recrystallised from aqueous ethanol to give \( \alpha \)-chlorobenzanilide (93\%) as colourless rods, m.p. 119-120\(^{\circ}\) (lit., 114\(^{\circ}\)).

\( \nu_{\text{max.}} \) 3430 and 3300 (NH), 1675 (amide CO) cm\textsuperscript{-1}

Benz-2,6-xylidide.-- The product was recrystallised twice from ethanol to give benz-2,6-xylidide (90\%) as colourless tablets, m.p. 164-165\(^{\circ}\) (lit., 168-168.5\(^{\circ}\)).

\( \nu_{\text{max.}} \) 3430 and 3310 (NH), 1670 (amide CO) cm\textsuperscript{-1}

\( \delta \) 2.17 (6 H, s, CH\textsubscript{3}) p.p.m. NH not visible.

Benz-\( p \)-bromoanilide.-- Benzoyl chloride (14 g., 0.1 mole) was added dropwise, with vigorous manual stirring to powdered \( p \)-bromoaniline (15 g., 0.09 mole). The reaction mixture was periodically cooled in an ice bath and the resulting solid finely ground with excess dilute sodium hydroxide solution. The product was collected, washed with water and recrystallised from methanol-acetic acid to give benz-\( p \)-bromoanilide (19 g., 80\%) as colourless plates, m.p. 205\(^{\circ}\) (lit., 230 202\(^{\circ}\)).

\( \nu_{\text{max.}} \) (KBr) 3330 (NH), 1650 (amide CO) cm\textsuperscript{-1}
The same procedure as for benz-\(\text{p}\)-bromoanilide was used to prepare the following amides:

\(\text{p-Chlorobenzanilide.}\) The product was crystallised from ethanol to give \(\text{p-chlorobenzanilide (85\%) as colourless plates, m.p. 199-200^\circ}\) (lit., \(^{231}\) 199.5-200).

\[\nu_{\text{max.}} (\text{KBr}) 3350 (\text{NH}), 1655 (\text{amide CO}) \text{ cm}^{-1}\]

\(\text{Benz-\(\text{p}\)-chloroanilide.}\) The product was recrystallised from ethanol to give benz-\(\text{p}\)-chloroanilide (87%) as colourless plates, m.p. 182-183^\circ (lit., \(^{232}\) 183-184^\circ).

\[\nu_{\text{max.}} (\text{KBr}) 3330 (\text{NH}), 1650 (\text{amide CO}) \text{ cm}^{-1}\]

\(\text{p-Chlorobenz-\(\text{p}\)-chloroanilide.}\) The product was recrystallised from ethanol to give p-chlorobenz-\(\text{p}\)-chloroanilide (83%) as colourless laths, m.p. 212^\circ (lit., \(^{233}\) 207-208^\circ).

\[\nu_{\text{max.}} (\text{KBr}) 3260 (\text{NH}), 1648 (\text{amide CO}) \text{ cm}^{-1}\]

\(\text{Benzoyl-\(\text{I}\)-naphthylamine.}\) This was prepared using Jacobs' acylation procedure. \(^{234}\) Two recrystallisations from chloroform-light petroleum gave benzoyl-\(\text{I}\)-naphthylamine (80%) as colourless needles, m.p. 160-161^\circ (lit., \(^{235}\) 160^\circ).

\[\nu_{\text{max.}} (\text{KBr}) 3240 (\text{NH}), 1645 (\text{amide CO}) \text{ cm}^{-1}\]
Benz-o-nitroanilide.— This was prepared using Ruggli's acylation procedure.\textsuperscript{236} Recrystallisation of the product from ethanol gave benz-o-nitroanilide (94\%) as golden rods, m.p. 96-97° (lit.,\textsuperscript{237} 94°).

\[ \nu_{\text{max}} \text{ 3360 (NH), 1695 (amide CO) cm}^{-1} \]

Benz-m-nitroanilide.— The procedure above was followed. Recrystallisation of the product from aqueous ethanol gave benz-m-nitroanilide (95\%) as fawn plates, m.p. 154-155° (lit.,\textsuperscript{237} 154°).

\[ \nu_{\text{max}} \text{ 3430 and 3340 (NH), 1675 (amide CO), 1555 and 1365 (NO}_2\text{) cm}^{-1} \]

p-Nitrobenzanilide.— Aniline (20 g., 0.22 mole) was added to a solution of p-nitrobenzyl chloride (20 g., 0.11 mole) in dry benzene (400 ml.), with shaking. The mixture was kept under reflux for 0.5 hr. and then cooled to room temperature. The solid was washed successively with dilute hydrochloric acid and water. Recrystallisation of the residue from ethanol gave p-nitrobenzanilide (25.3 g., 95\%) as colourless tablets, m.p. 213-214° (lit.,\textsuperscript{238} 214°).

\[ \nu_{\text{max}} \text{ (KBr) 3320 (NH), 1655 (amide CO), 1545 and 1350 (NO}_2\text{) cm}^{-1} \]

N-Cyclohexyl-p-nitrobenzamide.— The procedure as above was followed. Recrystallisation of the product from ethanol gave N-cyclohexyl-p-nitrobenzamide (92\%) as colourless needles, m.p. 202-203° (lit.,\textsuperscript{239} 203-204°).
\( \nu_{\text{max.}} \) 3430 and 3310 (NH), 1660 (amide CO), 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

**Cyclohexanecarbonanilide.**— The procedure as above, was followed. Recrystallisation of the product from chloroform-light petroleum gave cyclohexanecarbonanilide (92%) as colourless rods, \( m.p. \) 144-145\( ^0 \) (lit., \( 215 \) 147\( ^0 \))

\( \nu_{\text{max.}} \) 3440 and 3330 (NH), 1680 (amide CO) cm\textsuperscript{-1}

\( \delta \) 0.68-2.68 (11 H, m, methylene envelope), 7.73 (1 H, s \( W_{\frac{1}{2}} \)

12 Hz, NH⋅CO) p.p.m.

**Cyclohexanecarboncyclohexylamide.**— The procedure as above was followed except that after removal of the product by filtration, the filtrate was evaporated to dryness and the resulting solid treated in the same way as the main product. Recrystallisation of the total residue from chloroform-light petroleum gave cyclohexanecarboncyclohexylamide (95%) as colourless rhombs, \( m.p. \) 170-171\( ^0 \) (lit., \( 145 \) 172-173\( ^0 \)).

\( \nu_{\text{max.}} \) 3440 and 3330 (NH), 1660 (amide CO) cm\textsuperscript{-1}

\( \delta \) 0.33-3.00 (20 H, m, methylene envelope), 3.74 (2 H, s, \( W_{\frac{1}{2}} \)

18 Hz, CO⋅CH and NH⋅CH) 5.53 (1 H, s, \( W_{\frac{1}{2}} \) 16 Hz, NH⋅CO) p.p.m.

**2,2,2-Trichloroacetanilide.**— The procedure immediately above was followed. Recrystallisation of the product from chloroform-light petroleum gave 2,2,2-trichloroacetanilide (91%) as colourless rods, \( m.p. \) 94-95\( ^0 \) (lit., \( 240 \) 94-95\( ^0 \)).

\( \nu_{\text{max.}} \) 3420 and 3330 (NH), 1720 (amide CO) cm\textsuperscript{-1}
**o-Nitroacetanilide.**— Concentrated sulphuric acid (0.2 ml.) was added to a stirred solution of o-nitroaniline (30 g., 0.22 mole) in acetic anhydride (300 ml.). After 1 hr. the solution was poured on to ice (2 l.) and vigorously stirred. Recrystallisation from aqueous ethanol gave o-nitroacetanilide (37 g., 95%) as yellow plates, m.p. 94-95° (lit., 241 93°).

\[ v_{\text{max.}} = 3370 \text{ (NH), 1710 (amide CO) cm}^{-1} \]

\[ \delta = 2.27 \text{ (3 H, s, CO.CH₃), 10.20 \text{ (1 H, s, W₂ 8 Hz, NH.CO) p.p.m.} } \]

2,4,6-Tribromoacetanilide.— The procedure was the same as that above. Recrystallisation of the product from aqueous ethanol gave 2,4,6-tribromoacetanilide (100%) as colourless rods, m.p. 229-230° (lit., 242 232°).

\[ v_{\text{max.}} = 1730 \text{ (amide CO) cm}^{-1} \]

\[ \delta = 2.27 \text{ (3 H, s, CO.CH₃) cm}^{-1} \]

**Benz-2,4,6-tribromoanilide.**— Benzoyl chloride (15 g., 0.11 mole) was added to a refluxing solution of 2,4,6-tribromoaniline (18 g., 0.055 mole) in pyridine (100 ml.). After refluxing for 6 hr. the solution was poured on to crushed ice and stirred until the resulting oil crystallised. The solid was washed successively with dilute hydrochloric acid and water and recrystallised from ethanol to give benz-2,4,6-tribromoanilide (94%) as colourless tablets, m.p. 194-195° (lit., 243 198°).
\[ \nu_{\text{max.}} \text{(KBr)} \] 3420 and 3300 (NH), 1690 (amide CO) cm\(^{-1}\)

\(N,N'-\text{Dibenzoyl-}p\text{-phenylenediamine.}\) Benzoyl chloride (37 g., 0.26 mole) and \(p\text{-phenylenediamine (15 g., 0.13 mole)}\) were thoroughly mixed. Sodium hydroxide solution (110 ml., 10\%, 0.27 mole) was added and the mixture was warmed. After the vigorous reaction had finished, the resulting solid was finely ground, washed with water and then ethanol and crystallised from a large volume of ethanol to give \(N,N'-\text{dibenzoyl-}p\text{-phenylenediamine (96\%)}\) as colourless needles, m.p. 327-328° (lit., \(244°\) 300°).

\[ \nu_{\text{max.}} \text{(KBr)} \] 3322 (NH), 1653 (amide CO) cm\(^{-1}\)

The amides used in the following syntheses were dried at 50°/1 mm. for 12 hr. immediately before use.

\(N\text{-Methylbenzimidoyl Chloride (75a).}\) Powdered phosphorus pentachloride (61 g., 0.3 mole) was added to a suspension of dry \(N\text{-methylbenzamide (40 g., 0.3 mole)}\) in dry benzene (160 ml.). A drying tube was fitted and the mixture boiled under reflux until evolution of hydrogen chloride ceased (6 hr.). The solvent and phosphorus oxychloride were removed under vacuum and the residual oil distilled under vacuum to give \(N\text{-methylbenzimidoyl chloride (45 g., 90\%)}\) as a colourless liquid, b.p. 70-72°/2.5 mm. (lit., \(245\) 65-67°/2.5 mm.), \(n_D^{20}\) 1.5629 (lit., \(246\) \(n_D^{20}\) 1.5625).

\[ \nu_{\text{max.}} \] 3310, 2770 (N-CH\(_3\)), 2650 (broad), 2540, 2360 (broad), 1660 (C=N) cm\(^{-1}\)
The following imidoyl chlorides were made by the method given above:

**N-Ethylbenzimidoyl Chloride.**— Distillation gave a colourless oil (88%), b.p. 56–58°/3 mm. (lit., 47–48°/1 mm.).

\[ \nu_{\text{max.}} 3310, 1660 \text{ cm}^{-1} \]

**N-isoPropylbenzimidoyl Chloride.**— Distillation gave a colourless oil (78%), b.p. 62–63°/2 mm. (lit., 52–54°/1 mm.).

\[ \nu_{\text{max.}} 3310, 2650-2540 \text{ (broad), 2470, 2370 (sh), 1650 (C=N), 1380 and 1370 (C(CH)\text{)}_2 \text{ cm}^{-1}} \]

**N-Phenylbenzimidoyl Chloride.**— Distillation gave N-phenylbenzimidoyl chloride (99%) as a pale yellow oil, b.p. 162°/2.7 mm. (lit., 175-176°/12 mm.), which crystallised on cooling as plates, m.p. 39.5–40° (lit., 39–40°).

\[ \nu_{\text{max.}} 3290, 2640-2520 \text{ (broad), 2480, 1660 (C=N) cm}^{-1} \]

**N-Cyclohexylbenzimidoyl Chloride.**— Distillation gave N-cyclohexylbenzimidoyl chloride (44%) as a colourless oil, b.p. 105°/0.5 mm. (lit., 110-112°/1 mm.), which crystallised on cooling as plates, m.p. 66-67° (lit., 66-67°).

\[ \nu_{\text{max.}} 3290, 2660-2590 \text{ (broad), 2450, 2380, 1650 (C=N) cm}^{-1} \]

**N-Benzylbenzimidoyl Chloride.**— Distillation gave a colourless oil (60%), b.p. 135°/0.1 mm. (lit., 128-130°/1 mm.), which was used directly to synthesise N-hydroxy-N-phenyl-N'-benzylbenzamidine (loc. cit.).
$\nu_{\text{max.}}$ 3310, 2660-2450 (broad), 2350 (broad), 1660 (C=N) cm$^{-1}$

N-o-Tolylbenzimidoyl Chloride.— Distillation gave a lemon yellow oil (95%), b.p. 147$^\circ$ / 0.9 mm. (lit.,$^{247}$ 164$^\circ$ / 6 mm.), which was used directly to synthesise $\text{N-hydroxy-N-phenyl-N'}$-o-tolylbenzamidine (loc. cit.).

$\nu_{\text{max.}}$ 3290, 2620 (sh.), 2550, 2520-2400 (broad), 2310 (broad), 1670 (C=N) cm$^{-1}$

N-o-Anisylbenzimidoyl Chloride.— Distillation gave a pale yellow oil (80%), b.p. 150$^\circ$ / 0.4 mm. (lit.,$^{248}$ 188-190$^\circ$ / 6 mm.), which crystallised on cooling as laths, m.p. 56-57$^\circ$ (no m.p. previously recorded). This was used directly to synthesise $\text{N-hydroxy-N-phenyl-N'}$-o-anisylbenzamidine (loc. cit.).

$\nu_{\text{max.}}$ 2840 (OCH$_3$), 2570 (broad), 2450 (broad), 2350 (broad), 1665 (C=N) cm$^{-1}$

N-p-Tolylbenzimidoyl Chloride.— Distillation gave N-p-tolylbenzimidoyl chloride (97%) as a pale yellow oil, b.p. 156$^\circ$ / 1 mm. (lit.,$^{247}$ 186$^\circ$ / 10 mm.), which crystallised on cooling as rhombs, m.p. 52-53$^\circ$ (lit.,$^{249}$ 52$^\circ$).

$\nu_{\text{max.}}$ 3300, 2640-2490 (broad), 2450, 2350 (broad), 1670 (C=N) cm$^{-1}$

N-p-Anisylbenzimidoyl Chloride.— Distillation gave N-p-anisylbenzimidoyl chloride (80%) as a pale yellow oil, b.p. 155$^\circ$ / 0.35 mm. (lit.,$^{133}$ 198-200$^\circ$ / 20 mm.), which crystallised on standing as laths, m.p. 58-59$^\circ$ (lit.$^{133}$ 61-63$^\circ$).
$\nu_{\text{max.}}$ 3280 (broad), 2840 (OCH$_3$), 2650-2500 (broad), 2450, 2350 (broad), 1670 (C=O) cm$^{-1}$

$\text{N-Phenyl-o-tolimidoyl Chloride}$.— Distillation gave $\text{N-phenyl-o-tolimidoyl chloride}$ (86%) as a pale yellow oil, b.p. 141$^\circ$/0.45 mm. (lit. 133 141-144$^\circ$/1 mm.), which crystallised on cooling as leaflets, m.p. 35-36$^\circ$ (lit. 133 40-41$^\circ$).

$\nu_{\text{max.}}$ 2660-2500 (broad), 2450, 2350 (broad), 1685 (C=O) cm$^{-1}$

$\text{N-Phenyl-o-anisimidoyl Chloride}$.— Distillation gave a pale yellow oil (81%), b.p. 140$^\circ$/0.25 mm., which was used directly to synthesise $\text{N-hydroxy-N-phenyl-N'-phenylanisamidine}$ (loc. cit.).

$\nu_{\text{max.}}$ 3360, 2660-2500 (broad), 2440 (broad), 2350 (broad), 1680 (C=O) cm$^{-1}$

$\text{N-Phenyl-p-tolimidoyl Chloride}$.— Distillation gave $\text{N-phenyl-p-tolimidoyl chloride}$ (86%) as a pale yellow oil, b.p. 169$^\circ$/1.9 mm. (lit. 250 200$^\circ$/16 mm.), which crystallised on cooling as plates, m.p. 42-43$^\circ$ (lit. 250 45$^\circ$).

$\nu_{\text{max.}}$ 3300 (broad), 2640-2440 (broad), 2340 (broad), 1670 (C=O) cm$^{-1}$

$\text{N-Phenyl-p-anisimidoyl Chloride}$.— Distillation gave $\text{N-phenyl-p-anisimidoyl chloride}$ (70%) as a pale yellow oil, b.p. 165$^\circ$/0.45 mm. (lit. 133 183-189$^\circ$/3 mm.), which crystallised on cooling as plates, m.p. 72-73$^\circ$ (lit. 133 73-76$^\circ$).
\( \nu_{\text{max}} \) 3300, 2860 (OCH\(_3\)), 2650-2500 (broad), 2460, 2370 (broad), 1670 (C=N) cm\(^{-1}\)

**N-o-Tolyl-o-tolimidoyl Chloride.** Distillation gave a pale yellow oil (86\%), b.p. 136°/0.4 mm\(^{\ast}\), which was used directly to synthesise \( \text{N-} \)-hydroxy-\( \text{N-} \)-phenyl-\( \text{N'–} \)-o-tolyl-o-tolamidine (loc. cit.).

\( \nu_{\text{max}} \) 2570, 2450, 2350 (broad), 1690 (C=N) cm\(^{-1}\)

**N-p-Tolyl-p-tolimidoyl Chloride.** Distillation gave a pale yellow oil (82\%), b.p. 157°/0.4 mm\(^{\ast}\), which crystallised on cooling as rhombs, m.p. 54-55°. This was used directly to synthesise \( \text{N-} \)-hydroxy-\( \text{N-} \)-phenyl-\( \text{N'–} \)-p-tolyl-p-tolamidine (loc. cit.).

\( \nu_{\text{max}} \) 3300, 2660-2490 (broad), 2450, 2360 (broad), 1660 (C=N) cm\(^{-1}\)

**N-o-Anisyl-o-anisimidoyl Chloride.** Distillation gave a pale yellow oil (69\%), b.p. 160°/0.6 mm\(^{\ast}\), which was used directly to synthesise \( \text{N-} \)-hydroxy-\( \text{N-} \)-phenyl-\( \text{N'–} \)-o-anisyl-o-anisamidine (loc. cit.).

\( \nu_{\text{max}} \) 330, 3840 (OCH\(_3\)), 2630-2540 (broad), 2350 (broad), 1660 (C=N) cm\(^{-1}\)

**N-p-Anisyl-p-anisimidoyl Chloride.** The residue, after the removal of solvent and phosphorus oxychloride, was recrystallised from benzene-light petroleum to give \( \text{N-p–} \)-anisyl-p-anisimidoyl chloride (80\%) as pale green laths, m.p. 107-108° (lit.,\(^{251} 109°\)).
\( \nu_{\text{max.}} 2840 \, (\text{OCH}_3), \, 2640-2480 \, (\text{broad}), \, 2440, \, 2360 \, (\text{sh.}), \)
\( 1650 \, (\text{C=N}) \, \text{cm}^{-1} \)

\textbf{N-Phenyl-o-Chlorobenzimidoyl Chloride.--} Distillation gave \textit{N-phenyl-o-}
chlorobenzimidoyl chloride (76\%) as a pale yellow oil, b.p. 150°/0.2 mm.
(lit., \( \textit{^{252}_{182-183}^{\circ}/10} \, \text{mm.} \), which crystallised on cooling as rhombs,
m.p. 60-61° (lit., \( \textit{^{253}_{59}^{\circ}} \)).
\( \nu_{\text{max.}} 2560 \, (\text{broad}), \, 2440, \, 2310 \, (\text{broad}), \, 1685 \, (\text{C=N}) \, \text{cm}^{-1} \)

\textbf{N-2,6-Xylylbenzimidoyl Chloride.--} Distillation gave \textit{N-2,6-}
xylylbenzimidoyl chloride (80\%) as a pale yellow oil, b.p. 154-156°/1 mm.
(lit., \( \textit{^{133}_{153-156}^{\circ}/1} \, \text{mm.} \)).
\( \nu_{\text{max.}} 3300, \, 2630, \, 2560, \, 2450 \, (\text{broad}), \, 2340 \, (\text{broad}), \, 1670 \)
\( (\text{C=N}) \, \text{cm}^{-1} \)

\textbf{N-p-Bromophenylbenzimidoyl Chloride.--} Distillation gave \textit{N-p-bromo-}
phenylbenzimidoyl chloride (81\%) as a pale yellow oil, b.p. 172°/1.1 mm.,
which crystallised on cooling as laths, m.p. 69-70° (lit., \( \textit{^{254}_{70}^{\circ}} \)).
\( \nu_{\text{max.}} 3250, \, 2520, \, 2450, \, 1670 \, (\text{C=N}) \, \text{cm}^{-1} \)

\textbf{N-Phenyl-p-Chlorobenzimidoyl Chloride.--} Distillation gave \textit{N-phenyl-p-}
chlorobenzimidoyl chloride (77\%) as a pale yellow oil, b.p. 144°/0.5 mm.,
which crystallised on cooling as laths m.p. 67-68° (lit., \( \textit{^{255}_{66-67}^{\circ}} \)).
\( \nu_{\text{max.}} 3300, \, 2560, \, 2480, \, 1670 \, (\text{C=N}) \, \text{cm}^{-1} \)
N-p-Chlorophenylbenzimidoyl Chloride.-- Distillation gave a pale yellow oil (88%), b.p. 139°/0.3 mm., which crystallised on cooling as needles m.p. 60-61°. This was used directly for the synthesis of N-hydroxy-N-phenyl-N'-p-chlorophenylbenzamidine (loc. cit.).

ν\text{max.} 3290, 2550 (broad), 1665 (C=N) cm\textsuperscript{-1}

N-p-Chlorophenyl-p-chlorobenzimidoyl Chloride.-- Distillation gave a pale yellow oil (76%), b.p. 160°/0.2 mm., which crystallised on cooling as needles, m.p. 73-74°. This was used directly to synthesise N-hydroxy-N-phenyl-N'-p-chlorophenyl-p-chlorobenzamidine (loc. cit.).

ν\text{max.} 3300, 2560, 1665 (C=N) cm\textsuperscript{-1}

N-1-Naphthylbenzimidoyl Chloride.-- The residue after removal of solvent and phosphorus oxychloride, was recrystallised twice from light petroleum to give N-1-naphthylbenzimidoyl chloride (73%) as yellow rhombs, m.p. 58-59° (lit., 249° 60°).

ν\text{max.} 3300, 2610-2540 (broad), 2460, 2330 (sh.), 1660 (C=N) cm\textsuperscript{-1}

N-o-Nitrophenylbenzimidoyl Chloride.-- Distillation gave N-o-nitrophenylbenzimidoyl chloride (84%) as a yellow oil, b.p. 173°/0.35 mm., which crystallised on cooling as yellow rhombs, m.p. 68-69° (lit., 119° 67-68°).

ν\text{max.} 3300, 2570, 1670 (C=N), 1525 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

N-m-Nitrophenylbenzimidoyl Chloride.-- Distillation gave N-m-nitrophenylbenzimidoyl chloride (87%) as a pale yellow oil, b.p. 179°/0.4 mm.,
which crystallised on cooling as rhombs, m.p. 79° (lit. 256 80°).

\[ \nu_{\text{max.}} \] 3290, 2580, 2515, 1670 (C=N), 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

**N-Phenyl-p-nitrobenzimidoyl Chloride.** Distillation gave **N**-phenyl-p-nitrobenzimidoyl chloride (81%) as a yellow oil, b.p. 177°/0.3 mm., which crystallised on cooling as yellow rhombs, m.p. 130-132° (lit., 133 132-134°).

\[ \nu_{\text{max.}} \] 3290, 2440, 1660 (C=N), 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

**N-Cyclohexyl-p-nitrobenzimidoyl Chloride.** Distillation gave **N**-cyclohexyl-p-nitrobenzimidoyl chloride (83%) as a yellow oil, b.p. 162°/0.2 mm., which crystallised on cooling as yellow rods, m.p. 42-43° (lit., 133 40-42°).

\[ \nu_{\text{max.}} \] 3300, 2660, 2580, 2440, 1670 (C=N), 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

**N-Phenylcyclohexanecarbonimidoyl Chloride.** Distillation gave a colourless oil (81%), b.p. 110°/0.2 mm. (lit., 257 122-123°/1 mm.), which was used directly to synthesise **N**-hydroxy-**N**-phenyl-**N'**-phenylcyclohexanecarbonamidine (*loc. cit.*).

\[ \nu_{\text{max.}} \] 3250, 2660-2500 (broad), 2440, 2360 (sh.), 1700 (C=N) cm\textsuperscript{-1}

**N-Cyclohexylcyclohexanecarbonimidoyl Chloride.** Distillation gave a colourless oil (65%), b.p. 112-116°/0.9 mm., which was used directly to synthesise **N**-hydroxy-**N**-phenyl-**N'**-cyclohexylcyclohexanecarbonamidine (*loc. cit.*).

\[ \nu_{\text{max.}} \] 3280, 2660, 2590, 2450, 1715 (C=N) cm\textsuperscript{-1}
 Attempted Preparation of N-Phenyl-2,2,2-trichloroacetimidoyl Chloride.

The same procedure as for N-methyl benzimidoyl chloride but using 2,2,2-trichloroacetanilide gave, after a reaction time of 6 hr., a quantitative recovery of the anilide identified by its melting point and undepressed mixed melting point with an authentic sample.

N-o-Nitrophenylacetimidoyl Chloride. Distillation gave a pale yellow oil (56%), b.p. 123°/0.85 mm., which crystallised on standing as plates, m.p. 60-61°. This was used directly to synthesise N-hydroxy-N-phenyl-N'-o-nitrophenylacetamidine (loc. cit.).

\[ \nu_{\text{max.}} 3370, 2740-2550 \text{ (broad), 2500, 2450, 2340, 1710} \]
\[ (C=N), 1530 \text{ and 1350 (NO}_2\text{) cm}^{-1} \]

N-2,4,6-Tribromophenylacetimidoyl Chloride. Distillation gave a pale yellow oil (73%), b.p. 160°/0.7 mm., which crystallised on cooling as laths, m.p. 62-63°.

\[ \nu_{\text{max.}} 1730 \text{ (C=N), 860 (isolated aromatic ring H) cm}^{-1} \]

N-2,4,6-Tribromophenylbenzimidoyl Chloride. Distillation gave a very viscous, pale yellow oil (52%) b.p. 196-200°/0.5 mm., which set as a glass on cooling. This was used directly to synthesise N-2,4,6-tribromo-phenylbenzamidoxime (loc. cit.).

\[ \nu_{\text{max.}} 1670 \text{ (C=N), 865 (isolated aromatic ring H) cm}^{-1} \]
N-Phenyl-2-chloro-2-methylpropionimidoyl Chloride. — The procedure was
the same as that for N-methyl benzimidoyl chloride except that two moles
of phosphorus pentachloride per mole of isopropionanilide were used.
Distillation gave N-phenyl-2-chloro-2-methylpropionimidoyl chloride
(81%), b.p. 116–117°/15 mm. (lit., 115–117°/15 mm.).

\[ \nu_{\text{max.}} \text{ 3330, 1690 (C=N) cm.}^{-1} \]

A sample of the imidoyl chloride was hydrolysed with water and
the product recrystallised from chloroform-light petroleum to give
2-chloro-2-methylpropionanilide as colourless laths, m.p. 68° (lit., 68°).

\[ \nu_{\text{max.}} \text{ 3400 and 3350 (sh.) (NH), 1693 (amide CO), 1383 and 1365}
(\text{C(CH}_3}_2)\text{ cm.}^{-1} \]

\[ \delta \text{ 1.87 (6 H, s, C(CH}_3}_2), 8.49 (1 H, s broad, NH.CO) \text{ p.p.m.} \]

Reaction of Acetanilide with Phosphorus Pentachloride. — (a) Acetanilide
(5 g., 0.05 mole) and phosphorus pentachloride (23 g., 0.15 mole) were
refluxed together in benzene (80 ml.). When evolution of hydrogen
chloride had finished (6 hr.) the solvent and phosphorus oxychloride
were removed under vacuum. The residue was distilled under vacuum and
the distillate collected in three fractions:

**Fraction 1:** a colourless oil (1.5 g.), b.p. 70-100°/0.1 mm.

\[ \nu_{\text{max.}} \text{ 1690, 1665, 1655, 1635 cm.}^{-1} \]

A sample of the oil was hydrolysed with water to give a colourless solid.
\[ \nu_{\text{max.}} \] 1725, 1710, 1703, 1690 cm\(^{-1}\)

\[ \delta \] 2.14 (0.12 H, s, CH\(_3\)-CO), 4.12 (0.22 H, s, CH\(_2\)Cl\(_2\)-CO), 6.06 (0.34 H, s, CHCl\(_2\)-CO)p.p.m.

**Fraction 2:** a colourless oil (2.0 g.), b.p. 100-102°/0.1 mm.

\[ \nu_{\text{max.}} \] 1690, 1665, 1655, 1635 cm\(^{-1}\)

A sample of the oil was hydrolysed with water to give a colourless solid.

\[ \nu_{\text{max.}} \] 1725, 1710, 1703, 1690 cm\(^{-1}\)

\[ \delta \] 4.12 (0.14 H, s, CH\(_2\)Cl\(_2\)-CO), 6.00 (0.35 H, s, CHCl\(_2\)-CO)p.p.m.

**Fraction 3:** a colourless oil (1.6 g.), b.p. 102-126°/0.2 mm.

\[ \nu_{\text{max.}} \] 1690, 1665, 1655 cm\(^{-1}\)

A sample of the oil was hydrolysed with water to give a colourless solid.

\[ \nu_{\text{max.}} \] 1725, 1710, 1703 cm\(^{-1}\)

\[ \delta \] 4.10 (0.05 H, s, CH\(_2\)Cl\(_2\)-CO) 6.00 (0.60 H, s, CHCl\(_2\)-CO)p.p.m.

(b) Acetanilide (9.4 g., 0.07 mole) and phosphorus pentachloride (57.6 g, 0.28 mole) were refluxed together in benzene (200 ml.) for 24 hr. The solvent and phosphorus oxychloride were removed under vacuum. The residue was distilled under vacuum and the distillate collected in two fractions:

**Fraction 1:** a colourless oil (5.0 g.), b.p. 89-100°/0.15 mm.

\[ \nu_{\text{max.}} \] 1690, 1665 cm\(^{-1}\)

A sample of the oil was hydrolysed with water to give a colourless solid.
\( \nu_{\text{max.}} \) 1725, 1710 cm.\(^{-1}\)

\( \delta \) 6.00 (0.5 H, s, CHCl\(_2\).CO)p.p.m.

**Fraction 2:** a colourless oil (5.7 g.), b.p. 100–102\(^{\circ}\)/0.15 mm.

\( \nu_{\text{max.}} \) 1690, 1665 cm.\(^{-1}\)

A sample of the oil was hydrolysed with water to give a colourless solid.

\( \nu_{\text{max.}} \) 1725, 1710 cm.\(^{-1}\)

\( \delta \) 6.00 (0.14 H, s, CHCl\(_2\).CO)p.p.m.

**Reaction of Propionanilide with Phosphorus Pentachloride:**

Propionanilide (10 g., 0.067 mole) and phosphorus pentachloride (41.6 g., 0.21 mole) were warmed in benzene (200 ml.) for 0.5 hr. The solvent and phosphorus oxychloride were removed under vacuum. The residue was distilled under vacuum and the distillate collected in two fractions:

**Fraction 1:** a colourless oil (9 g.), b.p. 88\(^{\circ}\)/0.01 mm.

\( \nu_{\text{max.}} \) 1691 cm.\(^{-1}\)

A sample of the oil was hydrolysed with water to give 2,2-dichloropropionanilide as colourless rhombs, m.p. 101\(^{\circ}\) (lit.\(^{128b}\), 101\(^{\circ}\)) from chloroform-light petroleum.

\( \nu_{\text{max.}} \) 3415 and 3340 (sh.) (NH), 1712 (amide CO) cm.\(^{-1}\)

\( \delta \) 2.34 (3 H, s, CH\(_3\)CCl\(_2\).CO), 8.32 (1 H, s broad, NH.C0) p.p.m.

**Fraction 2:** a colourless oil (1 g.), b.p. 88–112\(^{\circ}\)/0.01 mm., which was not further investigated.
**Ethyl Benzimidate Hydrochloride (76).** This was made following Dox's procedure.\(^{259}\) The product was purified by precipitation from dry ethanol with ether to give ethyl benzimidate hydrochloride (85%) as colourless plates, m.p. 115-117° (decomp.) (lit.,\(^{260}\) 119-120, decomp.).

\[ \nu_{\text{max.}} 3410, 2800-2500 \text{ (broad), } 2440, 1635 \text{ (C=O) cm}^{-1} \]

\[ \delta 1.66 \text{ (3 H, t J 7 Hz, } \cdot \text{CH}_2\text{CH}_3) , 4.98 \text{ (2 H, q J 7 Hz, } \cdot \text{CH}_2\text{CH}_3) \]

11.21 (1 H, s broad, NH, exchangeable), 12.65 (1 H, s broad, NH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-methylbenzamidin (77a) Hydrochloride.** A solution of N-methylbenzimidoyl chloride (21.6 g., 0.14 mole) in dry ether (100 ml.) was added, with shaking, to a solution of dry N-phenylhydroxylamine (15.4 g., 0.14 mole) in dry ether (100 ml.). The mixture was boiled under reflux for 5 min. and then kept at 0° for several hours. The mixture was filtered and the solvent removed from the filtrate. The total product (30 g., 94%) was recrystallised from chloroform-benzene to give N-hydroxy-N-phenyl-N'-methylbenzamidin (77a) hydrochloride as colourless plates, m.p. 179-180° (decomp.).

\[ \nu_{\text{max.}} 3360, 2650 \text{ (broad), } 2470 \text{ (sh.}, 2360 \text{ (sh.}, 1635 \text{ (C=O) cm}^{-1} \]

\[ \delta 3.03 \text{ (3 H, s, W} _\frac{1}{2} 5 \text{ Hz, } \cdot \text{NH} \cdot \text{CH}_3) , 10.10 \text{ (1 H, s, W} _\frac{1}{2} 20 \text{ Hz, NH or N.OH, exchangeable) , 11.24 (1 H, s, W} _\frac{1}{2} 28 \text{ Hz, NH or N.OH, exchangeable) p.p.m.} \]
N-Hydroxy-N-phenyl-N'-methylbenzamidine (77a).— The hydrochloride was dissolved in the minimum volume of ethanol-water (1:1) and the solution basified to pH 11 with ammonium hydroxide solution. The mixture was left for 0.5 hr. to complete precipitation. Crystallisation from benzene-light petroleum gave N-hydroxy-N-phenyl-N'-methylbenzamidine (77a)(92%) as fine yellow needles, m.p. 141-142°.

Found: C, 74.2; H, 6.3; N, 12.2.

C₁₄H₁₄N₂O requires C, 74.4; H, 6.2; N, 12.4%.

νₘₐₓ. 3680, 3295, 2480, 1614 (C=O) cm⁻¹

λₘₐₓ. 301 nm (ε 6,000).

δ 2.84 (3 H, s, :N.CH₃), 8.53 (1 H, s broad, N.OH, exchangeable)

The following substituted benzamidines were made by the same method as above.

N-Hydroxy-N-phenyl-N'-ethylbenzamidine (77b) Hydrochloride.— The product was recrystallised five times from benzene-light petroleum to give N-hydroxy-N-phenyl-N'-ethylbenzamidine (77b) hydrochloride (32%) as colourless needles, m.p. 148-149° (decomp.).

Found: C, 65.5; H, 6.4; N, 9.9.

C₁₅H₁₆N₂O.HCl requires C, 65.3; H, 6.2; N, 10.1%.

νₘₐₓ. 3650, 3345, 2610 (broad), 2460 (broad), 2360 (sh), 1630 (C=O) cm⁻¹
\[ \delta 1.28 \ (3 \text{ H, t, J } 7 \text{ Hz, } \cdot \text{CH}_2\cdot \text{CH}_3), \ 3.39 \ (2 \text{ H, m, } \cdot \text{NH}\cdot \text{CH}_2\cdot \text{CH}_3), \]
\[ 8.70 \ (1 \text{ H, very broad, } \cdot \text{NH} \text{ or N.OH, exchangeable}), \ 9.66 \ (1 \text{ H, s} \ W_{1/2} 16 \text{ Hz, } \cdot \text{NH} \text{ or N.OH, exchangeable}) \text{ p.p.m.} \]

**N-Hydroxy-N-phenyl-N’-ethylbenzamidine (77b).** The free base failed to precipitate and was extracted with chloroform and the extract dried. Recrystallisation four times from benzene-light petroleum gave **N-hydroxy-N-phenyl-N’-ethylbenzamidine (77b) (80%)** as yellow plates, m.p. 122-124°.

\[ \nu_{\text{max}}. \ 3660, \ 3295, \ 2480, \ 1610 \ (\text{C=N}) \text{ cm}^{-1} \]
\[ \lambda_{\text{max}}. \ 301 \text{ nm} \ (\varepsilon 6,300). \]
\[ \delta 1.18 \ (3 \text{ H, t, J } 7 \text{ Hz, } \cdot \text{CH}_2\cdot \text{CH}_3), \ 3.15 \ (2 \text{ H, q, J } 7 \text{ Hz, } \cdot \text{CH}_2\cdot \text{CH}_3), \]
\[ 8.51 \ (1 \text{ H, very broad, } \cdot \text{N.OH, exchangeable}) \text{ p.p.m.} \]

**N-Hydroxy-N-phenyl-N’-2-methylpropylbenzamidine (77c) Hydrochloride.** The product was recrystallised four times from chloroform-benzene to give **N-hydroxy-N-phenyl-N’-2-methylpropylbenzamidine (77c) hydrochloride (60%)** as colourless rods, m.p. 172-174° (decomp.).

**Found:**

C, 66.2; H, 6.8; N, 9.9.

C_{16}H_{18}N_2O.HCl requires C, 66.2; H, 6.5; N, 9.6%.

\[ \nu_{\text{max}}. \ 3650, \ 3340, \ 2610 \ (\text{sh.}), \ 2560 \ (\text{broad}), \ 2440, \ 2360 \ (\text{sh.}), \]
\[ 1630 \ (\text{C= N}) \text{ cm}^{-1} \]
\[ \delta 1.38 \ (6 \text{ H, d, J } 6.8 \text{ Hz, } \cdot \text{CH} (\text{CH}_3)\text{ }_2), \ 3.56 \ (1 \text{ H, m, } \cdot \text{CH} (\text{CH}_3)\text{ }_2), \]
\[ 9.02 \ (1 \text{ H, s, } W_{1/2} 5.5 \text{ Hz, } \cdot \text{NH or N.OH, exchangeable}), \ 9.17 \]
\[ (1 \text{ H, s } W_{1/2} 4.5 \text{ Hz, } \cdot \text{NH or N.OH, exchangeable}) \text{ p.p.m.} \]
N-Hydroxy-N-phenyl-N' -2-methylpropylbenzamidine (77c).— The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Recrystallisation from benzene-light petroleum gave $N$-hydroxy-$N$-phenyl-$N'$-2-methylpropylbenzamidine (77c) (82%) as yellow rods, m.p. 116–117°.

$\nu_{\text{max}}$ 3650, 3280, 2470, 1603 (C=N) cm$^{-1}$

$\lambda_{\text{max}}$ 300 nm ($\varepsilon$ 8,300).

$\delta$ 1.20 (6 H, $d, J 6.5$ Hz, -CH(CH$_3$)$_2$), 3.46 (1 H, m, -CH(CH$_3$)$_2$), 8.53 (1 H, s broad, NH or N.OH, exchangeable) p.p.m.

$N$-Hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a) Hydrochloride.— The product was recrystallised three times from chloroform-light petroleum to give $N$-hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a) hydrochloride (93%) as colourless plates, m.p. 176–178° (decomp.). (lit.,$^{144}$ 176–177°).

$\nu_{\text{max}}$ 3650, 3320, 2620 (broad), 2530 (sh.), 2430, 2550 (sh.), 1620 (C=N) cm$^{-1}$

$\delta$ 11.64 (2 H, s $\tilde{W}$ 34 Hz, $\ddot{\text{NH}}$ and N.OH, exchangeable) p.p.m.

$N$-Hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a).— The product was crystallised three times from ethyl acetate to give $N$-hydroxy-$N$-phenyl-$N'$-phenylbenzamidine (78a) (80%) as fine yellow rods, m.p. 170–172°. (lit.,$^{144}$ 171°, decomp.).

$\nu_{\text{max}}$ 3660, 3240, 2470, 1605 (C=N) cm$^{-1}$

$\lambda_{\text{max}}$ 255 ($\varepsilon$ 8,050), 316 nm ($\varepsilon$ 7,900).
δ 8.56 (1 H, s W½ 15 Hz, N·OH, exchangeable) p·p·m·

**N-Hydroxy-N'-phenyl-N'-cyclohexylbenzamidine (77d) Hydrochloride.**
The product was washed with a little acetone and recrystallised from acetone to give **N-hydroxy-N'-phenyl-N'-cyclohexylbenzamidine (77d) hydrochloride** (85%) as colourless prisms, m.p. 177-178° (decomp.).

Found: C, 68.9; H, 7.0; N, 8.4.

C₁₉H₂₂N₂O·HCl requires C, 69.0; H, 7.0; N, 8.5%.

ν max. 3340, 2610 (sh.), 2540 (broad), 2430, 2340 (sh.) 1623 (C=O) cm⁻¹

δ 0.67-2.42 (10 H, m, methylene envelope), 3.20 (1 H, m, ḳ ḳ H.
CH₅(CH₂)₅), 9.17 (1 H, s broad, ḳ H or N·OH, exchangeable),
12.35 (1 H, s broad, ḳ H or N·OH, exchangeable) p·p·m·

**N-Hydroxy-N'-phenyl-N'-cyclohexylbenzamidine (77d).**—The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Recrystallisation from acetone gave **N-hydroxy-N'-phenyl-N'-cyclohexylbenzamidine (77d) (88%)** as yellow rhombs, m.p. 146-147°.

ν max. 3280, 2490, 1606 (C=O) cm⁻¹

λ max. 302 nm (ε 10,300).

δ 0.58-2.23 (10 H, m, methylene envelope), 3.01 (1 H, m,
N·CH₅(CH₂)₅) p·p·m· N·OH not visible.
N-Hydroxy-N-phenyl-N'-benzylbenzamidine (77e) Hydrochloride. The product was washed with acetone and recrystallised from acetone and a little ethanol to give N-hydroxy-N-phenyl-N'-benzylbenzamidine (77e) hydrochloride (72%) as colourless rhombs, m.p. 183-184° (decomp.) (lit. 119b 195°).

Found: C, 71.0; H, 5.6; N, 8.4.
Calc. for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O.HCl: C, 70.9; H, 5.6; N, 8.3%.

ν<sub>max</sub> 3660, 3340, 2620 (broad), 2440 (broad), 2340 (sh.), 1630 (C=N) cm<sup>-1</sup>
δ 4.72 (2 H, s W<sub>1</sub> 3 Hz, :NH·CH<sub>2</sub>·) 10.29 (2 H, s W<sub>2</sub> 13 Hz, NH and N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-benzylbenzamidine (77e). The product was crystallised from ethyl acetate to give N-Hydroxy-N-phenyl-N'-benzylbenzamidine (77e) (90%) as yellow prisms, m.p. 138-140°.

ν<sub>max</sub> 3650, 3280, 1610 (C=N) cm<sup>-1</sup>
λ<sub>max</sub> 233 (ε 9,320), 301 nm (ε 6,300).
δ 4.49 (2 H, s, :N·CH<sub>2</sub>·) p.p.m. N·OH not visible.

N-Hydroxy-N-phenyl-N'-o-tolylbenzamidine (79a) Hydrochloride. The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-o-tolylbenzamidine (79a) hydrochloride (81%) as colourless rhombs, m.p. 196-197° (decomp.).
Found: C, 71.1; H, 5.6; N, 8.3.

C₁₉H₁₈N₂O·HCl requires C, 71.0; H, 5.6; N, 8.3%.

νₘₐₓ. 3650, 3320, 2640, 2440 (broad), 2340 (sh.), 1620 (C=N) cm⁻¹

δ 2.46 (3 H, s, Ar·CH₃), 10.78 (2 H, s Wᵢ 7 Hz, ÑH and N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'·α-tolylbenzamidine (79a).— The free base failed to precipitate from alkaline solution and was extracted with chloroform. The extract was dried and the solvent was removed to give N-hydroxy-N-phenyl-N'·α-tolylbenzamidine (79a) as a green oil (94%) which could not be crystallised.

νₘₐₓ. 3660, 3240, 2480, 1595 (C=N) cm⁻¹

λₘₐₓ. 257 (ε 6,250), 313 nm (ε 6,350).

δ 2.42 (3 H, s, Ar·CH₃), 4.72 (1 H, s broad, N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'·α-anisylbenzamidine (79b) Hydrochloride.— The product was washed sparingly with acetone and recrystallised from acetone and a little methanol to give N-hydroxy-N-phenyl-N'·α-anisylbenzamidine (79b) hydrochloride (77%) as colourless rhombs, m.p. 161-162⁰ (decomp.).

Found: C, 67.8; H, 5.3; N, 7.9.

C₂₀H₁₈N₂O₂·HCl requires C, 67.7; H, 5.4; N, 7.9%.

νₘₐₓ. 3660, 3320, 2840 (OCH₃), 2610 (sh.), 2520 (sh.), 2430 (sh.), 1620 (C=N) cm⁻¹
δ 3.79 (3 H, s, Ar·O·CH₃), 10.60 (2 H, s very broad, NH and N·OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-o-anisylbenzamidine (79b).** The product was crystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-o-anisylbenzamidine (79b) (80%) as pale green rods, m.p. 145-147°.

ν max. 3660, 3270, 2840 (OCH₃), 2480, 1603 (C=N) cm⁻¹

λ max. 253 (ε 12,700), 322 nm (ε 14,150).

δ 3.88 (3 H, s, Ar·O·CH₃), 8.72 (1 H, s very broad, N·OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-p-tolylbenzamidine (80a) Hydrochloride.** The product was washed with acetone and recrystallised from acetone and a little ethanol to give N-hydroxy-N-phenyl-N'-p-tolylbenzamidine (80a) (76%) as colourless rods m.p. 200-202° (decomp.) (lit.,¹¹⁹b 201-202).

**Found:**

C, 70.7; H, 5.4; N, 8.5.

**Calc. for C₂₉H₁₈N₂O·HCl:**

C, 71.0; N, 5.6; N, 8.3%.

ν max. 3650, 3320, 2620 (broad), 2530 (sh.), 2440, 2360 (sh.)

1620 (C=N) cm⁻¹

δ 2.26 (3 H, s, Ar·CH₃), 11.64 (2 H, s W₁ 12.5 Hz, NH and N·OH, exchangeable) p.p.m.
N-Hydroxy-N-phenyl-N'-p-tolylbenzamidine (80a).— The product was crystallised from ethyl acetate to give N-hydroxy-N-phenyl-N'-p-tolylbenzamidine (80a) (88%) as yellow rods, m.p. 186-187° (decomp.) (lit., 119°, 191°).

\[ \nu_{\text{max.}} \quad 3660, 3260, 2480, 1603 \text{ (C=N) cm}^{-1} \]

\[ \lambda_{\text{max.}} \quad 255 (\epsilon 14,000), 317 \text{ nm (} \epsilon 12,950) \].

\[ \delta 2.22 (3 \text{ H, s, Ar.CH}_3), 7.99 (1 \text{ H, s very broad, N.OH, exchangeable}) \text{ p.p.m.} \]

N-Hydroxy-N-phenyl-N'-p-anisylbenzamidine (80b) Hydrochloride.— The product was washed sparingly with acetone and recrystallised from acetone and a little methanol to give N-hydroxy-N-phenyl-N'-p-anisylbenzamidine (80b) hydrochloride (75%) as colourless rods, m.p. 173-174° (decomp.).

Found: C, 67.9; H, 5.4; N, 8.2.

\[ \text{C}_{20}\text{H}_{18}\text{N}_{2}\text{O}_{2} \cdot \text{HCl requires C, 67.7; H, 5.4; N, 7.9\%} \]

\[ \nu_{\text{max.}} \quad 3330, 2840 (\text{OCH}_3), 2620 \text{ (broad), 2550 (sh.), 2440, 2360 (sh.), 1620 (C=N) cm}^{-1} \]

\[ \delta 3.65 (3 \text{ H, s, Ar.O.CH}_3), 11.12 (2 \text{ H, s, W}_1 14 \text{ Hz, NH and N.OH, exchangeable}) \text{ p.p.m.} \]

N-Hydroxy-N-phenyl-N'-p-anisylbenzamidine (80b).— The product was recrystallised from acetone to give N-hydroxy-N-phenyl-N'-p-anisylbenzamidine (80b) (90%) as yellow rods, m.p. 178-180°.
\( \nu_{\text{max.}} \) 3250, 2840 (OCH\(_3\)), 2480, 1602 (C=\( N \)) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 253 (\( \epsilon \ 8,750 \)), 316 nm (\( \epsilon \ 7,000 \)).

\( \delta \) 3.70 (3 H, s, Ar-OCH\(_3\)), 9.12 (1 H, s \( W_2 \) 12 Hz, N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-phenyl-o-tolamidine (81a) Hydrochloride.**—The product was washed sparingly with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-o-tolamidine (81a) hydrochloride (86%) as colourless rhombs m.p. 184-186° (decomp.).

**Found:**

C, 71.0; H, 5.7; N, 8.4.

C\(_{20}H_{18}N_2O\cdot HCl\) requires C, 71.0; H, 5.6; N, 8.3%.

\( \nu_{\text{max.}} \) 3320, 2630, 2440, 2360 (sh.), 1623 (C=\( N \)) cm\(^{-1}\)

\( \delta \) 2.24 (3 H, s, Ar-CH\(_3\)), 11.89 (2 H, s very broad, \( NH \) and N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-phenyl-o-tolamidine (81a).**—The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Recrystallisation from chloroform-light petroleum gave N-hydroxy-N-phenyl-N'-phenyl-o-tolamidine (81a) as pale green needles, m.p. 131-132°.

\( \nu_{\text{max.}} \) 3660, 3260, 2480, 1601 (C=\( N \)) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 260 (\( \epsilon \ 9,450 \)), 309 nm (\( \epsilon \ 11,750 \)).

\( \delta \) 2.09 (3 H, s, Ar-CH\(_3\)), 9.55 (1 H, s \( W_2 \) 12 Hz, N.OH, exchangeable) p.p.m.
N-Hydroxy-N-phenyl-N'-phenyl-o-anisamidine (81b) Hydrochloride.— The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-o-anisamidine (81b) hydrochloride (83%) as colourless rhombs, m.p. 173-175° (decomp.).

Found: C, 67.8; H, 5.4; N, 8.0.

C_{20}H_{18}N_2O_2·HCl requires C, 67.9; H, 5.4; N, 7.9%.

ν max. 3320, 2840 (OCH₃), 2610 (sh.) 2530 (broad), 2440, 2360
(sh.), 1630 (C=N) cm⁻¹

δ 3.48 (3 H, s, Ar·O·CH₃), 9.87 (2 H, s very broad, NH and N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-phenyl-o-anisamidine (81b).— The product failed to precipitate from alkaline solution and was extracted with chloroform. The extract was dried and the solvent removed to give N-hydroxy-N-phenyl-N'-phenyl-o-anisamidine (81b) (89%) as a pale yellow gum which could not be crystallised.

ν max. 3250, 2840 (OCH₃), 2470, 1603 (C=N) cm⁻¹

λ max. 261 (ε 10,800), 294 nm (ε 13,500).

δ 3.44 (3 H, s, Ar·O·CH₃), 7.73 (1 H, s broad, N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-phenyl-p-tolamidine (82a) Hydrochloride.— The product was washed with acetone and recrystallised five times from acetone.
to give \(\text{N-hydroxy-N-phenyl-N'-phenyl-p-tolamidine (82a)}\) hydrochloride (60%) as colourless rhombs, m.p. 175-176\(^\circ\) (decomp.).

Found: C, 71.3; H, 5.6; N, 8.5.

\(\text{C}_{20}\text{H}_{18}\text{N}_2\text{O} \cdot \text{HCl requires C, 71.0; H, 5.6; N, 8.3\%}.\)

\(\nu_{\text{max.}} 3650, 3320, 2650 \text{ (sh.) 2510 (sh.), 2430, 2360 (sh.),} 1625 \text{ (C=N) cm}^{-1}\)

\(\delta 2.19 (3 \text{ H, s, Ar.CH}_3), 11.68 (2 \text{ H, s W}_1 13 \text{ Hz, } \ddot{\text{NH}} \text{ and N.OH, exchangeable}) \text{ p.p.m.}\)

\(\text{N-Hydroxy-N-phenyl-N'-phenyl-p-tolamidine (82a).} - \text{The product was crystallised from ethyl acetate to give N-hydroxy-N-phenyl-N'-phenyl-p-tolamidine (82a) (90%) as pale yellow needles, m.p. 167-168\(^\circ\).}\n
\(\nu_{\text{max.}} 3240, 2470, 1603 \text{ (C=N) cm}^{-1}\)

\(\lambda_{\text{max.}} 254 (\varepsilon 9,400), 315 \text{ nm} (\varepsilon 8,800).\)

\(\delta 2.24 (3 \text{ H, s, Ar.CH}_3), 9.17 (1 \text{ H, s W}_1 13 \text{ Hz, N.OH, exchangeable}) \text{ p.p.m.}\)

\(\text{N-Hydroxy-N-phenyl-N'-phenyl-p-anisamidine (82b) Hydrochloride.} - \text{The product was crystallised twice from acetone to give N-hydroxy-N-phenyl-N'-phenyl-p-anisamidine (82b) hydrochloride (75%) as colourless plates, m.p. 158-160\(^\circ\) (decomp.).}\n
Found: C, 67.9; H, 5.4; N, 8.0.

\(\text{C}_{20}\text{H}_{18}\text{N}_2\text{O} \cdot \text{HCl requires C, 67.7; H, 5.4; N, 7.9\%.}\)
\[ \nu_{\text{max.}} = 3660, 3330, 2840 (\text{OCH}_3), 2630 (\text{sh.}), 2560 \text{ (broad)}, 2440, \\
2360 \text{ (sh.)}, 1625 \text{ (C=N)} \text{ cm}^{-1} \]

\[ \delta \ 3.69 \ (3 \text{ H, s, Ar-OCH}_3), 11.89 \ (2 \text{ H, s very broad, } \text{NH and N-OH, exchangeable}) \text{ p.p.m.} \]

\text{N-Hydroxy-N-phenyl-N'-phenyl-p-anisamidine (82b).-- The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-p-anisamidine (82b) (90%) as yellow rods, m.p. 175-176^\circ.} \\
\[ \nu_{\text{max.}} = 3240, 2470, 1603 \text{ (C=N)} \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} = 253 \text{ (e 14,900), 317 nm (e 13,350).} \]

\[ \delta \ 3.70 \ (3 \text{ H, s, Ar-OCH}_3), 8.59 \ (1 \text{ H, s W}_2 14 \text{ Hz, N-OH, exchangeable}) \text{ p.p.m.} \]

\text{N-Hydroxy-N-phenyl-N'-o-tolyl-o-tolamidine (83a) Hydrochloride.-- The product was washed sparingly with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-o-tolyl-o-tolamidine (83a) hydrochloride (81%) as colourless rhombs, m.p. 179-180^\circ (decomp.).} \\
\text{Found:} \quad \text{C, 71.6; H, 6.0; N, 8.0.} \\
\text{C}_{21}\text{H}_{20}\text{N}_2\text{O.HCl requires C, 71.5; H, 6.0; N, 8.0%.} \\
\[ \nu_{\text{max.}} = 3320, 2620, 2510 \text{ (sh.), 2430, 2350 \ (sh.), 1623 \ (C=N)} \text{ cm}^{-1} \]

\[ \delta \ 2.25 \ (3 \text{ H, s, C}_2'\text{-CH}_3), 2.58 \ (3 \text{ H, s, C}_2\text{-CH}_3), 11.25 \ (2 \text{ H, s very broad, } \text{NH and N-OH, exchangeable}) \text{ p.p.m.} \]
N-Hydroxy-N-phenyl-N'-o-tolyl-o-tolamidine (83a).— The product separated as a green oil from alkaline solution. The aqueous layer was decanted and extracted with chloroform and the extract combined with the green oil and dried. Removal of solvent left N-hydroxy-N-phenyl-N'-o-tolyl-o-tolamidine (83a) (81%) as a pale green gum which could not be crystallised.

\[ \nu_{\text{max.}} \ 3240, \ 2480, \ 1598 \ (C=\text{N}) \ \text{cm}^{-1} \]

\[ \lambda_{\text{max.}} \ 252 \ (\varepsilon \ 6,500), \ 308 \ \text{nm} \ (\varepsilon \ 8,560). \]

\[ \delta \ 2.07 \ (3 \ H, \ s, \ C_2\cdot\text{CH}_3), \ 2.45 \ (3 \ H, \ s, \ C_2\cdot\text{CH}_3), \ 8.39 \ (1 \ H, \ s \ \text{broad, N-OH, exchangeable}) \ p.p.m. \]

N-Hydroxy-N-phenyl-N'-p-tolyl-p-tolamidine (84a) Hydrochloride.— The product was washed sparingly with acetone and recrystallised twice from acetone to give N-hydroxy-N-phenyl-N'-p-tolyl-p-tolamidine (84a) hydrochloride (50%) as pale yellow plates, m.p. 176-177° (decomp.).

Found: C, 71.5; H, 6.0; N, 8.0%.

\[ \nu_{\text{max.}} \ 3650, \ 3320, \ 2620 \ (\text{broad}), \ 2440, \ 2360 \ (\text{sh.}), \ 1620 \ (C=\text{N}) \ \text{cm}^{-1} \]

\[ \delta \ 2.17 \ (6 \ H, \ s, \ 2\times\text{Ar}\cdot\text{CH}_3), \ 11.80 \ (2 \ H, \ s \ \text{very broad, NH and N-OH, exchangeable}) \ p.p.m. \]

N-Hydroxy-N-phenyl-N'-p-tolyl-p-tolamidine (84a).— The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-p-tolyl-p-tolamidine (84a) (90%) as yellow rods, m.p. 174-175°.
\( \nu_{\text{max.}} \) 3250, 2840 (OCH\(_3\)), 2480, 1603 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 255 (\( \epsilon \ 9,050 \)), 315 nm (\( \epsilon \ 12,650 \)).

\( \delta \) 3.58 (3 H, s, C\(_2\)OCH\(_3\)), 3.88 (3 H, s, C\(_2\)OCH\(_3\)), N.OH not visible.

**N-Hydroxy-N-phenyl-\( N'\)-o-anisyl-\( o\)-anisamidine (83b)** Hydrochloride.— The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-\( N'\)-o-anisyl-\( o\)-anisamidine (83b) hydrochloride (76%) as colourless rhombs, m.p. 170-172° (decomp.).

Found: \( C, 65.4; H, 5.5; N, 7.1\)%

C\(_{21}\)H\(_{20}\)N\(_2\)O\(_3\)HCl requires \( C, 65.6; H, 5.5; N, 7.3\)%.

\( \nu_{\text{max.}} \) 3330, 2840 (OCH\(_3\)), 2610 (sh.), 2520 (sh.), 2430, 2360 (sh.), 1635 (C=N) cm\(^{-1}\)

\( \delta \) 3.54 (3 H, s, C\(_2\)OCH\(_3\)), 3.87 (3 H, s, C\(_2\)OCH\(_3\)), 9.50

2 H, s, broad, \( \hat{\nu} \)H and N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-\( N'\)-o-anisyl-\( o\)-anisamidine (83b).—** The free base failed to precipitate from alkaline solution and was extracted with chloroform. The extract was dried and the solvent removed to give N-hydroxy-N-phenyl-\( N'\)-o-anisyl-\( o\)-anisamidine (83b) (90%) as a yellow gum which could not be crystallised.

\( \nu_{\text{max.}} \) 3250, 2840 (OCH\(_3\)), 2480, 1603 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 255 (\( \epsilon \ 9,050 \)), 315 nm (\( \epsilon \ 12,650 \)).

\( \delta \) 3.50 (3 H, s, C\(_2\)OCH\(_3\)), 3.88 (3 H, s, C\(_2\)OCH\(_3\)), N.OH not visible.
N-Hydroxy-N-phenyl-N'-phenyl-o-chlorobenzamidine (81c) Hydrochloride.- The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-o-chlorobenzamidine (81c) hydrochloride (91%) as colourless tablets, m.p. 173-175° (decomp.).

Found: C, 63.0; H, 4.6; N, 7.6.

C_{19}H_{15}N_{2}OCl・HCl requires C, 63.4; H, 4.5; N, 7.8%.

ν max. 3320, 2640, 2510 (sh.), 2440, 2360 (sh.), 1630 (C=N) cm⁻¹

δ 11.40 (2 H, s W \frac{1}{2} 14 Hz, NH and N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-phenyl-o-chlorobenzamidine (81c).- The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-o-chlorobenzamidine (81c) (98%) as pale green tablets, m.p. 110-112°.

ν max. 3260, 2470, 1603 (C=N) cm⁻¹

λ max. 266 (ε 12,600), 309 nm (ε 11,270).

δ 8.10 (1 H, s W \frac{1}{2} 14 Hz, N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-2,6-xylylbenzamidine (85) Hydrochloride.- The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-2,6-xylylbenzamidine (85) hydrochloride (86%) as colourless rhombs, m.p. 177-179°.

Found: C, 71.0; H, 6.3; N, 7.8.

C_{21}H_{20}N_{2}O・HCl requires C, 71.3; H, 6.0; N, 7.9%.
\( \nu_{\text{max.}} \) 3660, 3320, 2540 (sh.), 2560 (broad), 2440, 2360 (sh.), 1615 (C=N) cm\(^{-1}\)

\( \delta 2.37 \) (6 H, s, 2 x Ar\( \cdot \)CH\(_3\)), 11.02 (2H, s W\(_2\) 12 Hz, \( \ddagger \)H and N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-2,6-xylylbenzamidine (85).**—The free base failed to precipitate from alkaline solution and was extracted with chloroform. The extract was dried and the solvent removed to give N-hydroxy-N-phenyl-N'-2,6-xylylbenzamidine (85) (92%) as a yellow-brown oil which could not be crystallised.

\( \nu_{\text{max.}} \) 3240, 2460, 1603 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 250 (\(\epsilon\) 7,150), 312 nm (\(\epsilon\) 6,550).

\( \delta 2.25 \) (6 H, s, 2 x Ar\( \cdot \)CH\(_3\)), 7.82 (1 H, s broad, N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-p-bromophenylbenzamidine (80c) Hydrochloride.**—The product was washed with acetone and recrystallised from chloroform-acetone to give N-hydroxy-N-phenyl-N'-p-bromophenylbenzamidine (80c) hydrochloride (91%) as colourless rods, m.p. 178–180° (decomp.).

**Found:**

C, 56.8; H, 4.15; N, 6.3.

C\(_{19}\)H\(_{15}\)N\(_2\)OBr.HCl requires C, 56.6; H, 4.0; N, 6.9%.

\( \nu_{\text{max.}} \) 3320, 2800–2550 (broad), 2450, 2360 (sh.), 1619 (C=N) cm\(^{-1}\)

\( \delta 9.54 \) (2 H, s broad, \( \ddagger \)H and N.OH, exchangeable) p.p.m.
N-Hydroxy-N-phenyl-N'-p-bromophenylbenzamidine (60c) -- The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-p-bromophenylbenzamidine (60c) 95% as pale yellow rods, m.p. 184-185°.

\[ \nu_{\text{max.}} = 3230, 1595 \text{ (C=N) cm}^{-1} \]
\[ \lambda_{\text{max.}} = 261 (\varepsilon 8,260), 317 \text{ nm (}\varepsilon 9,160) \]
\[ \delta_{\text{ca.}} = 6.9 \text{ (N.OH, exchangeable, obscured by aromatic signals) p.p.m.} \]

N-Hydroxy-N-phenyl-N'-phenyl-p-chlorobenzamidine (62c) Hydrochloride.-- The product was washed sparingly with acetone and recrystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-phenyl-p-chlorobenzamidine (62c) hydrochloride (82%) as colourless rods, m.p. 168-170° (decomp.).

Found: C, 63.8; H, 4.4; N, 7.8.

\[ C_{19}H_{15}NOC\text{HCl requires C, 63.6; H, 4.5; N, 7.8%.} \]
\[ \nu_{\text{max.}} = 3320, 2650, 2550 \text{ (broad), 2430, 2360 (sh.), 1630 (C=N) cm}^{-1} \]
\[ \delta = 8.42 \text{ (2 H, s W}_{\frac{1}{2}}15 \text{ Hz, } {\H}H \text{ and N.OH, exchangeable) p.p.m.} \]

N-Hydroxy-N-phenyl-N'-phenyl-p-chlorobenzamidine (62c) -- The product was crystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-phenyl-p-chlorobenzamidine (62c) as fawn laths, m.p. 165-166°.

\[ \nu_{\text{max.}} = 3240, 2460, 1603 \text{ (C=N) cm}^{-1} \]
\[ \lambda_{\text{max.}} = 256 (\varepsilon 9,900), 321 \text{ nm (}\varepsilon 6,700) \]
\[ \delta = 8.29 \text{ (1 H, s broad, N.OH, exchangeable) p.p.m.} \]
N-Hydroxy-N-phenyl-N'-p-chlorophenylbenzamidine (80d) Hydrochloride. - The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-p-chlorophenylbenzamidine (80d) hydrochloride (66%) as colourless tablets, m.p. 177-179° (decomp.).

Found: C, 63.5; H, 4.6; N, 7.8%.

ν_max. 3320, 2650 (broad), 2440 (broad), 2360, 1620 (C=N) cm⁻¹

δ 9.44 (2 H, s very broad, NH and N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-p-chlorophenylbenzamidine (80d). - The product was crystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-p-chlorophenylbenzamidine (80d) (98%) as pale yellow rods m.p. 176-178°.

ν_max. 3240, 2460, 1600 (C=N) cm⁻¹

λ_max. 260 (ε 7,700), 317 nm (ε 8,050).

δ 7.90 (1 H, s W₁ 10 Hz, N·OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-p-chlorophenyl-p-chlorobenzamidine (84b) Hydrochloride. - The product was washed with acetone and recrystallised from acetone and a little ethanol to give N-hydroxy-N-phenyl-N'-p-chlorophenyl-p-chlorobenzamidine (84b) hydrochloride (63%) as colourless rods, m.p. 155-156° (decomp.).

ν_max. 3570, 3320, 2800-2580 (broad), 2460 (broad, 2350 (sh.), 1620 (C=N) cm⁻¹

δ 11.0 (2 H, s, NH and N·OH, exchangeable) p.p.m.
N-Hydroxy-N-phenyl-N'-p-chlorophenyl-p-chlorobenzamidine (84b).— The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-p-chlorophenyl-p-chlorobenzamidine (84b) 95% as pale yellow rods, m.p. 169-170°.

Found: C, 64.4; H, 4.0; N, 7.85.

\( \text{C}_{19} \text{H}_{14} \text{N}_2 \text{OCl}_2 \) requires C, 63.9; H, 4.1; N, 7.8%.

\( \nu_{\text{max}} \) 3240, 2475, 1598 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max}} \) 266 (e 11,660), 322 nm (e 9,060).

\( \delta \) 8.42 (1 H, s W\( \frac{1}{2} \) 7 Hz, N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-1-naphthylbenzamidine (78b) Hydrochloride.— The product was washed with acetone and recrystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-1-naphthylbenzamidine (78b) hydrochloride (72%) as pale yellow rods, m.p. 225-226° (decomp.) (lit., 167 229-230° decomp.).

Found: C, 73.5; H, 4.8; N, 7.5.

Calc. for \( \text{C}_{23} \text{H}_{18} \text{N}_2 \text{O.HCl} \): C, 73.3; H, 4.8; N, 7.7%.

\( \nu_{\text{max}} \) (KBr) 3440, 2520, 2420, 2360, 1620 (C=N) cm\(^{-1}\)

N-Hydroxy-N-phenyl-N'-1-naphthylbenzamidine (78b).— The free base only partially precipitated and was extracted with chloroform and the extract dried. Crystallisation from ethyl acetate gave N-hydroxy-N-phenyl-N'-1-naphthylbenzamidine (78b) (90%) as yellow rhombs, m.p. 153-154° (lit., 167 153.5-154°).
\( \nu_{\text{max.}} \) 1595 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 320 nm (\( \epsilon \) 15,100).

\( \delta \) 9.37 (1 H, s \( \text{H}_2 \) 11 Hz, N.OH, exchangeable) p.p.m.

**N-Hydroxy-N-phenyl-N'-o-nitrophenylbenzamidine (86) Hydrochloride**

The product was washed with acetone and recrystallised from acetone to give N-hydroxy-N-phenyl-N'-o-nitrophenylbenzamidine (86) hydrochloride (63%) as yellow rods, m.p. 171-173° (decomp.).

Found: C, 61.7; H, 4.6; N, 11.1.

**C\textsubscript{19}H\textsubscript{15}N\textsubscript{3}O\textsubscript{3}·HCl** requires C, 61.9; H, 4.3; N, 11.4%.

\( \nu_{\text{max.}} \) 3320, 2760-2420 (broad), 2330 (sh.), 1620 (C=N), 1530 and 1350 (NO\textsubscript{2}) cm\(^{-1}\)

**N-Hydroxy-N-phenyl-N'-o-nitrophenylbenzamidine (86).** The free base only partially precipitated from alkaline solution and was extracted with chloroform and the extract dried. Crystallisation from benzene-light petroleum gave N-hydroxy-N-phenyl-N'-o-nitrophenylbenzamidine (86) 97% as orange-red rods, m.p. 101-102°.

\( \nu_{\text{max.}} \) 3220, 2450, 1613 (C=N), 1520 and 1340 (NO\textsubscript{2}) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 251 (\( \epsilon \) 11,000), 314 (\( \epsilon \) 8,450), 390 nm (\( \epsilon \) 3,330).

\( \delta \) 9.57 (1 H, s broad, N.OH, exchangeable) p.p.m.

The hydrochloride was freely soluble in water to give a red coloured solution. Extraction with chloroform gave the free base.
N-Hydroxy-N-phenyl-N'-m-nitrophenylbenzamidine (87) Hydrochloride.

The product was recrystallised from chloroform to give N-hydroxy-N-phenyl-N'-m-nitrophenylbenzamidine (87) hydrochloride (86%) as colourless rods, m.p. 174-176° (decomp.).

\[ \nu_{\text{max.}} \quad 3660 \text{ (broad)} \quad 2900-2500 \text{ (broad), 2440 (sh.), 2340 (sh.)} \]
\[ 1620 \text{ (C=N), 1530 and 1350 (NO}_2\text{) cm}^{-1} \]

N-Hydroxy-N-phenyl-N'-m-nitrophenylbenzamidine (87).— The product was crystallised from chloroform-light petroleum to give N-hydroxy-N-phenyl-N'-m-nitrophenylbenzamidine (87) (97%) as orange rods, m.p. 177-178°.

Found: C, 68.6; H, 4.7; N, 12.6.

\[ \text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_3 \text{ requires C, 68.5; H, 4.5; N, 12.6%} \]

\[ \nu_{\text{max.}} \quad 3230, 2460, 1600 \text{ (C=N), 1540 and 1350 (NO}_2\text{) cm}^{-1} \]

\[ \lambda_{\text{max.}} \quad 258 \text{ (ε 12,500), 312 nm (ε 10,400).} \]

δ 8.67 (2 H, s very broad, N·OH, exchangeable) p.p.m.

The hydrochloride was freely soluble in water to give a red coloured solution. Extraction with chloroform gave the free base.

N-Hydroxy-N-phenyl-N'-phenyl-p-nitrobenzamidine (88) Hydrochloride.—

The product rapidly evolved hydrogen chloride on exposure to air and changed colour from yellow to red.
N-Hydroxy-N-phenyl-N'-phenyl-p-nitrobenzamidine (88).—The total product from above was treated with ammonium hydroxide solution in the usual way. The product was crystallised from acetone to give N-hydroxy-N-phenyl-N'-phenyl-p-nitrobenzamidine (88) (88%) as bright red needles, m.p. 175-176°.

Found: C, 68.5; N, 12.4%.

v\text{max}. 3250, 2460, 1600 (C=\text{N}), 1530 and 1350 (NO\text{2}) \text{ cm.}^{-1}

λ\text{max}. 284 (ε 11,200), 372 nm (ε 2,780).

δ 8.48 (1 H, s broad, N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-cyclohexyl-p-nitrobenzamidine (89) Hydrochloride.—The product was recrystallised from chloroform to give N-hydroxy-N-phenyl-N'-cyclohexyl-p-nitrobenzamidine (89) hydrochloride (92%) as colourless rhombs, m.p. 163-164° (decomp.).

v\text{max}. 3330, 2660 (sh.), 2540 (broad), 2440, 2360 (sh.), 1633 (C=\text{N}), 1535 and 1355 (NO\text{2}) \text{ cm.}^{-1}

δ 0.66-2.20 (10 H, m, methylene envelope), 2.88 (1 H, m, \text{NH} \cdot \text{CH} \cdot (\text{CH}_{2})_{5}) 9.20 (2 H, s very broad, NH and N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-cyclohexyl-p-nitrobenzamidine (89).—The product was recrystallised from acetone-light petroleum to give N-hydroxy-N-phenyl-N'-cyclohexyl-p-nitrobenzamidine (89) (97%) as fine purple laths, m.p. 140-141°.

Found: C, 66.8; H, 6.5; N, 12.4.

C_{19}H_{21}N_{2}O_{3} requires C, 67.3; H, 6.2; N, 12.4%.
\( \nu_{\text{max}} \) 3650, 3260, 2460, 1610 (C=\text{N}), 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}

\( \lambda_{\text{max}} \) 260 (ε 17,300), 366 nm (ε 2,380).

δ 0.88-2.02 (10 H, m, methylene envelope), 2.95 (1 H, m, \textit{N}-\textit{CH}-(\textit{CH}\textsubscript{2})\textsubscript{5}), ca. 7.1 (N.OH, exchangeable, obscured by aromatic signals) p.p.m.

The hydrochloride was moderately soluble in water to give a deep red coloured solution. Extraction with chloroform gave the free base.

\textit{N-Hydroxy-N-phenyl-N'-phenylcyclohexanecarbonamidine} (90) Hydrochloride.-

The product was recrystallised from chloroform-light petroleum to give \textit{N-hydroxy-N-phenyl-N'-phenylcyclohexanecarbonamidine} (90) hydrochloride (96%) as colourless rhombs, m.p. 137-139°.

Pound: C, 68.7; H, 7.1; N, 8.2.

\textit{C}_{19}\textit{H}_{22}\textit{N}_{2}O.HCl requires C, 69.0; H, 7.0; N, 8.4%.

\( \nu_{\text{max}} \) 3660, 3320, 2650 (broad), 2450 (sh.), 1630 (C=\text{N}) cm\textsuperscript{-1}

δ 0.33-3.02 (11 H, m, methylene envelope), 10.01 (2 H, s very broad, \textit{NH} and N.OH, exchangeable) p.p.m.

\textit{N-Hydroxy-N-phenyl-N'-phenylcyclohexanecarbonamidine} (90).- The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Removal of the solvent left \textit{N-hydroxy-N-phenyl-N'-phenylcyclohexanecarbonamidine} (90) (96%) as a dark-brown gum which could not be crystallised.
\( \nu_{\text{max.}} \) 3200, 2470, 1593 (C=N) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 270 nm (\( \varepsilon \) 10,300).

\( \delta \) 0.20-2.0 (10 H, m, methylene envelope), 2.57 (1 H, m, \( \text{C-CH}(\text{CH}_2)_5 \)), 8.27 (1 H, s broad, N.OH, exchangeable) p.p.m.

N-Hydroxy-N-phenyl-N'-o-nitrophenylacetamide (91) Hydrochloride.

The product was washed with acetone and recrystallised from chloroform and a little acetone to give N-hydroxy-N-phenyl-N'-o-nitroacetamide (91) hydrochloride (74\%) as colourless rods, m.p. 177-178\(^\circ\) (decomp.).

Found: C, 54.4; H, 4.6; N, 13.7.

\( \text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3\text{HCl} \) requires C, 54.7; H, 4.5; N, 13.7\%.

\( \nu_{\text{max.}} \) (KBr) 3401, 1647 (C=N), 1538 and 1357 (NO\(_2\)) cm\(^{-1}\)

N-Hydroxy-N-phenyl-N'-o-nitrophenylacetamide (91).-- The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Removal of the solvent gave N-hydroxy-N-phenyl-N'-o-nitrophenylacetamide (91) (85\%) as a red oil which could not be crystallised.

\( \nu_{\text{max.}} \) 3650, 3360, 2450 (broad), 1610 (C=N), 1520 and 1340 (NO\(_2\)) cm\(^{-1}\)

\( \lambda_{\text{max.}} \) 235 (\( \varepsilon \) 10,500), 339 nm (\( \varepsilon \) 6,230).

\( \delta \) 2.07 (3 H, s, CH\(_3\)), 9.23 (1 H, s W\(_{\frac{1}{2}}\) 20 Hz, N.OH, exchangeable) p.p.m.
The hydrochloride was moderately soluble in water to give a red
coloured solution. Extraction with chloroform gave the free base.

**Attempted Preparation of N-Hydroxy-N-phenyl-N'-2,4,6-tribromophenyl-
benzamidine (94a) Hydrochloride.**—The product failed to precipitate.
Removal of the ether left a red-brown oil which was washed with small
portions of ether. The washings were combined and the solvent removed to
give N-phenylhydroxylamine (97% before recrystallisation). The
remaining red-brown oil was stirred with water and the resulting solid
product recrystallised from ethanol to give benz-2,4,6-tribromoanilide
(100%).

**Attempted Preparation of N-Hydroxy-N-phenyl-N'-2,4,6-tribromophenyl-
acetamidine (94b) Hydrochloride.**—The reaction mixture was worked up
as above to give N-phenylhydroxylamine (95% before recrystallisation)
and an orange oil which slowly evolved hydrogen chloride on exposure
to air. The oil was stirred with water and the solid product recrystallised
from aqueous ethanol to give 2,4,6-tribromoacetanilide (95%).

**N-Hydroxy-N-phenyl-N'-phenyl-2-chloro-2-methylpropionamidine (92 )
Hydrochloride.**—The product precipitated as a dark-brown gum.
Crystallisation from acetone gave N-hydroxy-N-phenyl-N'-phenyl-2-
-chloro-2-methylpropionamidine (92) hydrochloride (65%) as colourless rods
m.p. 129-130° (decomp.).

**Found:**

\[
C, 59.5; H, 5.7; N, 8.8.
\]

\[
C_{16}H_{17}N_2OCl\cdot HCl \text{ requires } C, 59.1; H, 5.55; N, 8.6%.
\]
\[ \nu_{\text{max.}} \text{ 3190, 2740, 2620 (sh.), 2340, 1603 (C=\text{N}) cm}^{-1} \]

\[ \delta \text{ 1.60 (6 H, s, } \cdot \text{C(CH}_3\text{)_2}, \text{ 9.20 (1 H, s, } \frac{\text{W}}{}\text{ 3.5 Hz,} \]

\[ \text{NH or N.OH, exchangeable), 10.66 (1 H, s } \frac{\text{W}}{}\text{ 9 Hz,} \]

\[ \text{NH or N.OH, exchangeable) p.p.m.} \]

**N-Hydroxy-N-phenyl-N'-phenyl-2-chloro-2-methylpropionamidine (92).**

The free base failed to precipitate from alkaline solution and was extracted with chloroform and the extract dried. Removal of solvent gave **N-hydroxy-N-phenyl-N'-phenyl-2-chloro-2-methylpropionamidine (92)** as a dark brown gum (87%) which could not be crystallised.

\[ \nu_{\text{max.}} \text{ 3310 (broad), 1593 (C=\text{N}) cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ 235 (}\varepsilon\text{ 10,100), 283 (}\varepsilon\text{ 8,850), 372 nm (}\varepsilon\text{ 2,340).} \]

\[ \delta \text{ 1.32 (6 H, m, } \cdot \text{C(CH}_3\text{)_2}, \text{ 5.77 (1 H, s broad, N.OH, exchangeable) p.p.m.} \]

**N-Hydroxy-N-phenyl-N'-cyclohexylcyclohexanecarbonamidine (93) Hydrochloride.**

(a) The product was washed with acetone and recrystallised from chloroform-light petroleum to give **N-hydroxy-N-phenyl-N'-cyclohexylcyclohexanecarbonamidine (93) hydrochloride (79%) as colourless rods, m.p. 164-166° (decomp.).**

**Found:**

<table>
<thead>
<tr>
<th></th>
<th>C, 67.8; H, 8.6; N, 8.2.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{19H}<em>{28}N</em>{2}O.HCl</td>
<td>C, 68.2; H, 8.6; N, 8.3%</td>
</tr>
</tbody>
</table>

\[ \nu_{\text{max.}} \text{ 3330, 2660 (sh.), 2520 (sh.), 2440, 2360 (sh.),} \]

\[ 1633 (\text{C=\text{N}) cm}^{-1} \]
δ 0.40–2.93 (21 H, m, methylene envelope), 3.77 (1 H, m, \( \text{NH} \cdot \text{CH} \cdot (\text{CH}_2)_5 \)), 9.84 (2 H, m very broad, \( \text{NH} \) and N·OH, exchangeable p·p·m.

(b) The method of Harvill et al., 145 was followed using N-cyclohexyl-
cyclohexanecarbonamide as the amide and N-phenylhydroxylamine in place
of hydrazoic acid. After the work-up which omitted the period under
reflux and the treatment with ice, the product was a brown tar.
Washing this tar with acetone left N-hydroxy-N-phenyl-N'-cyclohexyl-
cyclohexanecarbonimidine (93) hydrochloride (20%) identical with
that from above.

\( \text{N-Hydroxy-N-phenyl-N'}-\text{cyclohexylcyclohexanecarbonimidine (93).} \)–
The free base failed to precipitate from alkaline solution and was
extracted with chloroform and the extract dried. Removal of the solvent
gave N-hydroxy-N-phenyl-N'-cyclohexylcyclohexanecarbonimidine (93)
(85%) as a dark-green gum which could not be crystallised.

\[ \nu_{\text{max.}} 3240, 2460, 1610 \text{ (C=N) cm}^{-1} \]

\[ \lambda_{\text{max.}} 245 (\epsilon 8,480), 276 \text{ nm (} \epsilon 4,850). \]

δ 0.2–2.20 (20 H, m, methylene envelope), 2.50 (1 H, m, 
\( \text{:C} \cdot \text{CH} \cdot (\text{CH}_2)_5 \)), 3.58 (1 H, m, \( \text{:N} \cdot \text{CH} \cdot (\text{CH}_2)_5 \)), 4.20 (1 H, s
broad, N·OH, exchangeable) p·p·m.

\( \text{N-Phenylbenzamidoxime (95a).} \)– To a solution of hydroxylamine
hydrochloride (3.01 g., 0.043 mole) in the minimum volume of dry
ethanol was added sodium ethoxide (from 0.99 g., 0.043 mole of sodium).
The filtrate was added to a solution of N-phenylbenzimidoyl chloride (3.72 g., 0.017 mole) in dry ether (100 ml.). After standing at room temperature for 12 hr., the volume was reduced to 15 ml. and water (50 ml.) added. The precipitate was filtered off and crystallised from aqueous ethanol to give N-phenylbenzamidoxime (3.3 g., 92%) as colourless rods, m.p. 138-139° (lit., 140 136°).

Found: C, 73.4; H, 5.9; N, 13.2.
Calc. for C₁₃H₁₂N₂O: C, 73.6; H, 5.7; N, 13.2%.

ν max. 3590, 3400, 3220, 1630 (C=N) cm⁻¹

λ max. 247 (ε 9,350), 268 nm (ε 6,350).

δ 8.00-9.17 (2 H, s broad, NH and N.OH, exchangeable) p.p.m.

The following amidoximes were made using the above procedure.

N-α-Tolylbenzamidoxime (95b).- Colourless rhombs (90%) from aqueous ethanol, m.p. 147-148° (lit., 140 147°).

Found: C, 74.5; H, 6.5; N, 12.4.
Calc. for C₁₄H₁₄N₂O: C, 74.4; H, 6.2; N, 12.4%.

ν max. 3580, 3390, 3210, 1630 (C=N) cm⁻¹

λ max. 240 (ε 8,400), 267 nm (ε 5,800).

δ 2.30 (3 H, s, Ar.CH₃), 8.17-9.16 (2 H, s very broad, NH and N.OH) p.p.m.

N-2,6-Xylylbenzamidoxime (96).- Colourless rhombs (98%) from acetone, m.p. 189-190°.
Found: C, 74.9; H, 6.8; N, 11.1.

C_{15}H_{16}N_2 requires C, 75.0; H, 6.7; N, 11.6%.

ν_{max.} 3590, 3390, 3200, 1630 (C=N) cm^{-1}

λ_{max.} 260 nm (ε 6,070).

δ 2.18 (6 H, s, 2 x Ar.CH_3), 8.34-9.00 (2 H, s broad, NH and N.OH) p.p.m.

**N-o-Nitrophenylbenzamidoxime (95c).**—Yellow rhombs from chloroform-light petroleum, m.p. 184-185° (lit. 140° 187°).

Found: C, 60.5; H, 4.1; N, 16.0.

Calc. for C_{13}H_{11}N_3O_3: C, 60.7; H, 4.3; N, 16.3%.

ν_{max.} (KBr) 3320, 3125, 2740, 1653 (C=N), 1534 and 1350 (NO_2) cm^{-1}

λ_{max.} 242 (ε 10,000), 256 (ε 9,750), 396 nm (ε 2,220).

δ (C\_3D\_2N) 10.20 (2 H, s W 12 Hz, NH and N.OH, exchangeable) p.p.m.

**N-o-Anisylbenzamidoxime (95d).**—Colourless plates (92%) from acetone-light petroleum, m.p. 139-140°.

Found: C, 69.4; H, 5.8; N, 11.5.

C_{14}H_{14}N_2O_2 requires C, 69.5; H, 5.8; N, 11.6%.

ν_{max.} 3590, 3400, 3210, 2840 (OCH_3), 1630 (C=N) cm^{-1}

λ_{max.} 248 (ε 12,100), 295 nm (ε 6,650).

δ 3.84 (3 H, s, Ar.O.CH_3), 8.44-9.01 (2 H, s broad, NH and N.OH, exchangeable) p.p.m.
N-2,4,6-Tribromophenylbenzamidoxime (97).- Colourless rhombs (83%)
from acetone-light petroleum, m.p. 179-180° (decomp.).

Found: C, 35.5; H, 2.0; N, 6.2.

C<sub>13</sub>H<sub>9</sub>Br<sub>3</sub>N<sub>2</sub>O requires C, 34.9; H, 2.0; N, 6.2%.

ν<sub>max</sub> = 3410, 3270, 1685 (C=N) cm<sup>-1</sup>

λ<sub>max</sub> = 272 nm (ε 5,390).

δ (C<sub>2</sub>D<sub>5</sub>N) 11.43 (2 H, s W<sub>2</sub> 5 Hz, NH and N=OH, exchangeable) p.p.m.

2-Nitropyridine.- Hydrogen peroxide (100 ml., 30%, 1 mole) was added
dropwise with vigorous stirring to ice cold fuming sulphuric acid
(25% sulphur trioxide, 200 ml.) at such a rate that the temperature
remained below 20°. A solution of 2-aminopyridine (10 g., 0.1 mole)
in concentrated sulphuric acid (50 ml.) was added dropwise to the stirred
mixture, the temperature being kept below 20°. Stirring was continued
for 48 hr. at room temperature. The solution was poured over ice (1 kg.)
and extracted with chloroform (5 x 100 ml.). The extracts were combined
and dried and the solvent removed to give a yellow oil (7.3 g., 55%).
Crystallisation from ether gave 2-nitropyridine as yellow tablets,
m.p. 69-70° (lit., 71°).

ν<sub>max</sub> = 1610, 1565, 1550 (NO<sub>2</sub>), 1460, 1430, 1355 (NO<sub>2</sub>) cm<sup>-1</sup>

2-Hydroxylaminopyridine.- Hydrated platinum oxide (400 mg.) in absolute
ethanol (12 ml.), was hydrogenated at 20° and 50 p.s.i. for 0.25 hr.
in a glass bomb (475 ml.). 2-Nitropyridine (4 g., 0.032 mole) in
absolute ethanol (56 ml.) was introduced and the bomb pressurised to 56 p.s.i. (contains 0.032 mole H₂ at 20°) and rocked until the bomb showed slight negative pressure. The catalyst was filtered off and the solvent rapidly removed under vacuum. The semicrystalline product was washed very sparingly with benzene and recrystallised from chloroform-light petroleum to give 2-hydroxylaminopyridine (2.4 g., 68%) as colourless rhombs, m.p. 81-83° (lit., 262 80-82°). The rhombs sublimed at 100° (bath)/0.01 mm raising the melting point to 84° (lit., 262 83-85°).

\[ \nu_{\text{max.}} \text{3555 (OH), 3230 (NH), 1610, 1580, 1480 and 1450 cm}^{-1} \]

\[ \lambda_{\text{max.}} 237 (\epsilon 5,300), 292 \text{ nm (} \epsilon 1,950): \lambda_{\text{max.}} (\text{EtOH-NaOH}) \]

\[ 243 (\epsilon 2,880), 272 \text{ nm (} \epsilon 2,340): \lambda_{\text{max.}} (\text{EtOH-HCl}) 243 (\epsilon 3,500), 313 \text{ nm (} \epsilon 2,68C). \]

δ 8.67 (2 H, s W₁ 7 Hz, NH and N.OH, exchangeable) p.p.m.

**N-Benzoylphenylhydroxylamine (99a).**—This was prepared by Bamberger's method. Recrystallisation from chloroform-light petroleum gave colourless laths (80%), m.p. 117-119° (lit., 121-122°).

\[ \nu_{\text{max.}} 3250 \text{ and 1620 (C=O) cm}^{-1} \]

\[ \lambda_{\text{max.}} 271 \text{ nm (} \epsilon 6,100): \lambda_{\text{max.}} (\text{EtOH + NaOH}) 306 \text{ nm (} \epsilon 4,380). \]

δ 8.95 (1H, s broad, N.OH, exchangeable) p.p.m.
N-p-Toluylphenylhydroxylamine (99b).— This was made by the same method as above. Recrystallisation from chloroform—light petroleum gave colourless plates (82%), m.p. 117–118° (lit., 264–116°).

\[ \nu_{\text{max.}} \text{ 3240 and 1615 (C=O) cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ 272 nm (c 9,000).} \text{ } \lambda_{\text{max.}} \text{ (EtOH + NaOH) 301 nm (c 9,000).} \]

δ 2.35 (3 H, s, Ar·CH₃) and 9.10 (1 H, s broad, N·OH, exchangeable) p.p.m.

N,N'—Diphenylbenzamidine (100) Hydrochloride.— This was made by von Pechmann's method²⁶⁵ from aniline and N—phenylbenzimidoyl chloride. The crystalline product was washed with ether and recrystallised from chloroform—methanol to give N,N’—diphenylbenzamidine (100) hydrochloride (95%) as colourless plates, m.p. 287–288° (decomp.) (lit., ²⁶⁶ 288–289°, decomp.).

\[ \nu_{\text{max.}} \text{ (KBr) 3450, 3255, 3145, 2960–2700 (b), 2330, 1628 and 1617 cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ 239 (c 13,400), 273 (c 9,700) and 305 nm (c 6,000).} \]

N,N’—Diphenylbenzamidine (100).— The hydrochloride was dissolved in aqueous methanol and the solution adjusted to pH 11 with ammonium hydroxide solution. The product was crystallised from n-hexane to give N,N’—diphenylbenzamidine (100) (90%) as colourless plates, m.p. 145–146° (lit., ²⁶⁶ 146°).
\[ \nu_{\text{max.}} \quad 3435 \text{ and } 3385 \text{ (NH)}, \quad 2480 \text{ w, } 1640 \text{ and } 1630 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \quad 237 \quad (\epsilon \ 13,100) \text{ and } 268 \text{ nm } (\epsilon \ 11,000). \]

\[ \delta \quad 6.23 \quad (1 \text{ H, s broad, NH, exchangeable}) \text{ p.p.m.} \]
Qualitative Tests with Metal Ions.— Dilute solutions (0.5%) of metal salts in aqueous-ethanol (4:1) were made up from the following salts: ferric chloride, mercuric acetate, nickel sulphate, cupric sulphate, plumbous nitrate, cobaltic nitrate, zinc chloride, ferrous sulphate, cadmium nitrate, and manganous sulphate. Dilute solutions (0.5%) of the compounds to be tested were made up in ethanol (95%). Solutions of the non-crystalline hydroxyamidine free bases were made by carefully neutralising an ethanolic solution of the corresponding hydrochloride.

An aliquot (2 ml.) of each metal ion solution was added to an aliquot (2 ml.) of each organic solution. The mixtures were allowed to stand for five minutes and then any changes noted. Blank tests were run to ensure that the free bases were not precipitating. In the cases where mixing the metal ion and organic base solutions gave only a colour change or no change at all, a few drops of sodium acetate solution (10%) were added and any change noted. In all cases where a coloured solution or precipitate was obtained, a little chloroform was added and the sample was shaken. The distribution of the colour or the solubility of the precipitate was noted.

The results of the foregoing tests are tabulated in appendix A.
The Nickel Chelate of N-Hydroxy-N-phenyl-N′-phenylbenzamidine (78a).—
An aqueous solution of nickel chloride (0.5% w/v, 20 ml., 4.2 mmole) was added to an ethanolic solution of N-hydroxy-N-phenyl-N′-
-phenylbenzamidine (78a) hydrochloride (0.5% w/v, 50 ml., 7.7 mmole). The solution was heated to 80° and the complex was precipitated by the addition of a slight excess of dilute ammonium hydroxide solution. The product was dissolved in chloroform and any residue filtered off. The complex was crystallised from chloroform to give yellow micro-
needles (93%), m.p. 298–300° (decomp.).

Found: C, 72.1; H, 5.1; N, 8.85.

\[ C_{38}H_{30}N_2O\text{Ni} \text{ requires } C, 72.25; H, 4.75; N, 8.85\% . \]

\[ \nu_{\text{max.}} \text{ (KBr) } 1593, 1510 \text{ and } 1206 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ (CHCl}_3\text{) } 307 \text{ (inf.) } (\epsilon 16,000) \text{ and } 380 \text{ nm } (\epsilon 6,500) \]

The Copper Chelate of N-Hydroxy-N-phenyl-N′-phenylbenzamidine (78a).—
The above procedure was followed. Crystallisation of the product from chloroform gave bronze leaflets (91%), m.p. 280–1° (decomp.).

Found: C, 71.3; H, 4.8; N, 8.7.

\[ C_{38}H_{30}N_2O\text{Cu} \text{ requires } C, 71.6; H, 4.7; N, 8.8\% . \]

\[ \nu_{\text{max.}} \text{ (KBr) } 1595, 1497 \text{ and } 1217 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ (CHCl}_3\text{) } 274 \text{ (} \epsilon 23,000 \text{) and } 340 \text{ nm } (\epsilon 14,600) \cdot \]
The Nickel Chelate of N-Hydroxy-N-phenyl-N'-1-naphthylbenzamidine (78b).

The above procedure was followed. The product was recrystallised twice from benzene to give yellow micro-needles (94%), m.p. 289-292° (decomp.) (lit., 167 290-291°, decomp.).

Found: \[ C, 75.1; H, 4.8; N, 7.4 \]

\[ C_{45}H_{34}N_4O_2Ni \] requires \[ C, 75.4; H, 4.6; N, 7.6\% \]

\[ \nu_{\text{max.}} \text{ (KBr)} = 1623, 1582, 1504 \text{ and } 1211 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \text{ (CHCl}_3\text{) 305 (infl.) (e 19,000) and 400 (infl.) (e 4,000)} \text{ nm.} \]
α-Phenyl-α-nitrocinnammonitrile (106).— Benzyl cyanide (11.3 g., 0.11 mole) and α-nitrobenzaldehyde (16.6 g., 0.11 mole) were dissolved in the minimum volume of dry ethanol at 0°. Sodium ethoxide (from 2.5 g., 0.11 mole of sodium) was added dropwise with vigorous stirring at such a rate that the temperature did not rise. The mixture was kept at room temperature for 12 hr. The product was washed with water and a little ethanol and recrystallised from ethanol to give α-phenyl-α-nitrocinnammonitrile (106) (25.0 g., 90%) as yellow plates, m.p. 126-127° (lit., 267 127-128°).

\[ \nu_{\max.} 3030 \text{ (CH} = \text{C)}, 2220 \text{ (C=O)}, 1620 \text{ (C=C)}, 1525 \text{ and 1345} \text{ (NO}_2\text{)} \text{ cm}^{-1} \]

δ 7.85 (1 H, s, Ar·CH·C), 8.22 (1 H, m, C_6·H) p·p·m.

2-Amino-3-phenylquinoline-1-oxide (107).— In a typical procedure, a solution of freshly recrystallised sodium sulphide (11.3 g., 0.48 mole) in water (30 ml.) at 60° was added to a solution of α-phenyl-α-nitrocinnammonitrile (6 g., 0.24 mole) in dioxan-ethanol (1:2, 40 ml.) at the same temperature. The reaction mixture was heated on a water bath for 5 min. and then poured into cold water (250 ml.). The solution was extracted with chloroform (2 x 50 ml.) and the extract dried. The solvent was removed and the residue recrystallised from benzene-light petroleum to give 2-amino-3-phenylquinoline-1-oxide (107) (5.05 g., 89%) as fawn plates, m.p. 179-180° (lit., 166 184-185°).
Found: C, 76.3; H, 5.05; N, 12.1.
Calc. for C_{15}H_{12}N_{2}O: C, 76.3; H, 5.0; N, 11.9%.

ν_{max} 3503 and 3345 (NH), 1627 (NH\_2 or C=\text{N}), 1163 (N-O) cm\textsuperscript{-1}

ν_{max} \text{ (KBr)} 3360, 3250 (sh), 3200, 3060 (sh), 2935 cm\textsuperscript{-1}

λ_{max} 253 (ε 50,000), 304 (ε 5,170), 312 (infl.) (ε 5,000)
and 364 nm (ε 5,450). λ_{max} (EtOH + HCl) 248, 296, 337,
and 350 (infl.) nm.

δ 6.64 (2 H, s, W\_2 10.5 Hz, NH\_2, exchangeable), 8.95 (1 H, d,
J\_8,7 9 Hz, C\_8\_H) p.p.m.

T.l.c. of the mother liquor showed that a small amount of a compound with the same R\_p value as 2-amino-3-phenylquinoline (108) (see below) was present. Both this and the major product showed up when the chromatogram was inspected in ultraviolet light.

Reduction of 2-Amino-3-phenylquinoline-1-oxide (107).— (a) Excess phosphorus trichloride was added to a solution of 2-amino-3-phenylquinoline-1-oxide (107) (1 g.) in chloroform (5 ml.). The solution was heated under reflux for 5 min., diluted with water and made alkaline with sodium hydroxide solution. The organic layer was dried and the solvent removed. Recrystallisation of the residue from ethanol gave 2-amino-3-phenylquinoline (108) (800 mg., 86%) as colourless tablets, m.p. 156-157\textdegree (lit., 163\textdegree 155\textdegree).
Found: C, 81.6; H, 5.7; N, 12.5.

Calc. for C_{15}H_{12}N_2: C, 82.0; H, 5.6; N, 12.7%.

ν_{max.} 3505 and 3402 (NH), 1625 (NH_2 or C=N) cm^{-1}

λ_{max.} 241 (ε 22,000), 246 (infl.) (ε 21,000), 279 (infl.) (ε 3,650) and 345 nm (ε 4,750). λ_{max.} (EtOH + HCl) 252, 300, 341 and 352 nm.

δ 5.35 (2 H, s W_2 8 Hz, NH_2, exchangeable) p.p.m.

(b) A solution of 2-amino-3-phenylquinoline-1-oxide (107) (100 mg) in glacial acetic acid (5 ml.) was refluxed with iron powder for 1 hr. The reaction mixture was worked up as above. T.l.c. of the product showed the presence of starting material and 2-amino-3-phenylquinoline (108) in the approximate ratio 2:1 as estimated from the sizes of the spots.

(c) A solution of 2-amino-3-phenylquinoline-1-oxide (107) (1 g., 4.2 m.mole) in glacial acetic acid (16 ml.) and water (4 ml.) was heated at 80° for 2 hr. with zinc dust (1 g., 20 m.mole). The reaction mixture was worked up as above to give a quantitative yield of 2-amino-3-phenylquinoline (108).

Reduction of α-PhenyI-α-nitrocinnamamitrile (106) with Zinc Dust-
Acetic Acid.— (a) A solution of α-phenyl-α-nitrocinnamamitrile (106) (1 g., 4.0 m.mole) in glacial acetic acid (16 ml.) and water (4 ml.) was refluxed with zinc dust (1 g., 20 m.mole). The reaction mixture
developed a green colour after 5 min. and refluxing was continued until the colour disappeared (3 hr.). The reaction mixture was worked up as above to give 2-amino-3-phenylquinoline (108) (95%).

(b) The above reaction was carried out at 80° for 2 hr. The reaction mixture was worked-up as above and the product chromatographed on a preparative t.l.c. plate in chloroform to give 2-amino-3-phenylquinoline-1-oxide (107) (10%) and 2-amino-3-phenylquinoline (108) (70%). The remainder was starting material.

(c) The above reaction was carried out at 20° with stirring for 1 hr. The reaction mixture was worked up as above and the product chromatographed on a preparative t.l.c. plate in chloroform to give 2-amino-3-phenylquinoline-1-oxide (107) (47%) and 2-amino-3-phenylquinoline (108) (35%). The remainder was starting material.

Ethyl-α-cyano-α-nitrocinnamate (109).—Ethyl cyanoacetate (7.5 g., 0.07 mole) and α-nitrobenzaldehyde (10 g., 0.07 mole) were warmed together and sufficient ethanol added to give a solution. Two drops of dilute aqueous potassium hydroxide solution were added and the mixture set aside for 6 hr. The product was washed with a little ethanol and recrystallised from ethanol to give ethyl-α-cyano-α-nitrocinnamate (109) (16 g., 97%) as yellow plates, m.p. 101-102° (lit.,268 101-103°).
\( \nu_{\text{max}} \) 3010 (CH=C), 2245 (C=N), 1735 (ester C=O), 1628 (C=C), 1530 and 1350 (NO\(_2\)) cm\(^{-1}\).

\( \delta \) 1.41 \( (3\ H, \ t, \ J \ 7\ Hz, \ \text{-CH}_2\text{-CH}_3) \), 4.42 \( (2\ H, \ q, \ J \ 7\ Hz, \ \text{-CH}_2\text{-CH}_3) \), 8.25 \( (1\ H, \ d, J_{5,6} \ 9\ Hz, \ C_6\text{-H}) \) and 8.72 \( (1\ H, \ s, \ Ar\text{-CH=CH}) \) p.p.m.

Reduction of Ethyl-\( \alpha \)-cyano-\( \beta \)-nitrocinnamate (109) with Sodium Sulphide.

Reduction of ethyl-\( \alpha \)-cyano-\( \beta \)-nitrocinnamate (109) using the same reaction conditions and work up procedure as for the reduction of \( \alpha \)-phenyl-\( \beta \)-nitrocinnamamoniitrile (106) with sodium sulphide gave a dark brown oil. Preparative t.l.c. in chloroform gave (a) starting material (12\%), (b) 2-amino-3-carbethoxyquinoline-1-oxide (110) (15\%) as yellow plates, m.p. 142-143\(^\circ\) (lit., 166\(^\circ\) 141-142\(^\circ\)) from benzene.

Found:

\[
\begin{align*}
\text{C}, & \ 62.1; \ \text{H}, \ 5.2; \ \text{N}, \ 11.8. \\
\text{Calc. for C}_{12}\text{H}_{12}\text{N}_2\text{O}_3:} & \ \text{C}, \ 62.0; \ \text{H}, \ 5.2; \ \text{N}, \ 12.1\%.
\end{align*}
\]

\( \nu_{\text{max}} \) 3463 and 3335 (NH), 1711 (ester C=O), 1623 (NH\(_2\) and C=N), 1306 (C=O ester band) and 1175 (N-O) cm\(^{-1}\).

\( \lambda_{\text{max}} \) 264 (\( \epsilon \ 52,200 \)), 307 (\( \epsilon \ 4,650 \)), 318 (\( \epsilon \ 4,180 \)) and 404 nm (\( \epsilon \ 3,490 \)). \( \lambda_{\text{max}} \) (EtOH + HCl) 245, 254 (infl.) 306 and 360 nm.

\( \delta \) 1.45 \( (3\ H, \ t, J \ 7\ Hz, \ \text{-CH}_2\text{-CH}_3) \), 4.47 \( (2\ H, \ q, J \ 7\ Hz, \ \text{-CH}_2\text{-CH}_3) \), 8.40 \( (1\ H, \ s, \ C_4\text{-H}) \) and 8.52 \( (1\ H, \ d, J_{8,7} \ 8.5\ Hz, \ C_8\text{-H}) \) p.p.m. The NH signal was obscured by the aromatic signals.
(c) 2-amino-3-carbethoxyquinoline (111) (14%) as colourless plates, m.p. 135-136° (lit., 176° 135°) from acetone,

Found: C, 66.8; H, 5.7; N, 13.3.
Calc. for C₁₂H₁₆N₂O₂: C, 66.7; H, 5.6; N, 12.9%.

νₘₐₓ. 3500 and 3380 (NH), 1700 (ester C=O) 1627 and 1612 (NH₂ and C=N), 1310 and 1290 (C-O ester bands) cm⁻¹

λₘₐₓ. 253 (ε 45,000), 292 (ε 4300), 300 (ε 4,300) and 382 nm (ε 2,800). λₘₐₓ. (EtOH + HCl) 244, 256, 307 and 362 nm.

δ 1.41 (3 H, t; J 7 Hz, CH₂CH₃), 4.41 (2 H, q; J 7 Hz, CH₂CH₃), 6.76 (2 H, s W₂ 13 Hz, NH₂, exchangeable) and 8.65 (1 H, s, C₄H) p.p.m.

Both the 1-oxide and the aminquinoline showed up when the chromatogram was inspected in ultraviolet light. The remainder of the material was present on the chromatogram as a heavy dark band at the origin and a series of fine highly coloured bands extending to the solvent front. None of these bands was further investigated.

The reaction was repeated on the same scale with the temperature kept at 25°C and then worked up as above. The chromatogram was practically identical with that from above.

The 2-amino-3-carbethoxyquinoline-1-oxide (110) was reduced with zinc in refluxing acetic acid in the same way as method (c) for the reduction of 2-amino-3-phenylquinoline-1-oxide (107) to give 2-amino-3-carbethoxyquinoline (111) (88%).
Reduction of Ethyl-α-cyano-γ-nitrocinnamate (109) with Zinc Dust-Acetic Acid.-- (a) The same reaction conditions and work up procedure as for the reduction of α-phenyl-γ-nitrocinnamonitrile (106) with zinc dust (method (a)) gave a yellow gum. Crystallisation of the gum from acetone gave 2-amino-3-carbethoxyquinoline (111) (85%).

(b) The above reaction was carried out at 80° for 2 hrs. The same work-up procedure and chromatography on a preparative t.l.c. plate in chloroform gave 2-amino-3-carbethoxyquinoline-1-oxide (110) (30%) and 2-amino-3-carbethoxyquinoline (111) (30%). The remainder consisted of starting material (8%) and a heavy black band at the origin which was not further investigated.

(c) The above reaction was carried out at 20° for 1 hr. The usual work-up and chromatography of the product gave starting material (86%) 2-amino-3-carbethoxyquinoline-1-oxide (110) (10%) and less than 1% of 2-amino-3-carbethoxyquinoline (111).

2-Aminoquinoline-1-oxide-3-carboxylic acid (112).-- 2-Amino-3-carbethoxyquinoline-1-oxide (110) (1.75 g., 7.5 m.mole) was dissolved in ethanolic potassium hydroxide solution (10%, 20 ml.) and kept at 80° for 0.25 hr. The solution was diluted with water and neutralised with hydrochloric acid. Filtration gave a fawn solid (1.3 g., 85%) which was crystallised from sodium acetate solution (10%) to give 2-aminoquinoline-1-oxide-3-carboxylic acid (112) as yellow micro-rods, m.p. 319-321° (lit.,269 318-320°).
\[ \nu_{\text{max.}} \text{ (KBr)} \ 3410, 3270, 3070, 2920, 2350, 1725 \text{ (sh)}, 1667, 1642 \text{ and } 1620 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \ 264 \text{ (e 36,700)}, 308 \text{ (e 3,700)}, 318 \text{ (e 3,300)} \text{ and } 402 \text{ nm (e 2,600)}. \lambda_{\text{max.}} \text{ (EtOH + HCl)} 245, 307 \text{ and } 362 \text{ nm}. \]

**2-Aminoquinoline-3-carboxylic Acid (113)**: 2-Amino-3-carbethoxyquinoline (111) was treated in the same way as above. The product was crystallised from a large volume of hot water to give 2-aminoquinoline-3-carboxylic acid (113) as pale yellow micro-rods (92%), m.p. 313-314° (lit., 187 320-320.5°).

**Found:** C, 64.2; H, 4.5; N, 14.7.

**Calc. for \( \text{C}_{10} \text{H}_{9} \text{N}_{2} \text{O} \):** C, 63.8; H, 4.3; N, 14.9%.

\[ \nu_{\text{max.}} \text{ (KBr)} \ 3440 \text{ (sh)}, 3245, 2930, 2740, 2600-2440 \text{ (broad)}, 1940, 1725, 1715, 1670 \text{ and } 1630 \text{ cm}^{-1} \]

\[ \lambda_{\text{max.}} \ 245 \text{ (e 12,400)}, 293 \text{ (e 3,000)}, 347 \text{ (e 2,800)} \text{ and } 355 \text{ nm (e 2,500)}. \lambda_{\text{max.}} \text{ (EtOH + HCl)} 244, 256, 304 \text{ and } 355 \text{ nm}. \]

**4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (2-Nitrovanillin) (115).** This was prepared from vanillin (114) using Butenandt's method. Recrystallisation of the product from chloroform-light petroleum gave 2-nitrovanillin (115) (60%) as fawn tablets, m.p. 139-140° (lit., 270 137°).
$\nu_{\text{max.}}$ 3500 (OH), 2840 (OCH$_3$), 1700 (aldehyde C=O), 1550 and 1315 (NO$_2$) cm$^{-1}$

$\delta$ 3.99 (3 H, s, Ar·O·CH$_3$), 6.48 (1 H, s, Ar·OH),
7.21 (1 H, d, $J_{5,6}$ 8 Hz, C$_5$·H), 7.67 (1 H, d, $J_{6,5}$ 8 Hz, C$_6$·H) and 9.81 (1 H, s, Ar·CHO) p.p.m.

**Ethyl-α-cyano-4-hydroxy-3-methoxy-2-nitrocinnamate (116).**—This was prepared by the condensation of ethyl cyanoacetate with 2-nitrovanillin (110) in the same way as for the preparation of ethyl-α-cyano-α-nitrocinnamate (109). Recrystallisation of the product from ethanol gave ethyl-α-cyano-4-hydroxy-3-methoxy-2-nitrocinnamate (116) (95%) as pale yellow rods, m.p. 182-183°.

**Found:**  C, 53.5; H, 4.2; N, 9.6.
C$_{13}$H$_{12}$N$_2$O$_6$ requires  C, 53.4; H, 4.1; N, 9.6%.

$\nu_{\text{max.}}$ 3500 (OH), 2840 (OCH$_3$), 2225 (C=N), 1732 (ester C=O),
1600 (C=C), 1540 and 1370 (NO$_2$) cm$^{-1}$

$\delta$ (CD$_3$COCD$_3$) 1.34 (3 H, t $J$ 7 Hz, ·CH$_2$CH$_3$), 3.87 (3 H, s, Ar·O·CH$_3$), 4.36 (2 H, q $J$ 7 Hz, ·CH$_2$CH$_3$), 7.32 (1 H, d, $J_{5,6}$ 9 Hz, C$_5$·H), 7.96 (1 H, s, Ar·CH·C), and 8.08 (1 H, d, $J_{6,5}$ 9 Hz, C$_6$·H) p.p.m.

This compound was reduced with sodium sulphide in the same way as α-phenyl-α-nitrocinnamonitrile (106) and the reaction followed by t.l.c. After heating on a water bath for 21 hr., a considerable
amount of starting material was still present, together with at least six other compounds, none of which was predominant.

The compound was reduced with zinc dust in refluxing acetic acid in the same way as for α-phenyl-α-nitrocinnamonic acid (106), method (a), except that the reaction was continued until no starting material remained (6 hr.). T.l.c. showed at least ten compounds to be present including those corresponding to products from the sodium sulphide reaction. In both cases two of the spots showed up in ultraviolet light.

Neither reaction mixture was worked up.

α-Phenyl-4-hydroxy-3-methoxy-2-nitrocinnamonic acid (117).— Benzylic cyanide (6 g., 0.05 mole) and 2-nitrovanillin (10 g., 0.05 mole) were dissolved in a solution of sodium ethoxide (from 2.3 g., 0.1 mole sodium) in ethanol (50 ml.). The mixture was heated on a water bath for 5 min. The deep red solution was stirred for a further 6 hr., diluted with water and neutralised with hydrochloric acid.

The precipitate was well washed with water and crystallised from ethanol to give α-phenyl-4-hydroxy-3-methoxy-2-nitrocinnamonic acid (117) (8 g., 53%) as pale yellow rods, m.p. 204–205°.

Found: C, 65.2; H, 4.1; N, 9.4.

C₁₆H₁₂N₂O₄ requires C, 64.9; H, 4.1; N, 9.5%. 

\( \nu_{\text{max}} \) (KBr) 3295 (OH), 2225 (C=N), 1610 (C=C), 1540 and 1370 (NO₂) cm\(^{-1}\)

δ 4.12 (3 H, s, Ar-O-CH₃), 7.28 (1 H, d, J₅,₆ 9 Hz, C₅-H), 8.10 (1 H, d, J₆,₅ 9 Hz, C₆-H), 8.67 (1 H, s, Ar-CH=C) and 10.39 (1 H, s, W₁ 10 Hz, Ar-OH, exchangeable) p.p.m.

This compound was reduced with sodium sulphide in the same way as \( \alpha \)-phenyl-\( \omega \)-nitrocinnammonitrile (106). After heating on a water bath for 20 hr., t.l.c. showed that mostly starting material remained together with six other very minor products.

The compound was reduced with zinc dust-acetic acid in the same way as \( \alpha \)-phenyl-\( \omega \)-nitrocinnammonitrile (106), method (a), for 6 hr. T.l.c. showed six minor compounds to be present and the bulk of the material as a black spot at the origin. In both cases two of the spots showed up in ultraviolet light. Neither reaction mixture was worked up.

Nitration of 2,3-Dimethoxybenzaldehyde (118).— Perkin and Robinson's procedure \(^{179}\) gave a mixture of the 5-nitro (119) and 6-nitro (120) isomers in an overall yield of 95%. A sample of the product (2 g.) was chromatographed on a silica gel column and eluted with chloroform-benzene (4:1) to give 2,3-dimethoxy-5-nitrobenzaldehyde (119) as colourless rods (124 mg.) from chloroform-light petroleum, m.p. 115-116° (lit., \(^{181}\) 115°).
\( \nu_{\text{max.}} \) 2840 (OCH\(_3\)), 1693 (aldehyde C=O), 1530 and 1350 (NO\(_2\)) cm\(^{-1}\)

\( \delta \) 4.04 (3 H, s, C\(_3\)O.CH\(_3\)), 4.17 (3 H, s, C\(_2\)O.CH\(_3\)),
7.95 (1 H, d, J\(_{4,6}\) 2.5 Hz, C\(_4\)H), 8.24 (1 H, d, J\(_{6,4}\) 2.5 Hz, C\(_6\)H) and 10.38 (1 H, s, Ar-CH\(_0\)) p.p.m.

Further elution gave a mixture of the two isomers (1.15 g.) and then 2,3-dimethoxy-6-nitrobenzaldehyde (120) as pale yellow rods (640 mg.), m.p. 110-111.5\(^{0}\) (lit.,\(^{181}\) 110\(^{0}\)) from chloroform-light petroleum.

\( \nu_{\text{max.}} \) 2840 (OCH\(_3\)), 1710 (aldehyde C=O), 1520 and 1340 (NO\(_2\)) cm\(^{-1}\)

\( \delta \) 3.90 (3 H, s, C\(_3\)O.CH\(_3\)), 4.02 (3 H, s, C\(_2\)O.CH\(_3\)),
7.08 (1 H, d, J\(_{4,5}\) 8.4 Hz, C\(_4\)H), 7.93 (1 H, d, J\(_{5,4}\) 8.4 Hz, C\(_5\)H) and 10.32 (1 H, s, Ar-CH\(_0\)) p.p.m.

The ratio of isomers in the crude reaction mixture was estimated as 1:1 from the integrals of the aromatic proton doublets in the n.m.r. spectrum.

**Ethyl-\( \alpha \)-cyano-2,3-dimethoxy-5-nitrocinnamate (121).**—This was prepared by the condensation of ethyl cyanoacetate with 2,3-dimethoxy-5-
-nitrobenzaldehyde (119) in the same way as for the preparation of ethyl-\( \alpha \)-cyano-\( \alpha \)-nitrocinnamate (109). The product was recrystallised from ethanol to give ethyl-\( \alpha \)-cyano-2,3-dimethoxy-5-nitrocinnamate (121) (90%) as colourless rods, m.p. 118-119.5\(^{0}\).
Found: C, 55.0; H, 4.6; N, 9.1.

C₁₄H₁₂N₂O₆ requires C, 55.0; H, 4.6; N, 9.15%.

λₘₐₓ. 3020 (CH=C), 2840 (OCH₃), 2230 (C≡N), 1730 (ester C=O), 1630 (C=C), 1515 and 1343 (NO₂) cm⁻¹.

λₘₐₓ. 299 (ε 14,200) and 343 nm (infl.) (ε 3,900).

δ 1.41 (3 H, t, J 7 Hz, CH₂CH₃), 4.02 (3 H, s, C₃=O.CH₃), 4.08 (3 H, s, C₂=O.CH₃), 4.42 (2 H, q, J 7 Hz, CH₂CH₃), 7.94 (1 H, d, J₄,₆ 2.4 Hz, C₄=H), 8.57 (1 H, s, Ar.CH=C) and 8.72 (1 H, d, J₆,₄ 2.4 Hz, C₆=H) p.p.m.

Ethyl-α-cyano-2,3-dimethoxy-6-nitrocinnamate (122).—The procedure was the same as that given above. Recrystallisation of the product from chloroform-light petroleum gave ethyl-α-cyano-2,3-dimethoxy-6-nitrocinnamate (122) (93%) as pale yellow rods, m.p. 98-99°.

Found: C, 55.35; H, 4.6; N, 9.2%.

νₘₐₓ. 3020 (CH=C), 2840 (OCH₃), 2225 (C≡N), 1728 (ester C=O), 1610 (C=C), 1530 and 1340 (NO₂) cm⁻¹.

λₘₐₓ. 236 (ε 12,200), 264 (ε 10,000) and 325 nm (ε 7,160).

δ 1.40 (3 H, t, J 7 Hz, CH₂CH₃), 3.91 (3 H, s, C₃=O.CH₃), 4.01 (3 H, s, C₂=O.CH₃), 4.41 (2 H, q, J 7 Hz, CH₂CH₃), 7.08 (1 H, d, J₄,₅ 9 Hz, C₄=H), 8.08 (1 H, d, J₅,₄ 9 Hz, C₅=H) and 8.48 (1 H, s, Ar.CH=C) p.p.m.
α-Phenyl-2,3-dimethoxy-5-nitrocinnamoni

The procedure was the same as that given above but using benzyl cyanide in place of ethyl cyanoacetate. Recrystallisation of the product from ethanol gave α-phenyl-2,3-dimethoxy-5-nitrocinnamoni

C₁₇H₁₄N₂O₄ requires C, 65.9; H, 4.5; N, 9.0%.

νₘₐₓ. 3020 (CH=C), 2820 (OCH₃), 2200 (C=N), 1600 (C=C), 1525 and 1340 (NO₂) cm⁻¹

λₘₐₓ. 312 nm (ε 21,400).

δ 3.98 (3 H, s, C₃·O·CH₃), 4.03 (3 H, s, C₂·O·CH₃), 7.83 (1 H, s, Ar·CH·C), 7.84 (1 H, d, J₄,6 2 Hz, C₄·H) and 8.61 (1 H, d, J₆,4 2 Hz, C₆·H) p.p.m.

α-Phenyl-2,3-dimethoxy-6-nitrocinnamoni

The procedure was the same as that given above. Recrystallisation of the product from ethanol gave α-phenyl-2,3-dimethoxy-6-nitrocinnamoni

C, 65.9; H, 4.5; N, 8.9%.

νₘₐₓ. 3020 (CH=C), 2830 (OCH₃), 2235 (C=N), 1595 (C=C), 1510 and 1338 (NO₂) cm⁻¹
\( \lambda_{\text{max.}} \) 281 (\( \epsilon \) 13,300) and 310 nm (infl.) (\( \epsilon \) 11,700).

δ 3.94 (3 H, s, C\(_3\)O\_CH\(_3\)), 4.05 (3 H, s, C\(_2\)O\_CH\(_3\)), 7.04 (1 H, d, J\(_4,5\), 9 Hz, C\(_4\)H), 8.07 (1 H, d, J\(_5,4\), 9 Hz, C\(_5\)H) and 8.65 (1 H, s, Ar\_CH\_C) p.p.m.

Condensation of 2,3-Dimethoxy-5(and-6)-nitrobenzaldehyde (119, 120) with Ethyl Cyanoacetate.— The mixture of isomers from the nitration of 2,3-dimethoxybenzaldehyde (10 g., 0.05 mole) and ethyl cyanoacetate (5.8 g., 0.05 mole) were dissolved in ethanol (500 ml.) and ten drops of dilute aqueous potassium hydroxide solution added. The solution was filtered at intervals of 0.5 hr. after precipitation of the 5-nitro condensation product first began until no more material precipitated. The mother liquor was carefully neutralised with hydrochloric acid and reduced in volume. Fractional crystallisation gave a total of 5.4 g., (72%) of the pure 5-nitro isomer and 6.0 g., (80%) of the pure 6-nitro isomer.

The 6-nitro isomer was reduced with sodium sulphide in the same way as for \( \alpha \)-phenyl-\( \alpha \)-nitrocinnamonic nitrile (106). After heating on a water bath for 20 hr., t.l.c. showed that mostly starting material remained together with five other minor products.

Reduction of the compound with zinc dust and acetic acid in the same way as for \( \alpha \)-phenyl-\( \alpha \)-nitrocinnamonic nitrile, method (a) (106) but with a reaction time of 6 hr. gave at least 9 compounds by t.l.c. five of which corresponded to those from the sodium sulphide
reduction. In both cases two of the spots showed up in ultraviolet light. Neither reaction mixture was worked up.

Condensation of 2,3-Dimethoxy-5(and-6)-nitrobenzaldehyde (119, 120) with Benzyl Cyanide.-- The same procedure and relative quantities as above were used. This gave 75% of the pure 6-nitro isomer and 82% of the pure 6-nitro isomer.

The 6-nitro isomer was reduced with sodium sulphide as above for 20 hr. on a water bath. T.l.c. showed mainly starting material and small amounts of four other compounds.

Reduction of the compound with zinc dust and acetic acid as above gave nine compounds by t.l.c. The bulk of the material appeared at the origin as a black spot. In both cases, two of the spots showed up in ultraviolet light. Neither reaction mixture was worked up.

The Nickel Chelate of 2-Amino-3-phenylquinoline-N-oxide (107).-- The procedure given on p. 171 was followed. The product was recrystallised twice from chloroform-light petroleum to give dark green plates (98%), m.p. 288-289° (decomp.).

Found: C, 57.7; H, 3.7; N, 8.8; Cl, 16.0.

C₃₀H₂₂N₄O₂Ni·CHCl₃ requires C, 57.6; H, 3.6; N, 8.7; Cl, 16.25%. 
m/e (Mass spectrum) 528.1087 (M⁺)

C₃₀H₂₂N₄O₂⁵²Ni requires m/e 528.1096 (M⁺)

νₘₐₓ. 3415, 1625, 1526 and 1188 cm⁻¹ νₘₐₓ. (KBr) 3415,
3320, 1623, 1535, 1530 and 1186 cm⁻¹

λₘₐₓ. 244 (infl.) (ε 20,000), 250 (infl.) (ε 24,500),
256 (ε 28,300, 262 (ε 27,200) 317 (ε 4,900) 362 (infl.)
(ε 3,100) and 434 nm (ε 2,000); λₘₐₓ. (EtOH + HCl) 245,
249, 255, 298, 336 and 348 nm.

δ 3.87 (2 H, s broad, 2xNH, exchangeable) and 7.76 (2 H, 
d; J₇,₈ 9 Hz, 2xC₆H₆) p.p.m.

The compounds 2-amino-3-phenylquinoline-1-oxide (107) and
2-amino-3-carbethoxyquinoline-1-oxide (110) were tested for chelating ability with solutions of metal salts following the procedure given on p. 170. The results are tabulated in appendix 4. Tests were not carried out for 2-aminoquinoline-1-oxide-3-carboxylic acid (112) because of its lack of solubility.
| C-N,      | SH       | Mercaptobenzothiazole |
| C-NH,     | SH       | Rubianic acid         |
| C-NOH,    | OH       | Benzohydroxamic acid  |
| N-NONH₄,  | O        | Cupferron             |
| C,C-N,    | NOH      | Phenyl-1-pyridyl ketoxime |
| C,C-N,    | OH       | 8-Hydroxyquinoline    |
| C,C-N,    | SH       | 8-Thioquinoline       |
| C,C-NH,   | SH       | Thionanilide          |
| C,C-NH₂,  | OH       | Glycine               |
| C,C-NOH,  | NOH      | Dimethylglyoxime      |
| C,C-NOH,  | O        | 1-Nitroso-2-naphthol  |
| C,C-O,    | OH       | Oxalic acid           |
| C,C-OH,   | SH       | Thioglycolic acid     |
| C,C-OH,   | OH       | Catechol              |
| C,C-OH,   | S        | Thiohydantoic acid    |
| C,N-NH,   | NOH      | Nitrosoguanidine      |
| C,N-NH₂,  | OH       | Hydrazinecarboxylic acid |
| C,N-NH₂,  | SH       | Dithizone             |
| C,C,C-N,  | NH       | Chlorophyll type      |
| C,C,C-NOH,| OH       | Salicylaldoxime       |
| C,C,C-O,  | OH       | Alizarin              |
| C,C,N-N,  | NH       | Phthalocyanine        |
| C,C,N-NH, | NH       | Biguanidine           |
| C,C,N-NH₂,| NH₂      | Biuret                |
| C,N,C-NH, | O        | Guanylurea            |

a The atom or atoms connecting the two functional groups are expressed by their conventional symbols in alphabetical order.

b The functional groups are given by their usual symbols in the alphabetical order of the atoms by which they are attached to the original compound before chelation.
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| b 75a    | 243 (12,800) | 277 (930) | 290 (465) |
| b 75b151 | 244 (13,000) | 277 (900) | 310 (9,000) |
| b 98a151 | 262 (16,700) | 320 (1,840) |
| b 98b152 | 242 (20,650) | 315 (3,760) |
| b 98o    | 252 (18,000) | 292 (3,580) | 312(infl.)(4,080) |
| b 100    | 270 (9,350)  | 312 |
| a 2-Hydroxylaminopyridine | 237 (5,300) | 292 (2,340) |
contd.

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a Ethanol solution  
b Cyclohexane solution  
c Chloroform solution  
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* The precipitate and/or the colour was taken up in chloroform.
- The colour was not taken up in chloroform.

* Addition of sodium acetate solution was necessary to give a precipitate.

Where only the colour is given, no precipitate was formed.
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A 2-Nitropyridine

B 2-Hydroxylamino pyridine

The compounds were tested against L-1210 lymphoid leukemia in mice and the results judged on the basis of mean survival times.

Col 1 Compound number in this work
Col 18 Dose in mg./kg.
Col 19 Survivors
Col 20 No. of animals in test
Col 21 Cures
Col 22 Average control body wt. change in g.
Col 23 Animal weight difference Test-Control
Col 24 Mean survival time of test animals in days
Col 25 Mean survival time of control animals
Col 26 % T/C. Ratio of survival times
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(a) M. Ochoa and E. Hirschberg, Vol. V, p.13; (b) V.M. Rosenoer, Vol. IV, p.9; (c) J.A. Stock, Vol. IV, p.94;


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[Signature] Christopher Allen
$$R \cdot \text{NHCO}_2(\text{CH})_{2n} \text{CH}_3$$

(a) \( R = \text{aryl} \)

(b) \( R = \text{arylN(CH}_2\text{CH}_2\text{Cl)}_2 \)

(1)

$$\text{OPO} - \text{N(CH}_2\text{CH}_2\text{Cl)}_2$$

R \cdot \text{N(CH}_2\text{CH}_2\text{Cl)}_2

(a) \( R = \text{-H} \)

(b) \( R = \text{-CH}_3 \)

(2)

$$\text{HO}_2 \cdot \text{CHCH}_2\text{NH}_2$$

NH

(4)

$$\text{R}_2 \cdot \text{N}$$

(a) \( R_1 = \text{-CHO; R}_2 = \text{-CO}_2\text{CH}_3 \)

(b) \( R_1 = \text{-CH}_3; R_2 = \text{-CO}_2\text{CH}_3 \)

(5)
\[
\begin{align*}
&\text{(11)(a)} \quad \text{SH} \quad \text{NH}_2 \\
&\text{CH}_2 - \text{CH} \cdot \text{C}_2 \text{H} \\ \\
&\text{(b)} \quad \text{HSe} \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{C}_2 \text{H} \\ \\
&\text{(c)} \quad \text{\phiSe} \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{C}_2 \text{H}
\end{align*}
\]

\[
\begin{align*}
&\text{(12)(a)} \quad \text{H}_3 \cdot \text{C} \cdot \text{C}_2 \text{O} \\
&\text{H} \cdot \text{C} \cdot \text{O} \\ \\
&\text{(b)} \quad \text{H}_3 \cdot \text{C} \cdot \text{C}_2 \text{N} \cdot \text{NH} \cdot \text{C} \cdot \text{NH}_2 \\ \\
&\text{H} \cdot \text{C} \cdot \text{N} \cdot \text{NH} \cdot \text{C} \cdot \text{NH}_2 \\
&\text{(13)} \quad \text{H}_2 \cdot \text{N} \cdot \text{C}_2 \text{O}_2 \cdot \text{C} \cdot \text{NH}_2 \\
&\text{O} \cdot \text{C}_2 \text{H}_2 \cdot \text{O} \cdot \text{CH}_2 \\
&\text{busulfan} \quad n = 4
\end{align*}
\]

\[
\begin{align*}
&\text{(14)} \quad \text{H}_3 \cdot \text{C} \cdot \text{O} \cdot \text{SO}_2 \cdot \text{C}(\text{CH}_2)_n \cdot \text{O}_2 \cdot \text{SO} \cdot \text{C} \cdot \text{H}_3 \\
&\text{(15)} \\
&\text{(16)(a)} \quad \text{R} = \text{-OH} \\
&\text{(b)} \quad \text{R} = \text{-SH} \\
&\text{(16)(c)} \quad \text{R} = \text{-OH} \\
&\text{(17)} \\
&\text{(18)}
\end{align*}
\]
(29)

(a) R₁ = -H; R₂ = -OH
(b) R₁ = -Cl; R₂ = -H

(30)

(31)

(32)

(33)

(34)

(35)

(36)

(37)

(38)

(39)

(40)
(41) 

(42) 

(43) 

(44) 

(45)(a) 

(b) 

(c) 

(d) 

(46) 

(47)(b) R = H; R' = CH₃ 

(c) R = R' = CH₃ 

(48)
(80) R = -CH₃
(b) R = -OCH₃
(c) R = -Br
(d) R = -Cl

(81) R = -CH₃
(b) R = -OCH₃
(c) R = -Cl

(82) R = -CH₃
(b) R = -OCH₃
(c) R = -Cl

(83) R = -CH₃

(84) R = -CH₃
(b) R = -Cl

(85) R = -CH₃

(86) R = -NO₂

(87) R = -NO₂
(a) R = -H  
(b) R = -CH₃  
(c) R = -Cl  
(98)

(100)

(101)

(102)

(103)

(104)

(105)