HETEROCYCLIC IMINES AND PYRAZINE N-OXIDES
FROM IMINODIACETONITRILE.

A Thesis submitted to the
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by

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GUILDFORD
PART I. HETERO CYCLIC IMINES FROM IMINODIACETONITRILE.

Reaction of \(\text{N}\)-benzyliminodiacetonitrile with alcoholic ammonia under pressure but best as sodamide in formamide under nitrogen gives the imidine, 4-benzyl-2,6-diiminopiperazine. The imino groups of this compound undergo stepwise displacement reaction with water and hydroxylamine. The hydroxylamine product, 4-benzyl-2,6-dihydroxyiminopiperazine, is also obtained by cyclisation of the bisamidoxime and direct from the dinitrile. The dinitrile with aniline and 2-aminopyridine (as anion) affords 4-benzyl-2-imino-6-phenyliminopiperazine and the 6-(2-pyridyl)-imino analogue, although attempts to prepare these compounds from the imidine were abortive.

Iminodiacetonitrile itself with sodamide in formamide gives 2,6-diformyliminopiperazine. Iminodiacetonitrile and its \(\text{N}\)-acetyl and benzoyl derivatives add hydroxylamine at room temperature giving acyclic amidoximes which with aqueous alcoholic hydroxylamine hydrochloride at reflux temperature afford the corresponding 2,6-dihydroxyiminopiperazines which are prepared directly from the dinitriles by refluxing with aqueous
alcoholic mixture of hydroxylamine and its hydrochloride. However, tri(cyanomethyl)amine under similar reaction condition yields the acyclic trisamidoxime. Nevertheless, the trinitrile with sodamide in formamide gives the imidine, 2,6-diiminopiperazine-4-acetonitrile, which is hydrolysed by water to 6-imino-2-oxopiperazine-4-acetamide.

PART II. PYRAZINE N-OXIDES FROM IMINODIACETONITRILE.

Iminodiacetonitrile with hydroxylamine under optimum reaction conditions (which was discovered by experiment) affords 2,6-dihydroxyiminopiperazine with hydroxylamine hydrochloride together with 2-amino-6-hydroxyiminopyrazine 1-oxide. The former separates as its insoluble complex and after this has been filtered off, the latter crystallises out from the solution as monohydrate. Catalytic reduction of the latter using Adam's catalyst results in uptake of one molecular equivalent of hydrogen and formation of 2,6-diaminopyrazine 1-oxide. Acetylation at room temperature then gives 2,6-diacetamidopyrazine 1-oxide.

Treatment of 2,6-dihydroxyiminopiperazine with 10% palladium-on-charcoal catalyst in boiling o-dichlorobenzene affords 2,6-diaminopyrazine in poor yield, which with acetic-anhydride at room temperature gives 2,6-diacetamidopyrazine and is also obtained by deoxygenation of 2,6-diacetamidopyrazine 1-oxide using sodium dithionite.
ACKNOWLEDGEMENTS

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PART I

HETEROCYCLIC IMINES FORM IMINODIACETONITRILE.
INTRODUCTION
The imidines (i), namely succinimidine (ii) and glutarimidine (iv), were first described by Pinner\(^1\). They were prepared by passing hydrogen chloride into an alcoholic solution of their corresponding dinitriles to give imino-ethers which were treated with ammonia. The products were not fully investigated however.

\[
\text{(i)} \quad \text{R} \quad \text{(ii, } R=\text{H}; \text{ iii, } R=\text{CH}_3) \\
\text{(iv, } R=\text{H}; \text{ v, } R=\text{Ph)} \\
\text{(vi)}
\]

From 1952, Elvidge, Linstead and co-workers have published a series of papers describing imidines, prepared directly from dinitriles and ammonia. These include 1:3-diimino-iso-indo-
line (vi)$^{2,3}$, succinimidine (ii)$^4$, α-dimethylsuc rimidine (iii)$^5$, glutarimidine (iv) and α-phenylglutarimidine (v)$^6$. These imidines were further converted into imino-imides (vii) and finally to imides (viii). Some were converted into macrocyclic compounds, azaporphins and indigoid derivatives.

In the present work, dinitriles containing a hetero atom, namely iminodiacetonitrile (Ia) and its N-substituted derivatives (Ib-Ie) were examined. From these, imidines, 4-benzyl-2,6-di imino-piperazine (IIb) and 2,6-diiminopiperazine-4-acetonitrile (IIe) have been prepared.

There is little in the literature relating to the work described in this thesis. Dubsky et al.$^7$ described the preparation of 4-benzyl-2,6-dioxopiperazine (m.p. 105°) (VIIb) from N-benzyliminodiacetonitrile (Ib) by the following route.
Similarly other imides, namely 2,6-dioxopiperazine (VIIa)\(^8\) and 4-acetyl-2,6-dioxopiperazine (VIIId)\(^9\) were obtained from the corresponding dinitriles. Attempts to prepare the 4-benzoyl analogue were not successful, even from mono- or di-amide as above\(^10\).

In related work, Eddy et al\(^11\), synthesised imino-bisacetamidoxime (IVa) from iminodiacetonitrile (Ia) and hydroxylamine and recorded for the product a m.p. of 126\(^0\)-127\(^0\) (decomp.). Their ultimate interest in this compound was its ability to form metal complexes of the formula XL\(_2\)Cl\(_2\) (where X= Ni, Mn, or Cu and LH\(_2\) is the ligand IVa). We observed that this bisamidoxime (IVa) really had a higher m.p. of 138\(^0\) (decomp.). Eddy et al., had failed to recrystallise their sample and so this finding was hardly surprising.

\[
\begin{align*}
R-N(-CH_2CN)_2 & \xrightarrow{\text{hydro.}} R-N(-CH_2CO_2H)_2 & R-N(-CH_2CO_2H)_2 & \xrightarrow{R'OH/NH_3} R-N(CH_2CONH_2)_2 \\
\text{Ia, Ib, Id.} & & & \\
\text{sublimation} & \rightarrow & & \\
& & \text{VIIa, VIIb, VIIId.} & \text{Eq.3}
\end{align*}
\]
Another American chemist, Norman Rainer, patented tris(amidoxime methyl)amine or 2,2',2''-nitriloacetamidoxime (IVe) in 1965. It was shown that compound (IVe) and similar types of amidoximes are useful as thickening agents and surface-active chelating agents.

Apart from repreparing these two known amidoximes (IVA and IVe), we synthesised other N-substituted amidoximes (IVb, IVc and IVd) for an investigation of their cyclisation which appeared not to have been studied before.

Recently, Hullmann has reported that 1,2-bis(3,5-dioxo-piperazine-1-yl-)ethane (R=H)

\[
\text{HN} \quad \text{N} \quad \text{CH}_2 \quad \text{CH} \quad \text{N} \quad \text{NH} \\
\text{O} \quad \text{O} \\
\text{HN} \quad \text{N} \quad \text{CH}_2 \quad \text{CH} \quad \text{N} \quad \text{NH} \\
\text{O} \quad \text{O}
\]

is a potent inhibitor of all three of the tumor used as a primary screen for anticancer agents. It was found totally inactive in man, however, probably because it is not absorbed into the body. But when R=CH\textsubscript{3}, it turned out to be well absorbed and highly active against malignant cells of man.\textsuperscript{13}
DISCUSSION
The addition of nitrogen bases across the nitrile groups of iminodiacetonitrile\(^{14,15}\) (Ia) has been examined. If this proceeded as with glutaronitrile and its \(\alpha\)-phenyl analogue\(^6\) then hitherto unknown 2,6-diiminopiperazines would result. Because of uncertainty as to whether the imino group present in the dinitrile (Ia) would interfere, \(N\)-substituted derivatives viz. \(N\)-benzyl- (Ib), \(N\)-benzoyl- (Ic), \(N\)-acetyl- (Id), and the \(N\)-cyanomethyl- (Ie) iminodiacetonitriles were tried initially. However, iminodiacetonitrile (Ia), itself, was found to react successfully in some reactions. The nitrogen bases employed as nucleophiles with the above dinitriles (Ia-Ie) were ammonia, sodamide, hydroxylamine and aromatic amines like aniline and 2-aminopyridine.

(i) Reactions of \(N\)-benzyliminodiacetonitrile with nitrogen bases.

(A) Ammonia:

\(N\)-Benzyliminodiacetonitrile\(^7,16\) (Ib) with methanolic ammonia at 90\(^\circ\) under pressure underwent cycloaddition of one mole of ammonia and afforded the imidine, 4-benzyl-2,6-diiminopiperazine (IIb), but a better yield (85\%) with a cleaner
product was achieved when the dinitrile (Ib) was treated with soda-

mide in formamide under nitrogen and excluding light. This new
imidine (IIb) (m/e 202) was also characterised as its picrate and
as a dihydrochloride monohydrate. Further evidence for the cyclic
structure (IIb) was obtained from its i.r. spectrum. It showed no
nitrile absorption (ν 2300-2200 cm⁻¹) and a broad absorption
appeared in the NH region (ν 3400-3000 cm⁻¹), comparable to that
from 1:3-dimino-iso-indoline²,³, glutarimidine⁶ etc. Similarly
in the u.v. absorption of the imidine (IIb) (λ max. 2505 nm., 13.8
10⁻³ ε ) to that of glutarimidine (λ max. 252 nm., 17.2 10⁻³ ε )
reinforced the above evidence and thence the cyclic structure (IIb).
Like succinimidine⁴, this imidine (IIb) was sensitive to light and
moisture and was best kept at 0°.

The imidine (IIb) dissolved slowly in warm water, ammo-
nia was evolved, and subsequently an intermediate hydrolysis pro-
duct, 4-benzyl-6-imino-2-oxopiperazine (VIb) crystallised out
almost quantitatively. This imino-imide (VIb) was a stable compound
(m.p. 192°-194°) and so a detailed study of it was made. The
p.m.r. spectrum of this compound (VIb) (Table I) showed three
chemical shifts for non-equivalent methylene groups which strongly
favoured the imino-imide structure (VIb). Subsidiary informa-
tion from its i.r. and u.v. spectra (Table VII,XIV) and comparison
with similar known ⁴,⁶ compounds, afforded strong additional
support for the structure (VIb). Boiling water was ineffective
for hydrolysing the imino-imide (VIb) but slightly acidic boil-
ing water afforded the known⁷ imide (VIIb) (m.p. 105°-106°;
reported m.p. 105°) which had the expected p.m.r. spectrum (Table I) and i.r. spectrum (Table XII). With boiling 3N-hydrochloric acid, the imino-imide (VIb) hydrolysed to the imide hydrochloride (VIIb') which was also obtained when the imidine hydrochloride (IIb') was boiled in aqueous methanol.

**TABLE I**

**p.m.r. results for the compounds VIb, VIIb, and VIIb'.**

<table>
<thead>
<tr>
<th>Structure of the compound</th>
<th>Solvent</th>
<th>Chemical shift (τ) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3-H₂ 5-H₂ 4-H₂ Phenyl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Δ₁ Δ₂ Δ₃</td>
</tr>
<tr>
<td>Ph—CH₂—N₄</td>
<td>CF₃CO₂H</td>
<td>5.36 5.21 5.07 2.46</td>
</tr>
<tr>
<td></td>
<td>CDCl₃</td>
<td>6.66 6.66 6.34 2.69</td>
</tr>
<tr>
<td></td>
<td>D₂O</td>
<td>5.84 5.84 5.53 2.46</td>
</tr>
</tbody>
</table>

It is well known that for a given solute, different solvents give rise to different sets of chemical shifts if the solvent molecules are not chemically inert and magnetically iso-
tropic\textsuperscript{17}. It is also known\textsuperscript{17} that in different polar solvents (such as D\textsubscript{2}O, CF\textsubscript{3}CO\textsubscript{2}H, Me2SO) the solute is specifically associated with the solvent in different ways, so that the differential shielding between reference and solute will vary with the solvent and lead to different chemical shifts in each of such solvents. Hence the difference between two chemical shifts ($\Delta_1 - \Delta_2$) within the molecule can be expected to be solvent dependent. However, accidently, the difference in chemical shifts ($\Delta_1 - \Delta_2$) for the compounds (VIIb and VIIb') were 0.32 c/s and 0.31 c/s respectively. The average difference in these chemical shifts is 0.315 c/s, close to one value found for the compound (VIb), the other value being 0.15 c/s. This implies that the methylene group protons with shifts of 5.36 c/s and 5.07 c/s in the compound (VIb) correspond to the $3$-$H_2$ and $4$-$H_2$ respectively, whilst the middle chemical shift ($\Delta_2$) corresponds to the $5$-$H_2$ protons.

(B) Hydroxylamine:

The imidine (IIb) condensed with 2 moles of hydroxylamine hydrochloride in boiling methanol and gave 4-benzyl-2,6-dihydroxyiminopiperazine (IIIb) which was also obtained from the dinitrile (Ib) and hydroxylamine (2 mole or excess) in boiling aqueous methanol. But at room temperature the dinitrile (Ib) with hydroxylamine afforded an adduct, the bisamidoxime (IVb). This cyclised to give the same cyclic dioxime (IIIb), when heated under reflux in the presence of
an acid catalyst, hydroxylamine hydrochloride. Benzylation of the dioxime (IIIa) (see later) also gave the dioxime (IIIb). Although glutarimidoxime had been successfully obtained by the sublimation of glutarobisamidoxime, a similar attempt to cyclise the bisamidoxime (IVb) was unsuccessful.

### TABLE II

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>i.r. spectra</th>
<th>u.v. spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assignment and v max. cm⁻¹</td>
<td>λmax.</td>
</tr>
<tr>
<td></td>
<td>C=O OH 1-NH</td>
<td>nm.</td>
</tr>
<tr>
<td>Glutarimidoxime⁶</td>
<td>1667 3400-2400 br 3436</td>
<td>234</td>
</tr>
<tr>
<td>4-Benzyl-2,6-dihydroxyimino-piperazine</td>
<td>1667 3400-2400 br 3440</td>
<td>234</td>
</tr>
</tbody>
</table>

The striking similarities in the characteristic absorption values from the i.r. and u.v. spectra of the dioxime (IIIb) and the known glutarimidoxime as shown in (Table II) supported the cyclic dioxime structure (IIIb). This was confirmed by the p.m.r. (TableXXV) and mass spectrum (m/e 234).

Implication from the above reactions were:

(i) The reactivity of the exo-cyclic imino groups of the imidine (IIb) towards hydroxylamine hydrochloride parallels that of...
other imidines\(^2,3,4,6\). This indicates that the imidine (IIb) probably has the di-imino structure (XVII) rather than an imino-amino (XVIII) or diamino (XVII) structure, and (ii) in the reaction of the dinitrile (Ib) with hydroxylamine to afford the dioxime (IIIb), the bisamidoxime (IVb) is probably an intermediate.

When imino-imide (VIb) and an equimolar proportion of hydroxylamine hydrochloride were boiled in methanol 4-benzyl-6-hydroxyimino-2-oxopiperazine (Vb) was obtained in 77\% yield. Partial hydrolysis of the dioxime (IIIb) with nitrous acid gave the monoxime hydrochloride (Vb') which after addition of silver nitrate solution (one molecular proportion), removal of the silver chloride and evaporation of the filtrate afforded the identical monoxime (Vb).

As the imidine (IIb), like other imidines\(^2,3,4,6\), followed stepwise hydrolysis and gave the imide (VIIb) as an end product, it was expected to obtain either the imide (VIIb) or its hydrochloride (VIIb') from the monoxime (Vb) when treated again with nitrous acid, but surprisingly this monoxime (Vb) was resistant to nitrous acid hydrolysis even in sulphuric acid media at room temperature. However, the hydrolysis was achieved successfully when either the monoxime (Vb) or the dioxime (IIIb) was boiled with 3\% hydrochloric acid to give the imide hydrochloride (VIIb'). The dinitrile (Ib) in acetic acid saturated with hydrogen chloride afforded the identical imide hydrochloride (VIIb') after
The reaction solution had been kept at room temperature for 120 hr. The formation of the hydrochloride (VIIb') presumably occurred via a halogen acid induced cyclisation of an intermediate, 2-chloro-6-imino derivative (a) which eventually hydrolysed either because of the presence of moisture in the reaction solution or during the recrystallisation process and gave the imide hydrochloride (VIIb'):

\[ \text{Ia} \xrightarrow{\text{HCl} \text{HOAc}} \text{a} \xrightarrow{\text{H}_2\text{O}} \text{VIIb'} \]  

Eq. 4

The above presumption was supported by the reaction described by Johnson et al., in which 2,2'-dicyanobiphenyl when treated with hydrogen bromide in acetic acid afforded the intermediate (ix), 7-bromo-5-imino-5H-dibenz(c,e)azepine hydrochloride, which was subsequently separately hydrolysed to the corresponding imide-diphenimide (x):

\[ \text{Dinitrile} \xrightarrow{\text{HBr} \text{HOAc}} \text{ix} \xrightarrow{\text{H}_2\text{O} \text{HOAc}} \text{x} \]  

Eq. 5
SCHEME I

Reactions of N-benzyliminodiacetonitrile: (Ib):  \( R = \text{CH}_2\text{Ph} \)

Diagram showing the reactions and intermediates involving compound Ib.
(C) Aromatic Amines:

(i) Aniline:

Attempts to prepare N-substituted imidines were at first unsuccessful. Fusion of N-benzyliminodiacetonitrile (Ib) with aniline hydrochloride, as in the case of glutaronitrile, failed to give tractable product. Efforts to condense aniline with the imidine (IIb) analogous to glutaronitrile, were also abortive, even using anaerobic conditions and excluding light, much tar being formed.

However, the mono-N-phenylimidine (VIIIb) and analogue (VIIIb') were successfully prepared as discussed below. By analogy with the ready reaction of dinitriles with sodamide (in formamide) (which provides the strongly nucleophilic \( \text{NH}_2 \)), it appeared likely that sodio-aryl-amines would be more reactive towards the dinitrile (Ib) than simple base: application of this concept was quite satisfactory.

When the dinitrile (Ib) was treated with aniline and boiling ethanolic sodium ethoxide, 4-benzyl-2-imino-6-phenylimino-piperazine (VIIIb) was formed, though in rather low yield (25%). Much more effective was sodio-aniline formed in situ from the calculated amount of sodamide and an excess of aniline under nitrogen and excluding light, which afforded 80% of the mono-N-phenylimidine (VIIIb). An equally successful reaction (yield 70% of the imidine VIIIb) was achieved when aniline (2 mols) was added to a suspension of sodamide (2 mols) in boiling benzene
under nitrogen, followed by the addition of the dinitrile (Ib) solution in benzene. This last method is a modification of Cooper and Partridge's preparation of mono-N-phenyl substituted amidines by the interaction of sodio-aniline with mono-nitriles by which e.g. benzonitrile afforded N-phenyl-benzamidine.

(ii) 2-Aminopyridine:

Analogously to the above second reaction, 4-benzyl-2-imino-6-(2-pyridyl)iminopiperazine (VIIib') was obtained when the sodio-derivative of 2-aminopyridine in N,N-dimethylaniline was treated with the dinitrile (Ib).

(iii) m-Nitroaniline:

Similar reaction of m-nitroaniline with the dinitrile (Ib) was unsuccessful and the amine was recovered quantitatively.

(iv) Diacid bases:

As the sodio-derivative of the mono acid bases, aniline and 2-aminopyridine, gave their corresponding mono-N- arylimidines (VIIib and VIIib'), use of the homologous diacid bases viz. mphenylenediamine, p-phenylenediamine, and 2,6-diaminopyridine was attempted. All these bases were so reluctant to react with the dinitrile (Ib) that they were recovered almost quantitatively without appreciable reaction being detected.

The p.m.r. spectra (Tablexxvi) of the mono-N-phenylimidine (VIIib) and the 2-pyridyl analogue (VIIib') showed singlets from
the three non-equivalent methylene groups, confirming the unsymmetrical structures. Further confirmation of their structures came from their i.r. and u.v. spectra which are given in chapter III (Tables VIII and XVII).

Endeavours to obtain the NN'-disubstituted imidines from compounds (VIIIb and VIIIb') by extension of the foregoing reaction were abortive, the unsubstituted imino group appearing unreactive under the basic conditions employed. This lack of reactivity persisted under acidic condition also, the mono-N-phenyl imidine (VIIIb) being hydrolysed to the imino-imide (VIb) rather than to the N-phenylimino-imide as expected from the previous results\(^2,3,4,6\). With hydroxylamine hydrochloride, however, both the mono-N-phenylimidine (VIIIb) and its 2-pyridyl analogue (VIIIb') underwent replacement of both substituents to give the dioxime (IIIb), a behaviour for which there were precedents\(^20\).

(ii) Reactions of N-acyliminodiacetonitriles with nitrogen bases.

Although the N-acyl group was expected to be a less satisfactory function than e.g. the benzyl group for the protection of the imino group of iminodiacetonitrile, nevertheless because of the accessibility of the acyl derivatives, N-benzoyliminodiacetonitrile\(^{14}\) (Ic) and N-acetyliminodiacetonitrile\(^8\) (Id) were used for reactions with nitrogen bases.

(A) Ammonia:
With liquid ammonia under pressure \( \text{N-benzoyliminodiacyetonitrile (Ic)} \) afforded neither imidine nor the dinitrile (Ic) but the hydrolysed product of the starting material, benzamide and some intractable material.

When this dinitrile (Ic) was treated under milder reaction condition using sodamide in formamide under nitrogen, it gave no imidine. Addition of water to the above reaction solution to hydrolyse the imidine, if any, and so obtain more stable imino-imide was a complete failure.

Similar reactions of \( \text{N-acetyliminodiacyetonitrile (Id)} \) with liquid ammonia and sodamide in formamide, again gave neither the imidine, nor imino-imide, nor the starting material (Id), but only intractable material.

\[
\begin{align*}
\text{R} & \overset{\text{\textbf{CN}}}{\text{\textbf{CN}}} \overset{\text{\textbf{C}}}{\text{\textbf{= O}}} \\
\text{CN} & \text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \overset{\text{\textbf{CN}}}{\text{\textbf{CN}}} \overset{\text{\textbf{C}}}{\text{\textbf{= O}}} \overset{\text{\textbf{NH}_2}}{\text{\textbf{C}}} \\
\text{CN} & \text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \overset{\text{\textbf{CN}}}{\text{\textbf{CN}}} \overset{\text{\textbf{C}}}{\text{\textbf{= O}}} \overset{\text{\textbf{NH}_2}}{\text{\textbf{C}}} \\
\text{CN} & \text{CN} \\
\end{align*}
\]

\[
\text{RCONH}_2 + \overset{\text{\textbf{CN}}}{\text{\textbf{CN}}} \rightarrow \overset{\text{\textbf{NH}_2}}{\text{\textbf{C}}} \\
\text{CN} & \text{CN} \\
\]  

No imidine, polymerisation or degradation.

When \( \text{R = Ph, Ic;} \) or \( \text{R = CH}_3, \text{Id.} \) Eq.6
Reactions of N-acyliminodiacetonitriles: (Ic and Id):

R= PhCO, Ic
R= CH$_3$CO, Id.

SCHEME II
From the above results, it appeared that these dinitriles (Ic and Id) were not reactive in the expected direction in strongly basic media. They (Ic and Id) were attacked by the nucleophile at the imide bond and the protective groups were removed as shown above. This presumption was supported by the fact that N-benzyloliminodiacetonitrile (Ic) gave benzamide and remaining part of the dinitrile was either polymerised or degraded to intractable material.

(B) Hydroxylamine:

Although the dinitriles (Ic and Id) failed to give the imidines with ammonia or sodamide, hydroxylamine, however, was found to react satisfactorily with these dinitriles (Ic and Id).

The expected acyclic amidoximes, N-benzyloliminobisacetamidoxime* (IVc) and N-acetyliminobisacetamidoxime (IVd), were obtained when two molecular proportions of hydroxylamine was added (at room temperature) to the dinitrile (Ic and Id) respectively. But at refluxing temperature (boiling aqueous methanol), the dinitriles reacted with hydroxylamine with cyclisation and formation of the cyclic dioximes (IIIc and IIId). It was shown that the later reaction was exothermic and the dioximes (IIIc and IIId) crystallised out quantitatively in 0.5 hr. The same dioximes (IIIc and IIId) were also afforded when the bisamidoximes (IVc and IVd) were boiled in aqueous methanol in the presence of an acid catalyst, hydroxylamine hydrochloride. The 4-acetyl-2,6-dihydroxyiminopiperazine (IIId) was also obtained as a result of the acetylation of the dioxime (IIIa) using

* see addendum page 142.
acetic anhydride in pyridine.

The structure of the amidoximes (IVc and IVd) and the dioximes (IIIC and IIIId) were supported by their i.r. spectra (Tables IX and X) and confirmed by their p.m.r. spectra given in chapter III. The cyclic dioxime structures (IIIC and IIIId) were further supported by their light absorptions (Table XV) which were closely similar to those of other dioximes (IIIA and IIIB) included in the same table.

Nitrous acid affected the dioxime (IIIC) only partially when the reagents were left together overnight and gave the half-hydrolysed 4-benzoyl-6-hydroxyimino-2-oxopiperazine (Vc). Attempts to hydrolyse this further to the imide using nitrous acid were abortive as only starting material was recovered. Applying the same reagent, dilute hydrochloric acid, as used with 4-benzyl-derivatives (IIIB and Vb), the dioxime (IIIC) was hydrolysed at the hydroxyimino groups as well as at the 4-position and afforded the imide hydrochloride (VIIa') and benzoic acid.

In contrast, the dioxime (IIIId) with nitrous acid underwent smooth hydrolysis to yield the known imide (VIIId). However, the parent imide hydrochloride (VIIa') was also obtained from the dioxime (IIIId) when it was treated with dilute hydrochloric acid as discussed above.

The spectral data for the monoxime (Vc) and the imides (VIIId and VIIa') are included in Tables XI, XII, and XVI.

(C) Aromatic amines:
Because of the failure to get the imidines from the dinitriles (Ic and Id) as discussed in (A) (pp.25) no attempts were made to react these dinitriles with any aromatic amines.

(iii) Reactions of Iminodiacetonitrile with nitrogen bases.

(A) Ammonia:

Similarly to the N-acyl-dinitriles (Ic and Id), iminodiacetonitrile\(^*\) (Ia) failed to add ammonia and gave intractable material. This failure suggested that the anion (\(\text{NH}_2\)) attacked at the imino end of the dinitrile (Ia) and after removal of the proton from it, the anion formed underwent either polymerisation or degradation which afforded only intractable material. This can be represented by putting H instead of R-CO in (Eq.6) (pp.25). However, the dinitrile (Ia) with sodamide in formamide under nitrogen, in the dark for seven days, underwent cycloaddition of a new anion and the product C\(_6\)H\(_8\)N\(_4\)O\(_2\) (Iia) (m/e, 168) slowly separated (in poor yield) instead of the expected imidine\(^2,3,4,6\). This new compound was 2,6-diformimidopiperazine. It had longer wavelength absorption (A\(_{\text{max nm.}}\), 249.5, 347; 18.3, 12.65 \(10^{-3}\varepsilon\)) than the imidine (IIb) (A\(_{\text{max nm.}}\), 250.5; 13.8 \(10^{-3}\varepsilon\)) because of longer conjugation.

Although the parent dinitrile (Ia) failed to give the imidine in liquid ammonia, the same dinitrile (Ia) with sodamide in formamide, surprisingly gave the product (IIa) as discussed above. In this particular reaction there must be
Reactions of Iminodiacetonitrile: (Ia):

SCHEME III

IVa

HON=CH2

Ia

CN

HON=CH2

CN

IIa

HON=CH2

IIIa

HON=CH2

IIIb, IIId

VIIa

IIIc

RON

R
equilibration of amide (\(\text{NH}_2\)) and formamide (\(\text{HNCHO}\)) anion in the medium and so the isolation of the diformyl derivative (IIa) is presumably an accident of its sparing solubility.

(B) Hydroxylamine:

Iminodiacetonitrile (Ia) added two molecular proportions of hydroxylamine at room temperature overnight and afforded an acyclic bisamidoxime, iminobisacetamidoxime (IVa). The i.r. spectrum of this compound showed no nitrile absorption but there was new absorption in NH region (Table IX). The acyclic structure for the amidoxime (IVa) was supported by the lack of absorption in the u.v. region and confirmed by its cyclisation to a complex of the dioxime (IIia''). On recrystallisation this salt (IIia'') dissociated into a free base, 2,6-dihydroxyiminopiperazine (IIia) which was also synthesised independently (though in poorer yield than obtained from the \(N_4\)-derivatives, IIIb, IIIc, and IIId) from the dinitrile (Ia) and hydroxylamine at elevated temperature (boiling aqueous methanol). The base (IIia) when boiled, in the presence of hydroxylamine hydrochloride, in aqueous methanol gave the complex (IIia'').

Up to this stage the complex (IIia'') was formulated as the hydrochloride of the dioxime (IIia'), but this misunderstanding was rectified when the dioxime (IIia) in hydrochloric acid solution formed the hydrochloride (IIia') whose i.r. spectrum was not identical with the i.r. spectrum of the complex (IIia'') (Fig.1 and 2). The behaviour of these salts (IIia' and IIia'')
was not consistent in the sense that the hydrochloride (IIIA') was stable in solution and could be recovered whilst the complex (IIIA'') was dissociated into free base as discussed above.

Reactivity of the labile protons of the dioxime (IIIA) was studied as discussed below. The dioxime (IIIA) with benzyl chloride and with acetic anhydride in pyridine afforded the 4-benzyl-(IIIB), and 4-acetyl-(IIId) dioximes respectively which were already encountered. These reactions showed that the imino group at 4-position in the dioxime (IIIA) was more basic than the nitrogen functions at the 1, 2, and 6-positions. When the dioxime (IIIA) was subjected to benzoyl chloride in pyridine for a longer time (13 days) acylation occurred at the 2, 4, and 6-positions and afforded the tribenzoylated product (IIIC'). The 1-NH group is probably too acidic to undergo acylation, as earlier results suggest or it may be because of the steric hindrance of the bulky groups present at the 2- and 6-positions. The structure of the compound (IIIC') was supported by its p.m.r. spectrum (Table xxv) and i.r. spectrum (Table III). The absence of the oximino protons was first realised from the fact that it gave no specific colour with iron(III)chloride, although the dioxime (IIIC) gave a greyish-violet colour under similar condition.

The spectral information (Table III) confirmed the stretching frequency for the 1-NH bond in many other piperazine derivatives (described in this part of the thesis) because the
TABLE III
The i.r. spectrum of 4-benzoyl-2,6-dibenzoyloxyiminopiperazine.

(IIIc') (characteristic \( \nu_{\text{max}} \)s. only)

<table>
<thead>
<tr>
<th>Structure</th>
<th>( \nu_{\text{max}} ) cm(^{-1})</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>3430</td>
<td>1-NH</td>
</tr>
<tr>
<td></td>
<td>1740 s</td>
<td>CO ester</td>
</tr>
<tr>
<td></td>
<td>1660 and</td>
<td>C=(N) and</td>
</tr>
<tr>
<td></td>
<td>1638</td>
<td>CO amide</td>
</tr>
</tbody>
</table>

compound (IIIc') was the only example in which only this 1-NH was free.

Lastly, nitrous acid treatment of the dioxime (IIIa) gave the imide hydrochloride (VIIa'), already encountered.

(C) Aromatic amines:

Attempts were made to condense the dinitrile (Ia) with aniline in boiling ethanol (base catalysed by sodium ethoxide) and also to effect condensation by fusing the dinitrile (Ia) with aniline hydrochloride. Even though almost anaerobic conditions were used, and light was excluded, the experiments were abortive.
Reactions of N-cyanomethyliminodiacetonitrile or nitrilodiacetonitrile with nitrogen bases.

The following were the major reasons for selecting the trinitrile (Ie) for an extension of the studies of the dinitriles (Ia -Id).

(i) That the trinitrile (Ie) was readily accessible from the same starting material as iminodiacetonitrile (Ia).22

(ii) That the trinitrile (Ie) had a third nitrile group which would be interesting to study under conditions similar to those used for other dinitriles (Ia-Id) and.

(iii) That the trinitrile (Ie) lacked an NH group and would not just give an anion with strongly basic reagents but would be expected to react to give the imidine or related products.

With these considerations in mind, attempts were made to react the trinitrile (Ie) with nitrogen bases.

(A) Ammonia:

As the dinitrile (Ib) added the elements of ammonia to afford the imidine (IIb) (pp.14) more smoothly and quickly with sodamide in formamide than with liquid ammonia, the former reaction conditions were used for the trinitrile (Ie).

The trinitrile (Ie) added only one mole of ammonia, rather than two or three moles, when treated with sodamide in formamide in the absence of light and under nitrogen, and afforded the cyclic imidine namely 4-cyanomethyl-2,6-diiminopiperazine
Reactions of \(N\)-cyanomethyliminodiacetonitrile: (Ie):

\[
\begin{align*}
\text{Ie} & \\
\rightarrow & \\
\text{IIe} & \quad \text{PICRATE} \quad \text{IVe} \\
\rightarrow & \\
\text{Vle} & \quad \text{IVe}'
\end{align*}
\]
(IIe). Surprisingly one nitrile group was unaffected, a result which helped to elucidate the reaction mechanism (chapter IV). This nitrile-imidine (IIe) was comparatively more stable, less soluble in ethanol and needed a longer time (100 hr.) to crystallise out from the reaction solution than that of the imidine (IIb) (needed only 1 hr.).

The proof of the cyclic structure of the imidine (IIe) came from its u.v. absorption which was the same as that of the imidine (IIb) (Table XIII), and its i.r. spectrum (typical broad absorption in the NH region) (Table VI). However, the nitrile stretching did not show, as sometimes happens. This imidine (IIe) was further identified as its picrate, C_{12}H_{12}N_{3}O_{7}.

The imidine (IIe) was readily hydrolysed by water to a product C_{6}H_{10}N_{4}O_{2}. That this had the imino-imide structure was supported by the u.v. spectrum (\lambda_{\text{max}} 238 \text{ nm}, 15.3 \times 10^{-3} \varepsilon) which was closely similar to that of the imino-imide (VIb) (\lambda_{\text{max}} 238 \text{ nm}, 15 \times 10^{-3} \varepsilon). During the hydrolysis with water the nitrile group in the imidine (IIe) was also hydrolysed to an amide as shown by the i.r. spectrum (Table VII) and by the p.m.r. spectrum (Table IV) which showed a broad peak at 2.2\tau. The values in the Table IV also showed the non-equivalence of the three methylene groups, which were assigned respectively by comparison of their chemical shifts with the compounds (VIb, VIIb, and VIIb') (Tab. I).

(B) Hydroxylamine:

The trinitrile (Ie) with hydroxylamine either at room
TABLE IV
p.m.r. results of 4-carbamoylmethyl-6-imino-2-oxopiperazine(VIe).

<table>
<thead>
<tr>
<th>Structure of the compound</th>
<th>Solvent</th>
<th>Chemical shift (τ) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CF₃CO₂H</td>
<td>3-H₂ 5.89 4-H₂ 5.51 -CONH₂ 2.2</td>
</tr>
</tbody>
</table>

temperature or in boiling aqueous ethanolic solution gave no cyclic product as expected from the behaviour of the previous dinitriles (Ia-Id), but gave instead the adduct, tri(amidoximino-methyl)amine (IVe). The acyclic structure of this was proved by the lack of absorption in the u.v. region and its p.m.r. spectrum which gave a single peak at 6.86τ (in D₂O) (symmetrical methylene groups). The above reaction was reminiscent of glutaronitrile (xi), where the bisamidoxime (xii) was obtained at 60° and then cyclised by sublimation to the cyclic dioxime (xiii), which was also obtained directly from the dinitrile when treated with hydroxylamine at 90° as shown below.
Further investigation showed that glutaronitrile (xi) cyclised quickly (0.5 hr.) to the dioxime (xiii) when treated with hydroxylamine in the presence of its hydrochloride.

But extension of the above findings to the trinitrile (Ie) or trisamidoxime (IVe) were unsuccessful because in all the attempts the trinitrile (Ie) formed the triamidoxime (IVe) and when this was boiled either in the presence of hydroxylamine or its hydrochloride, (IVe) was recovered in full. Attempts to sublime the amidoxime (IVe) were abortive as it decomposed on heating before any sublimation occurred even under high vacuum. The triamidoxime (IVe) with acetic anhydride in pyridine afforded tri(N-acetylamidoximinomethyl)amine (IVe'). This was still an acyclic material as shown by its p.m.r. spectrum (singlets at 6.67 and 7.83) (in D2O). Each acetyl group in compound (IVe') was attached to NH rather than to oximino oxygen as the compound gave a reddish brown colour with iron(III)chloride (cf. IIIc and IIIc') (pp.273). It had been thought that acetic anhydride would effect cyclisation to a tris-oxadiazine.

(v) Reactions of o-cyanobenzylcyanide with hydroxylamine.

\(^{23}\) o-Cyanobenzylcyanide (If) does not fall in the imino-diacetonitrile family (Ia-Ie). However, because Elvidge et al\(^{24}\) have already described the reactions of this dinitrile (If) with nitrogen bases such as ammonia, hydroxylamine etc., comparisons
can be made. One difference is that the dinitrile (If) with hydroxylamine (4 mols) in boiling aqueous methanol for 4 hr. gave 1-amino-3-hydroxyaminoisoquinoline\textsuperscript{24} (XVII) whereas iminodiacetonitrile (Ia) with hydroxylamine (2 mols) (in the presence of an excess of hydroxylamine hydrochloride) in boiling aqueous methanol for 1.5 hr. afforded 2-amino-6-hydroxyaminopyrazine 1-oxide (IX) (cf. part II of this thesis). Apart from the trivial difference of lacking the fused benzene ring, the latter product (IX) has an additional N-oxide group. It seemed of interest to investigate further the effect of hydroxylamine on the dinitrile (If) under different conditions and if possible, to obtain the N-oxide (XII) from the dinitrile (If).

With that intention, the dinitrile (If) and hydroxylamine (2 mols) (in the presence of its hydrochloride) were boiled together in aqueous methanol for 1.5 hr. The product which separated (45\%) had m.p. 220°-225° (decomp.), a melting point higher than for the known aromatised product (XVII) (m.p. 95°)\textsuperscript{24} and also higher than for the expected N-oxide (XII). However, although the molecular formula, C\textsubscript{9}H\textsubscript{7}N\textsubscript{3}O\textsubscript{2}, was correct for the N-oxide (XII), the product surprisingly gave a reddish brown colour with iron(III) chloride which was reminiscent of the cyclic-dioximes (IIIa-IIId). Hence the non-aromatised cyclic-dioxime structure (IIIf) was proposed. This was supported by the i.r. spectrum which showed typical oxime absorptions (Table XVIII). The cyclic structure (IIIf) was duly established by its p.m.r. spectrum. For comparison,
Reactions of o-cyanobenzylcyanide with hydroxylamine.

Scheme V

If → IIIf → XII → XVII → VIIf
### TABLE XVIII

The i.r. spectrum of 1,3-dihydroxyimino-1,2,3,4-tetrahydroisoquinoline (homophthalimide dioxime) (IIIf) ($\nu_{\text{max.}} \text{cm}^{-1}$).

<table>
<thead>
<tr>
<th>Alkyl imidoxime *</th>
<th>Aryl imidoxime *</th>
<th>2-NH</th>
<th>OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I band (s)</td>
<td>II band (w)</td>
<td>I band (s)</td>
<td>II band (w)</td>
</tr>
<tr>
<td>1666</td>
<td>1604</td>
<td>1644</td>
<td>1578</td>
</tr>
</tbody>
</table>

### TABLE XIX

p.m.r. results for homophthalimide, the monoxime and the dioxime (IIIf) in dimethylsulphoxide at 40°.

<table>
<thead>
<tr>
<th>Structure of the compound</th>
<th>$\tau$, multiplicity and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-CH$_2$</td>
</tr>
<tr>
<td>![Structure 1]</td>
<td>5.98</td>
</tr>
<tr>
<td>![Structure 2]</td>
<td>6.16</td>
</tr>
<tr>
<td>![Structure 3]</td>
<td>6.215</td>
</tr>
</tbody>
</table>

* The assignments were made by comparison with the i.r. spectrum of 2-(o-cyanophenyl)-propionitrile bisamidoxime. (Ref. 25).
the p.m.r. spectra of homophthalimide\textsuperscript{24}(VIII\textsubscript{f}) and the monoxime\textsuperscript{26} are also given in Table XIX. The values in this table show that substitution of the C=NOH group by the C=O group gradually moved the chemical shifts towards lower field. The signal from a methylene group was powerful evidence for the structure of the dioxime.

From the foregoing evidence, it was concluded that the dinitrile (I\textsubscript{f}) with hydroxylamine in acidic medium (same as used for the dinitrile I\textsubscript{a}) at elevated temperature afforded the non-aromatised dioxime (III\textsubscript{f}) but not the aromatised \textsubscript{N}oxide (XII). The formation of the cyclic dioxime (III\textsubscript{f}) can be explained by the following mechanism (7) in which the dinitrile (I\textsubscript{f}) first adds two mols of hydroxylamine and forms the intermediate, bisamidoxime (IV\textsubscript{f}) which cyclises to give the dioxime (III\textsubscript{f}).

\[
\text{If} \quad \begin{array}{c}
\text{CN} \quad 2 \text{NH}_2\text{OH} \\
\text{slow} \\
\text{IVf} \quad \begin{array}{c}
\text{NH}_2 \\
\text{NOH} \\
\text{NH}_2 \\
\text{NOH} \\
\text{fast} \\
\text{IIIf Eq. 7} \\
\end{array}
\end{array}
\]

In accord with this mechanism (7), glutaronitrile\textsuperscript{6} and the dinitriles (I\textsubscript{a}-I\textsubscript{d}) with hydroxylamine, in fact, gave their corresponding bisamidoximes, and these were independently cyclised to the dioximes. In a series of attempts to prepare the bisamidoxime (IV\textsubscript{f}) from the dinitrile (I\textsubscript{f}), only the known 1-amino-3-hydroxyaminoisoquinoline (XVII) was obtained whether
4 mols, 2 mols, or 1 mole of hydroxylamine were used or even, as in the last case, in the presence of an excess of hydroxylamine hydrochloride. A mechanism for the formation of (XVII) has already been suggested by D.E.H. Jones\textsuperscript{25}, as shown below.

\[
\text{If } \xrightarrow{\text{fast}} \text{ XIV} \xrightarrow{\text{slow}} \text{ IVf'} \xrightarrow{\text{fast}} \text{ XVII} \text{ NH}_2
\]

The i.r. and p.m.r. spectra and also the m.p. of the product (XVII) were the same as those published for that compound\textsuperscript{24}. The product (XVII) also gave turquoise colour with iron(III)-chloride which is a characteristic of aromatic hydroxyamino compounds \textit{viz.} 2-hydroxyaminopyridine\textsuperscript{27}.

Both the aromatised product (XVII) and the cyclic dioxime (III\textit{f}) when boiled with dilute hydrochloric acid afforded the known homophthalimide\textsuperscript{24}.

Now, the only possibility, apparently remaining, for obtaining the bisamidoxime (IV\textit{f}) was to reduce the reaction time in the above reaction (7) where the cyclic dioxime (III\textit{f}) was obtained. Here again, when the dinitrile was boiled in aqueous
methanol with hydroxylamine (in the presence of its hydrochloride in excess) for 45 mins., 30 mins., and 20 mins. (each separate reaction), the same dioxime (IIIf) was obtained in gradually decreasing yield. While the same reaction for 10 mins., failed to afford any dioxime (IIIf), only starting material was recovered.

The conclusion to be drawn from these results is that the intermediate (IVf) is not obtained because the second stage reaction is so fast that only the cyclic dioxime (IIIf) or the aromatised product (XVII) is isolated.
(i) Tabulated i.r. spectral data:

**TABLE V**

1. Dinitriles: N-Iminodiacetonitriles: I:

\[ R-N\left(-CH_2CN\right)_2 \]

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>( \nu_{\text{max.}} \text{ cm}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Ia</td>
<td>H</td>
<td>2230</td>
</tr>
<tr>
<td>N-Benzyl-</td>
<td>Ib</td>
<td>PhCH(_2)^-</td>
<td>2270</td>
</tr>
<tr>
<td>N-Benzoyl-</td>
<td>Ic</td>
<td>PhCO^-</td>
<td>2280w</td>
</tr>
<tr>
<td>N-Acetyl-</td>
<td>Id</td>
<td>CH(_3)CO^-</td>
<td>2270w</td>
</tr>
<tr>
<td>N-Cyanomethyl-</td>
<td>Ie</td>
<td>CNCH(_2)^-</td>
<td>2230</td>
</tr>
</tbody>
</table>

**TABLE VI**

2. Imidines: 2,6-Diiminopiperazines: II:

![Diagram of Imidines]

46
<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>(\nu_{\text{max. cm}^{-1}}) NH</th>
<th>(\nu_{\text{max. cm}^{-1}}) C=N</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Benzyl-</td>
<td>IIb</td>
<td>PhCH(_2)-</td>
<td>3400-3000</td>
<td>1690 &amp; 1620</td>
</tr>
<tr>
<td>4-Cyanomethyl-</td>
<td>IIe</td>
<td>CNCH(_2)-</td>
<td>3450-3000</td>
<td>1668 &amp; 1626</td>
</tr>
</tbody>
</table>

**TABLE VII**

3. Imino-imides: 6-Imino-2-oxopiperazines: VI:

![Structure of 6-Imino-2-oxopiperazines](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>(\nu_{\text{max. cm}^{-1}}) 1-NH</th>
<th>(\nu_{\text{max. cm}^{-1}}) 2-CO</th>
<th>(\nu_{\text{max. cm}^{-1}}) N-CH(_2)CONH(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Benzyl-</td>
<td>VIb</td>
<td>PhCH(_2)-</td>
<td>3320</td>
<td>1652</td>
<td>--</td>
</tr>
<tr>
<td>4-Carbamoylmethyl-</td>
<td>VIe</td>
<td>NH(_2)COCH(_2)-</td>
<td>3310</td>
<td>1660</td>
<td>3390 &amp; 3190 NH(_2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1660 CO</td>
</tr>
</tbody>
</table>

**TABLE VIII**

4. 6-Imino-N-substituted imidines: 4-Benzyl-2-imino-6-( )-piperazines: VIII:

![Structure of 6-Imino-N-substituted imidines](image)
<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>$\nu_{\text{max. cm.}^{-1}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-NH</td>
</tr>
<tr>
<td>6-Phenylimino-</td>
<td>VIIIb</td>
<td>Ph-</td>
<td>3460</td>
</tr>
<tr>
<td>6-(2-pyridyl)imino-</td>
<td>VIIb</td>
<td>2-Py-</td>
<td>3300</td>
</tr>
</tbody>
</table>

**TABLE IX**

5. Amidoximes: $\text{N-Iminobisacetamidoximes: IV:}$

$$\text{R-N} \left(-\text{CH}_2\text{C-NH}_2\right)_2$$

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>$\nu_{\text{max. cm.}^{-1}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>NH$_2$</td>
</tr>
<tr>
<td>Parent</td>
<td>IVa</td>
<td>H</td>
<td>3398 &amp; 3310</td>
</tr>
<tr>
<td>N-Benzyl-</td>
<td>IVb</td>
<td>PhCH$_2$-</td>
<td>3430 &amp; 3330</td>
</tr>
<tr>
<td>N-Benzoyl-</td>
<td>IVc</td>
<td>PhCO-</td>
<td>3455 &amp; 3360</td>
</tr>
<tr>
<td>N-Acetyl-</td>
<td>IVd</td>
<td>CH$_3$CO-</td>
<td>3400 &amp; 3300</td>
</tr>
<tr>
<td>N-Amidoxime-methyl-</td>
<td>IVe</td>
<td>C-CH$_2$-NH$_2$</td>
<td>3470 &amp; 3380</td>
</tr>
</tbody>
</table>

**TABLE X**

6. 2,6-Dihydroxyimino-piperazine: III:
### TABLE XI

7. Monoximes: 6-Hydroxyimino-2-oxopiperazine: V:

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>ν max. cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-NH</td>
</tr>
<tr>
<td>Parent</td>
<td>IIIa</td>
<td>H</td>
<td>3410</td>
</tr>
<tr>
<td>4-Benzyl-</td>
<td>IIIb</td>
<td>PhCH₂⁻</td>
<td>3440</td>
</tr>
<tr>
<td>4-Acetyl-</td>
<td>IIId</td>
<td>CH₃CO⁻</td>
<td>3420</td>
</tr>
<tr>
<td>4-Benzoyl-</td>
<td>IIIC</td>
<td>PhCO⁻</td>
<td>3350</td>
</tr>
</tbody>
</table>

### TABLE XII

8. Imides: 2,6-Dioxopiperazine: VII:

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>ν max. cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-NH</td>
</tr>
<tr>
<td>4-Benzyl-</td>
<td>Vb</td>
<td>PhCH₂⁻</td>
<td>3250</td>
</tr>
<tr>
<td>4-Benzyl-</td>
<td>Vb'</td>
<td>PhCH₂⁻</td>
<td>3250</td>
</tr>
<tr>
<td>4-Benzoyl-</td>
<td>Vc</td>
<td>PhCO⁻</td>
<td>3150</td>
</tr>
</tbody>
</table>
\[
\begin{array}{cccc}
\text{Compound} & \text{No.} & R= & v_{\text{max. cm.}}^{-1} \\
\hline
\text{Imide} & \text{NH- or N-CO}^2R & \\
\hline
\text{Parent, HCl} & \text{VIIa}^1 & H & 3300-2300; 1725 & 1685 & 3300-2300 \\
\text{4-Benzyl, HCl} & \text{VIIb}^1 & \text{PhCH}_2 & 3150-2750; 1780 & 1735 & 2490 & 2420 \\
\text{4-Benzyl} & \text{VIIb} & \text{PhCH}_2 & 3180 & 3080; 1722 & 1690 & -- \\
\text{4-Acetyl} & \text{VIIId} & \text{CH}_3\text{CO} & 3190 & 3080; 1730 & 1702 & 1650^a \\
\end{array}
\]

(ii) Tabulated u.v. spectral data:

Solvent: methanol, ethanol\(^a\) or water\(^b\).

**TABLE XIII**

1. Imidines: 2,6-Diiminopiperazines: II:

\[
\begin{array}{cccc}
\text{Compound} & \text{No.} & R= & R'= & \lambda_{\text{max. nm.}} & 10^{-3} \varepsilon \\
\hline
\text{4-Benzyl}\(^a\)- & \text{Iib} & \text{PhCH}_2 & H & 250.5 & 13.8 \\
\text{4-Cyanomethyl}\(^a\)- & \text{Ile} & \text{CNCH}_2 & H & 250.5 & 18.0 \\
\text{2,6-diformyl}- & \text{IIa} & H & \text{CHO} & 249.5, 347 & 18.3, 12.65 \\
\end{array}
\]
### TABLE XIV

**2. Imino-imides: 6-Imino-2-oxopiperazine: VI:**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>λmax. nm.</th>
<th>10⁻³ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Benzyl-</td>
<td>VIb</td>
<td>PhCH₂⁻</td>
<td>238</td>
<td>15</td>
</tr>
<tr>
<td>4-Carbamoylmethyl-</td>
<td>VIE</td>
<td>H₂NCOCH₂⁻</td>
<td>238</td>
<td>15.3</td>
</tr>
</tbody>
</table>

### TABLE XV

**3. Dioximes: 2,6-Dihydroxyiminopiperazines: III:**

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>λmax. nm.</th>
<th>10⁻³ε</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>IIIa</td>
<td>H</td>
<td>234</td>
<td>15.8</td>
</tr>
<tr>
<td>Parent, ¹/₂NH₂CH.HCl</td>
<td>IIIa</td>
<td>H</td>
<td>234</td>
<td>17.0</td>
</tr>
<tr>
<td>4-Benzyl-</td>
<td>IIIb</td>
<td>PhCH₂⁻</td>
<td>234</td>
<td>14.9</td>
</tr>
<tr>
<td>4-Acetyl-</td>
<td>IIId</td>
<td>CH₃CO</td>
<td>234</td>
<td>15.0</td>
</tr>
<tr>
<td>4-Benzoyl-</td>
<td>IIIc</td>
<td>PhCO</td>
<td>232</td>
<td>19.4</td>
</tr>
<tr>
<td>4-Benzoyl-2,6-di-benzoyloxy-</td>
<td>IIIc</td>
<td>PhCO</td>
<td>254 infl.</td>
<td>29.0,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16.5</td>
</tr>
</tbody>
</table>
TABLE XVI

4. Monoximes: 6-Hydroxyimino-2-oxopiperazines: V:

\[
\text{R-N} \begin{array}{c} \text{OH} \\ \text{NH} \end{array}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>( \lambda_{\text{max.}} ) nm.</th>
<th>( 10^{-3} \epsilon )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Benzyl-</td>
<td>Vb</td>
<td>PhCH(_2)</td>
<td>224 infl.</td>
<td>9.4</td>
</tr>
<tr>
<td>4-Benzoyl-</td>
<td>Vc</td>
<td>PhCO</td>
<td>220 infl.</td>
<td>10.2</td>
</tr>
</tbody>
</table>

TABLE XVII

5. 6-Imino-\(N\)-substituted imidines: 4-Benzyl-2-imino-6- ( )-piperazines: VIII:

\[
\text{Ph-CH}_2 \text{-N} \begin{array}{c} \text{NH} \\ \text{N-R} \end{array}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>R=</th>
<th>( \lambda_{\text{max.}} ) nm.</th>
<th>( 10^{-3} \epsilon )</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Phenylimino-</td>
<td>VIIIb</td>
<td>Ph</td>
<td>260, 291.5</td>
<td>10.0, 10.5</td>
</tr>
<tr>
<td>6-(2-pyridyl)imino</td>
<td>VIIIb'</td>
<td>2-Py</td>
<td>257, 282</td>
<td>17.0, 12.6</td>
</tr>
</tbody>
</table>
(iii) **Tabulated p.m.r. spectral data:**

p.m.r. results for solutions in CDCl$_3$ or CF$_3$CO$_2$H, containing SiMe$_4$, at 60 MHz.

**TABLE XXIII**

1. Dinitriles: **N**-Iminodiacetonitriles: I:

$$R-N-(-CH_2-CN)_2$$

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>$\tau$, multiplicity*($J$ in Hz) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>Ia</td>
<td>8.19 (br) (NH), 6.31 (d)(6.3)(2 x CH$_2$).</td>
</tr>
<tr>
<td>N-Benzyl-</td>
<td>Ib</td>
<td>6.41 (2 x CH$_2$), 6.20 (CH$_2$), 2.63 (Ph).</td>
</tr>
<tr>
<td>N-Benzoyl-</td>
<td>Ic</td>
<td>5.53 (2 x CH$_2$), 2.45 (Ph).</td>
</tr>
<tr>
<td>N-Acetyl-</td>
<td>Id</td>
<td>7.76 (CH$_3$), 5.59 (2 x CH$_2$).</td>
</tr>
<tr>
<td>N-Cyanomethyl-</td>
<td>Ie</td>
<td>5.94 (3 x CH$_2$).</td>
</tr>
</tbody>
</table>

* Singlets unless otherwise indicated.
TABLE XXIV

2. Amidoximes: N-Iminobisacetamidoximes: IV:

\[
\begin{align*}
\text{NOH} \\
\text{R-N-\{CH}_2\text{-O-NH}_2\}^2
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>Solvent</th>
<th>(\tau), multiplicity*((J\ in\ Hz)) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>IVA</td>
<td>D(_2)O</td>
<td>6.79 ((2 \times CH_2)).</td>
</tr>
<tr>
<td>N-Benzyl-</td>
<td>IVb</td>
<td>D(_2)O/ CF(_3)CO(_2)H</td>
<td>6.57 ((2 \times CH_2)), 6.34 ((CH_2)), 2.6 ((Ph)).</td>
</tr>
<tr>
<td>N-Benzoyl-</td>
<td>IVc</td>
<td>D(_2)O</td>
<td>5.31 ((2 \times CH_2)).</td>
</tr>
<tr>
<td>N-Acetyl-</td>
<td>IVd</td>
<td>D(_2)O</td>
<td>7.83 ((CH_3)), 5.91 ((2 \times CH_2)).</td>
</tr>
<tr>
<td>N-Cyanomethyl-</td>
<td>IVe</td>
<td>D(_2)O</td>
<td>6.36 ((3 \times CH_2)).</td>
</tr>
</tbody>
</table>

TABLE XXV

3. Dioximes: 2,6-Dihydroxyiminopiperazines: III:
<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>$\tau$ multiplicity*(J in Hz) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent*</td>
<td>IIIa</td>
<td>5.21 ($2 \times \text{CH}_2$).</td>
</tr>
<tr>
<td>4-Benzyl*</td>
<td>IIIb</td>
<td>5.28 (d)(4) ($2 \times \text{CH}_2$), 4.47 (4-CH$_2$), 2.46 (Ph).</td>
</tr>
<tr>
<td>4-Benzoyl*</td>
<td>IIIc</td>
<td>4.94 ($2 \times \text{CH}_2$), 2.43 (Ph).</td>
</tr>
<tr>
<td>4-Acetyl*</td>
<td>IIId</td>
<td>7.58 (CH$_3$), 4.98 (d)(6)($2 \times \text{CH}_2$).</td>
</tr>
<tr>
<td>4-Benzoyl-2,6-dibenzoyloxy-</td>
<td>IIIC$'$</td>
<td>5.24 ($2 \times \text{CH}_2$), 2.51 ($2 \times \text{Ph}$), 2.7-2.3 (m) ($3'-,4'$-,$5'$-H of 4-benzoyl), 1.98 (ca. dd)($2'-,6'$-H of 4-benzoyl), 1.26 (br)(NH).</td>
</tr>
</tbody>
</table>

**TABLE XXVI**

4. $\text{4-imino-N}$-substituted imidines: 4-Benzyl-2-imino-6-( )piperazines: VIII:
<table>
<thead>
<tr>
<th>Compound</th>
<th>No.</th>
<th>( \tau ), multiplicity and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Phenylimino-</td>
<td>VIIIb</td>
<td>6.99 (d) (1.5) (3-H(_2)), 6.70 (5-H(_2)), 6.42 (4-H(_2)), 3.3-2.4 (m) (PhN), 2.65 (Ph), ca. 4-2 (br) (2 x NH).</td>
</tr>
<tr>
<td>6-(2-pyridyl)imino-</td>
<td>VIIIb'</td>
<td>6.63 (br) (3-H(_2)), 6.51 (5-H(_2)), 6.33 (4-H(_2)), 2.65 (Ph), 3.2-2.0 (m) (3'-, 4'-, 5'-H of pyridyl ring), 1.60 (ca. dd) (6'-H of pyridyl ring), 3.2-2.0 (br) (2 x NH).</td>
</tr>
</tbody>
</table>
(A) Reaction mechanisms:

All the reactions discussed in chapter II (excluding the reaction of o-cyanobenzylcyanide) can be explained by either of the two possible reaction mechanisms as described below:

Reagent: Nitrogen base:

\[ R'_-NH_2 \rightleftharpoons R_\text{amine}-NH + H^+ \]

where \( R' = H \) (or Na), CHO, HO, Ph, or 2-pyridyl.

Possible mechanism (1):

\begin{align*}
\text{mono-adduct} & \quad R = H, \text{CH}_2\text{Ph, COPh, COCH}_3, \text{or CH}_2\text{CN.} \\
\text{di-adduct} & \quad R' = H, \text{CH}_2\text{Ph, COPh, COCH}_3, \text{or CH}_2\text{CN.}
\end{align*}
Possible mechanism (2):

- di-$N$-substituted imidine

- mono-adduct

- mono-$N$-substituted imidine

- di-$N$-substituted imidine
Reaction mechanism (1) involves the stepwise addition of two mols of nucleophilic reagent to the dinitrile to give the acyclic di-adduct which subsequently loses ammonia and cyclises to give the di-\text{N}-substituted cyclic product. In the reaction mechanism (2) the dinitrile adds on one mole of a reagent and forms the mono \text{N}-substituted imidine. This imidine adds another molecule of a reagent and subsequently loses ammonia to give the di-\text{N}-substituted imidine.

Reactions of the dinitriles (Ia-Id) with weak nucleophilic reagent i.e. hydroxylamine appear to be best explained by the mechanism (1). This is because the dinitriles (Ia-Id) added two mols of hydroxylamine and produced the di-adduct, which was isolated in each case. Each di-adduct was then cyclised to the di-\text{N}-substituted imidine i.e. to a cyclic dioxime (IIIa-IIIId) so that the final stage of the mechanism (1) was achieved separately. Reactions of the dinitrile (Ib) with a stronger nucleophilic reagent like sodio-aniline or sodio derivative of 2-aminopyridine are better explained by the reaction mechanism (2) because here the product obtained, the mono-\text{N}-substituted imidine, corresponds to a middle stage, the reaction not continuing to give the di-\text{N}-substituted imidine. It was then intriguing to decide the particular mechanism by which the dinitrile (Ib or Ie) interacted with either ammonia or sodamide, as these reagents lack a distinguishing substituent group. However, as a result of careful observation, and by analogy, it has been possible to select the mechanism (2) for the reactions where sodamide was used as a reagent.
Thus if the trinitrile (Ie) (having three nitrile groups each equally active), had undergone reaction by the mechanism (1), the tri-amidine would have been formed (analogous to the trisamidodioxide IVe) which then would have cyclised to the imidine having a 4-amidinomethyl substituent. In fact, the cyclic imidine isolated had a 4-cyanomethyl group instead. This fact can only be explained straightforwardly by the mechanism (2) and so this is favoured. By analogy the same mechanism (2) is favoured for the reaction of the dinitrile (Ib) under similar conditions.

Reviewing the above discussion, it appears that all the reactions, excluding the reactions of the dinitriles with hydroxylamine (which followed the mechanism (1)), can be best explained by the mechanism (2).

(B) Structure determination:

The compounds resulting from the reactions described in chapter II can be represented by one of the following structures.

\[
\text{XVIIIa} \quad \text{XVIIIb} \quad \text{XVIIIc}
\]

\[
\begin{align*}
\text{X} & = \text{H}, \text{OH}, \text{Ph}, \text{or 2-Pyridyl} \\
\text{Y} & = \text{NH, O or NOH}
\end{align*}
\]
The structures (XVIIIb) and (XVIIIc) may be rejected by analogy with α-phenylglutarimidine. α-Phenylglutarimidine and the imidines (IIb and IIe) (Table XIII), all absorb at 250±nm. (18.0 \(10^{-3}\) \(\varepsilon\)) whereas amino substituted dienes such as structures (XVIIIb) and (XVIIIc) should absorb at least as far as 300 nm. Also the p.m.r. spectrum of such structures (where \(XNH = YH\)) would be expected to show two different chemical shifts for the acyclic protons, and of different line intensities in the case of (XVIIIc), but in practice only one chemical shift was observed.

Exceptionally the difomylimidine (IIa) absorbed as far as 347 nm. (Table XIII). It might be concluded therefore that for the difomylimidine the 1:3-diene structure (XVIIIb) contributes appreciably so that in alcoholic solution the imidine (IIa) may be a tautomeric mixture as follows:

\[
\begin{array}{c}
\text{OHCHN} \quad \text{NCHO} \\
\text{OHCHN} \quad \text{NCHO}
\end{array}
\]

Previous work indicated that the fine structures of mono- and di-aryl substituted imidines are less certain because they absorb light at longer wave-lengths than expected for the exocyclic double bond structure (XIXa). The present mono-N-aryl imidines have similar light absorptions (Table XVII) and hence they may all have tautomeric contributions from 1:3-diene...
structures (XIXb, XIXc) as shown below:

![Structures XIXa, XIXb, XIXc, XIXd]

R' = phenyl or pyridyl.

However, reference to the unsubstituted imino-compounds (Table XX) and the mono-N-phenyl substituted imine and imidine (Table XXI) shows that aryl substituted imino-compounds absorb as high as 276-280 nm., whilst unsubstituted imino compounds no higher than 236 nm. The values under consideration (Table XVII) are no higher than 291.5 nm., which is just 10-12 nm. higher than for the model compounds (Table XXI). It seems therefore that the 1:4-diene system (XIXa) is favoured over the 1:3-diene system (XIXb and XIXc) because compounds with the latter chromophores would definitely absorb higher than 300 nm. (refer Table XXII). A further point is that the i.r. spectrum of the mono-N-phenyl imidine (VIIIb)
shows a single sharp band at 3460 cm\(^{-1}\) which excludes the amino tautomer (XIXc). The band position at 3460 cm\(^{-1}\) is a characteristic of the ring NH (pp.48) so that the tautomer (XIXb) is also excluded. This leaves then only the 1:4-diene structure (XIXa). Furthermore the pyridyl analogue (VIIib\(^{1}\)) shows broad absorption at 3300 cm\(^{-1}\) suggestive of hydrogen bonding and so necessarily of the exo-cyclic structure (XIXd). In solution, the spectrum of this compound (VIIib\(^{1}\)) showed some free NH. From all of the various points, it appears that the N-aryl imidines (VIIIb and VIIib\(^{1}\)) also have a 1:4-diene structure (XIXa).

### TABLE XX

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>structure</th>
<th>(\lambda) max. nm.</th>
<th>(10^{-3} \epsilon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetamidine(^{28})</td>
<td>(\text{NH} \quad \text{H}_2\text{C} = \text{C} \quad \text{NH}_2)</td>
<td>224</td>
<td>4.0</td>
</tr>
<tr>
<td>(\text{N-Phenylbenzamidine}^{30})</td>
<td>(\text{NH} \quad \text{Ph} \text{--} \text{C} \quad \text{NHPh})</td>
<td>234</td>
<td>18.1</td>
</tr>
<tr>
<td>Biguanidine(^{28})</td>
<td>(\text{NH}_2 \quad \text{NH}_2 \quad \text{HN} \quad \text{H} \quad \text{HN} \quad \text{HN})</td>
<td>231</td>
<td>9.5</td>
</tr>
<tr>
<td>(\text{N-Phenyl-N'--iso--propylbiguanidine}^{28})</td>
<td>(\text{Ph-} \text{NH} \text{NH} \text{P}_{2}^{1})</td>
<td>236</td>
<td>12.7</td>
</tr>
</tbody>
</table>
### TABLE XXI

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>Structure</th>
<th>$\lambda_{\text{max}}$ nm</th>
<th>$10^{-3} \varepsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-(Phenylimino)pentane$^{29}$</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>280</td>
<td>2.0</td>
</tr>
<tr>
<td>$N,N'$-Diphenylformamidines$^{29}$</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>276</td>
<td>20</td>
</tr>
</tbody>
</table>

### TABLE XXII

<table>
<thead>
<tr>
<th>Name of the compound</th>
<th>Structure</th>
<th>$\lambda_{\text{max}}$ nm</th>
<th>$10^{-3} \varepsilon$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinnamylideneaniline$^{29}$</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>304</td>
<td>31.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>325</td>
<td>25.1</td>
</tr>
<tr>
<td>1:2:4:5-Tetraphenyl-1:3:5-triazapenta-1:3-diene$^{30}$</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>230</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>280</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>345</td>
<td>12</td>
</tr>
</tbody>
</table>
EXPERIMENTAL
Notes on the Spectroscopic Data:

The ultra violet (u.v.) absorption information was obtained on the Unicam SP 800 B U.V. Spectrophotometer. Abbreviations used after the absorption values have the following significance: infl., inflection; sh., shoulder.

The infra red (i.r.) absorption spectra were recorded on the Unicam SP 200 I.R. Spectrophotometer for the compounds as a nujol mull unless otherwise stated. Letters given after frequency values have the following meanings: s, strong or sharp; br, broad; w, weak; sh, shoulder.

The mass spectra were observed on the Associated Electric Industries MS 12 Spectrometer using 70 EV energy for ionisation unless otherwise indicated.

The proton magnetic resonance (p.m.r.) results were obtained using the Perkin Elmer 60 MHz N.M.R. Spectrometer. The spectra were recorded at 34° using tetramethylsilane (t.m.s.) as an internal standard with all the solvents except when deuterium oxide was used as a solvent, where the standard was (d.s.s.)
sodium 2,2-dimethyl-2-silapentane-5-sulfonate. Peak multiplicities are indicated by the following letters in parentheses after each chemical shift values: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet.

Thermogravimetric analysis (t.g.a.) was observed on the Stanton Instruments Thermobalance.

Notes on the use of the reagents and solvents:

**Nitrogen** used to deoxygenate the solvents, and for performing reactions under anaerobic conditions, was dried by passing through, consecutively, calcium chloride, concentrated sulphuric acid, and a mixture of solid sodium hydroxide and soda-lime.

**Aniline** (analytical grade) was redistilled under nitrogen before use.

**NN-Dimethylaniline** (laboratory reagent) was redistilled under nitrogen and then used.

**Iminodiacetonitrile** (practical grade) supplied either by Fluka AG, Switzerland or by Eastman Organic Chemicals, N.Y., U.S.A., was recrystallised from boiling benzene to a constant m.p. of 76°C.

**Hydroxylamine hydrochloride** (analytical grade) was used without any purification.

**Sodamide** of 80-90% purity was used as such.
All the reagents, except iminodiacetonitrile, were supplied by British Drug House, Poole, England. Other common solvents were purified, if required.

Microanalysis were carried out either by: Dr. Alfred Bernhardt, Microanalytisches Laboratorium, West Germany, or by: Microanalytical Service, Chemistry Department, University of Surrey, Guildford.
(1) Compounds from N-benzyliminodiacetonitrile:

N-Benzyliminodiacetonitrile (Ib) had m.p. 41° and sometimes m.p. 45° (lit: ref. 16, m.p. 41°-41.5° and ref. 7, m.p. 45°-45.5°). (Found: C, 71.35; H, 5.95. Calc. for C₁₁H₁₁N₃: C, 71.05; H, 6.0%; m/e 185; ν max. 2270 (C=N), 1610 (w), 1590 (w), 1508, 1438, 1352 (w), 1336, 1308 (w), 1290 (w), 1215 (w), 1148, 1135 (s) cm⁻¹.

4-Benzyl-2,6-diiminopiperazine (Iib):

(a) Formation: (α) To N-benzyliminodiacetonitrile (Ib) (2.77 g.) in dry methanol (10 ml.), liquid ammonia (10 ml.) was added cautiously and the solution heated in a Carius tube at 90° for 24 hr. Evaporation of the solution gave the imidine (Iib) which was washed with ethyl acetate and then ether, yield, 1.5 g. (50%); i.r. spectrum identical with that of the sample next prepared.

(β) A solution of N-benzyliminodiacetonitrile (11.1 g.) in formamide (40 ml.) was added to a solution of sodamide (6 g.) in formamide (40 ml.), with stirring under nitrogen and exclusion of light. After 1 hr., the colourless crystalline imidine

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(IIb) was collected and washed with formamide (1 ml.), butanol (2 ml.), ethyl acetate (excess) and then ether (excess); yield, 10.3 g. (85 %), m.p. 157-159° (decomp.) (Found : C, 57.8; H, 6.8; N, 27.35, 27.8. C\textsubscript{11}H\textsubscript{14}N\textsubscript{4}·HO\textsubscript{2}NH\textsubscript{2} requires C, 58.3; H, 6.9; N, 28.0%); m/e, 202; v max. 3400-3000 (NH), 1690 (C=N), 1620, 1558 (s), 1446, 1345 (s), 1305 (w), 1207, 1150, 1105 (s), 1028 (w), 934 (s), 910, 897, 753 (s), 698 (s) cm\textsuperscript{-1}; \lambda max. nm. 250.5, 13.8 10\textsuperscript{-3}.

The picrate crystallised from ethanol as yellow needles, m.p. 237°(decomp.) (Found : C, 47.2; H, 4.0; N, 23.0. C\textsubscript{17}H\textsubscript{17}N\textsubscript{7}O\textsubscript{7} requires C, 47.3; H, 3.9; N, 22.7%).

4-Benzyl-2,6-diiminopiperazine dihydrochloride monohydrate: (IIb'): 4-benzyl-2,6-diiminopiperazine (0.4g) solution in dry n-butanol (10 ml.) was mixed with hydrochloric acid (2 ml.) and after 15 mins., the product (0.5 g., 83%) was filtered off, washed with n-butanol and dried m.p. 340° (chars, without decomp.) (Found : C, 45.5; H, 5.8; N, 19.1. C\textsubscript{11}H\textsubscript{18}Cl\textsubscript{2}O requires C, 45.1; H, 6.1; N, 19.1%); v max. 3280 (s) (NH), 2530 (NH\textsuperscript{+}), 3400-2200 (OH, NH), 1667 (C=N), 1520 (s) (br), 1345, 1318, 1215 (s), 1187, 1100, 1083 (s), 1048 (s), 1015, 930 cm\textsuperscript{-1}.

(b) Hydrolysis: -- The dihydrochloride (IIb') boiled in aqueous methanol for five minutes and charcoaled. Filtrate on cooling afforded the imide hydrochloride. m.p. 243°-244°(decomp., darkening from 230°).

4-Benzyl-6-imino-2-oxopiperazine (VIIb):

(a) Formation: -- When 4-benzyl-2,6-diiminopiperazine (2.02 g.) was dissolved in warm water, ammonia was evolved.
Next day, the product was recrystallised from aqueous ethanol to give needles, m.p. 192°-194° (decomp.) of 4-benzyl-6-imino-2-oxo-piperazine (1.9 g., 93%) (Found: C, 65.2; H, 6.5; N, 20.6. C_{11}-H_{13}N_{2}O requires C, 65.0; H, 6.4; N, 20.7%); m/e, 203; ν max. 3320 (s) (1-NH), 1652 (s) (C0), 1600 (br), 1525 (s), 1353 (s) cm^{-1}; τ (CF_{3}CO_{2}H) 5.36 (s), 5.21 (s), 5.07 (s) (each CH_{2}), 2.46 (s) (Ph); λ max. 238 nm., 15 10{\textsuperscript{3}}.

(b) Hydrolysis:-(a) The imino-imide (VIb) (0.4 g.) in water (10 ml.) containing 3 drops of hydrochloric acid was heated under reflux for 2 hr. Treatment with charcoal, filtration and evaporation gave 4-benzyl-2,6-dioxopiperazine (VIIb) (0.2 g., 49%), m.p. 105°-106° from aqueous ethanol (lit: ref. 7, m.p. 106°), (Found: C, 64.5; H, 5.9; N, 13.7. Calc. for C_{11}H_{12}N_{2}O_{2} C, 64.7; H, 5.9; N, 13.7%); m/e 204; ν max. 3180 (w) and 3080 (w) (NH), 1722, 1690 (s), 1405, 1355, 1320, 1280 (br), 1193, 1150, 1024, 840 (br), 760 (s), 705 (s) cm^{-1}; τ (CDCl_{3}) 6.66 (s) (2 x CH_{2}), 6.34 (s) (CH_{2}), 2.69 (s) (Ph).

(b) The imino-imide (VIb) when boiled with 3N. hydrochloric acid afforded the imide hydrochloride (VIIb') having the same m.p. to that of authentic sample.

4-Benzyl-2,6-dihydroxyiminopiperazine (IIIb):

(a) Formation:-(a) 4-Benzyl-2,6-diiminopiperazine (2.02 g.), hydroxylamine hydrochloride (1.38 g.) and methanol (30 ml.) were heated together under reflux for 2 hr. After removal of ammonium chloride, treatment with charcoal, filtration and cooling, 4-benzyl-2,6-dihydroxyiminopiperazine
separated (1.4 g.) (60%), m.p. 196°-197° (decomp.) after recrystallisation from aqueous ethanol. (Found: C, 56.3; H, 6.05; N, 24.1. C_{11}H_{14}N_{4}O_{2} requires C, 56.4; H, 6.0; N, 23.9%); m/e 234; ν max. 3440 (ν-NH), 3400-2400 (OH), 1667 (s) (C=N), 1505 (w), 1403, 1322 (w), 1110 cm^{-1}; λ max. 234 nm, 15.8 10^{-3}; τ (CF_{3}CO_{2}H) 5.28 (d) (2 x CH_{2}), 4.47 (s) (CH_{2}), 2.46 (s) (Ph). The dioxime (IIib) gave a reddish brown colour with iron(III) chloride in aqueous ethanol.

(β) N-Benzyliminodiacetonitrile (1.85 g.) in ethanol (5 ml.) was heated with 10 ml. of ethanolic hydroxylamine (from 1.38 g. of the hydrochloride) for 14 hr. under reflux. Evaporation and crystallisation of the residue from aqueous ethanol afforded the dioxime (IIib) (1.17 g., 50%), m.p. and mixed m.p. 196°-198° (decomp.) and i.r. absorption identical with authentic material.

(b) Hydrolysis:- 4-Benzyl-2,6-dihydroximinopiperazine (1.17 g.) was refluxed in 3N. hydrochloric acid (10 ml.) for 1.5 hr., then the solution was treated with charcoal and evaporated. Recrystallisation of the residue (0.3 g., 30%) from 96% ethanol gave flakes, m.p. 243°-244° (decomp., darkening from 230°), of 4-benzyl-2,6-dioxopiperazine hydrochloride. (Found: C, 54.6; H, 5.5; N, 11.65. C_{11}H_{13}Cl_{1}N_{2}O_{2} requires C, 54.9; H, 5.4; N, 11.65%); m/e 204; 17.5 (100%), 18.5 (50%); ν max. 3150 (w) (1-NH), 2490 (s) and 2420 (NH^{+}), 1735 (s) (CO), 1417, 1334, 1280 (s), 1205 cm^{-1}; τ (D_{2}O) 5.84 (s) (2 x CH_{2}), 5.53 (s) (CH_{2}), 2.46 (s) (Ph).
4-Benzyl-6-hydroxyimino-2-oxopiperazine (Vb):

(a) Formation: The preceding dioxime (IIIb) (0.7 g.) in ethanol (7.5 ml.), dioxan (15 ml.) and water (7.5 ml.) was treated with 10% sodium nitrite (6 ml.), followed by 2N. hydrochloric acid (6 ml.). Next day, evaporation and recrystallisation of the residue from aqueous ethanol gave 4-benzyl-6-hydroxyimino-2-oxopiperazine hydrochloride (0.5 g., 77%) (Vb), m.p. 194°-195° (decomp.); m/e 219 (21%), 190 (8.4%), 128 (10.9%), 100 (13.4%), 91 (100%), and 18.5, 17.5 in ratio 35:100; ν max. 3250 (s) (NH), 3150 (OH), 2710 (w) and 2560 (s) (NH+), 1734 (s) (CO), 1680 (C=N), 1350 (s), 1300 cm⁻¹. This monoxime gave a yellow brown colour with iron(III) chloride in aqueous ethanol.

Treatment of the hydrochloride (Vb') (225 mg.) in ethanol (3 ml.), water (3 ml.) and dioxan (6 ml.) with silver nitrate (85 mg.) in water, filtration and evaporation gave 4-benzyl-6-hydroxyiminopiperazine (Vb) (110 mg., 50%), which crystallised as needles, m.p. 200°-201° (decomp.), from aqueous ethanol (Found: C, 60.7; H, 6.0; N, 19.55. C₁₁H₁₃N₃O₂ requires C, 60.3; H, 5.9; N, 19.2%); m/e 219; ν max. 3250 (s) (br) (NH, OH), 1680 (sh) (C=N), 1659 (s) (CO), 1402, 1320 (w), 1298 cm⁻¹; λ max. 224 (infl.) nm., 9.4 10⁻³ ε .

(β) 4-Benzyl-6-imino-2-oxopiperazine (VIb) (0.2 g.) and hydroxylamine hydrochloride (69 mg.) in methanol (5 ml.) was heated under reflux for 2 hr. Filtration and cooling afforded 4-benzyl-6-hydroxyimino-2-oxopiperazine (0.12 g., 51%), which
after recrystallisation from aqueous ethanol had m.p. and mixed m.p. 201°-202° (decomp.) and correct i.r. absorption.

(b) Hydrolysis: 4-benzyl-6-hydroxyimino-2-oxopiperazine (0.219 g.), refluxed in 3N. hydrochloric acid (30 ml.), afforded (as from the dioxime as above), 4-benzyl-2,6-dioxopiperazine hydrochloride (0.14 g., 70%), m.p. 242°-244° (decomp., darkening from 230°), was obtained after 120 hr. in 40% yield by saturating a solution of N-benzyliminodiacetonitrile in acetic acid with dry hydrogen chloride.

Attempted preparation of 4-benzyl-2,6-diphenylimino-piperazine:

(a) By the reaction between N-benzyliminodiacetonitrile and aniline hydrochloride: N-Benzyliminodiacetonitrile (3.7 g.) and aniline hydrochloride (5.14 g.) were fused (cf. ref.4,6) together at 260° for 20 mins. No exothermic reaction was observed although there was considerable sublimation of ammonium chloride. Attempts to purify the fused brown material were unsuccessful because it was insoluble in solvents like water, alcohol etc. (which have been used in previous similar reactions4,6). The i.r. spectrum of the polymeric material showed broad generalised absorption.

(b) By the condensation of aniline with imidine:

(a) With 4-benzyl-2,6-dimino-piperazine: 4-Benzyl-2,6-dimino-piperazine (0.41 g.) and aniline (0.36 g.) were heated under reflux in either ethanol or methoxyethanol for 12-20 hr. under nitrogen.
The reaction solution, in all cases, was poured into deoxygenated water and extracted with chloroform, and the dried chloroform solution was concentrated in vacuo. The thick brown liquid, thus obtained, was poured into ether, giving a yellowish solid. This solid turned into tar immediately it became dry and hence no investigation was possible. (β) Similarly, attempts to condense 4-benzyl-2-imino-6-phenyliminopiperazine with aniline gave only tar.

4-Benzyl-2-imino-6-phenyliminopiperazine (VIIIb):

(a) Formation:- (a) Aniline (5.58 g., 0.06 mol) was added slowly to sodamide (3 g.) suspended in benzene (40 ml.) under nitrogen and the mixture was refluxed for 2.25 hr. to drive off ammonia. (cf. ref. 19). N-Benzyliminodiacetonitrile (5.55 g., 0.03 mol) in benzene (10 ml.) was added and refluxing under nitrogen continued for 0.5 hr. After filtration, the solution was evaporated under reduced pressure, and the dark residue triturated with ether to give a pale yellow product (6.75 g., 80%), m.p. 125° (decomp.). From aqueous methanol, 4-benzyl-2-imino-6-phenyliminopiperazine (VIIIb) crystallised as fine pale yellow needles, m.p. 129° (decomp.) (Found : C, 73.4; H, 6.5; N, 20.0. \( C_{17}H_{18}N_4 \) requires C, 73.4; H, 6.5; N, 20.1%); m/e 278; \( v \) max. 3460 (s) (1-NH), 3070 (br)(2-NH), 1665 (s) and 1648 (s) (C=N), 1595 (w), 1575 (s), 1493, 1340, 1318 (s), 1300 (s), 1278 (w), 1278 (w), 1243, 1223 (w), 1205 (w), 1165 (w), 1115 (s) cm\(^{-1}\); \( \lambda \) max. 260, 291.5 nm., 10.0, 10.5 \( 10^{-3} \) ε; \( T \) (CDCl\(_3\)) 6.99 (d)
Sodamide (2 g.) was cautiously added to a solution of
N-benzyliminodiacetonitrile (Ib) (3.7 g., 0.02 mol) in aniline
(7.28 g., 0.08 mol) under nitrogen and with exclusion of light.
After 3 hr. stirring, the thick brown liquid was poured into de-
oxogenated water and the mixture extracted with chloroform into
dry ether, the pale yellow mono-N-phenylimidine (VIIIb) was
obtained (3.9 g., 70%), m.p. and mixed m.p. 127°-129° (decomp.)
and correct i.r. spectrum.

Sodium (0.23 g., 0.01 mol) was added to ethanol (30 ml.)
and when the reaction was over, aniline (5.58 g., 0.06 mol) and
the dinitrile (Ib) (5.55 g., 0.03 mol) were added and the
reaction solution refluxed for 19 hr. under nitrogen. Excess of
ethanol was evaporated, the dark brown residue was poured into
air-free water and the mixture extracted with chloroform. The
extract was dried (Na₂SO₄) and evaporated and treated with dry
ether to give the product (1.8 g., 25%), m.p. 126°-127°
decomp.) raised to 129°-130° (decomp.) by recrystallisation
from aqueous methanol: identity with compound (VIIIb) was shown
by i.r. and mixed m.p.

Hydrolysis: 4-Benzyl-2-imino-6-phenyliminopiper-76
azine (VIIIb) (278 mg.), methanol (5 ml.) and hydrochloric acid
(2 drops) were heated together under reflux for 2 hr. Next day,
colourless crystals were collected (50 mg.) shown by the i.r.
spectrum to be 4-benzyl-6-imino-2-oxopiperazine (VIb).
(c) Reaction with hydroxylamine:-- 4-Benzyl-2-imino-6-phenyliminopiperazine (278 mg.) and hydroxylamine hydrochloride (138 mg., 2 mols) were boiled together in methanol for 1.5 hr. After filtration, cooling of the filtrate afforded the dioxime (IIIb) (150 mg., 64%) m.p. 196° (decomp.) (from aqueous ethanol) and mixed m.p. 196°-197° (decomp.), i.r. spectrum identical with authentic sample.

4-Benzyl-2-imino-6-(2-pyridyl)iminopiperazine:

(a) Formation:-- Sodamide (2 g.) was added to a stirred solution of the dinitrile (Ib) (3.7 g.) and 2-aminopyridine (3.76 g., 2 mols) in N,N-dimethylaniline (15 ml.) under nitrogen and with exclusion of light. After 4 hr., the dark liquid was poured into deoxygenated water, the mixture was extracted with chloroform and the extract dried (Na₂SO₄). Evaporation and treatment with dry ether gave pale yellow 4-benzyl-2-imino-6-(2-pyridyl)iminopiperazine (3.52 g., 62.5%) which crystallised from acetone as needles, m.p. 144°-145° (decomp.) (Found: C, 68.5; H, 6.0; N, 24.9. C₁₆H₁₇N₅ requires C, 68.8; H, 6.1; N, 25.1%).

m/e 279; v max. 3300 (1-NH bonded) and 3100 (s)(br)(2-NH), 1665 and 1635 (s) (C=N), 1595, 1540 (s), 1428, 1357, 1338 (s), 1310 (w), 1283, 1262, 1238 (w), 1148 (s) cm⁻¹; A max. 257, 282 mm⁻¹, 17.0, 12.6 10⁻³ ε ; r (CDCl₃) 6.63 (br)(3-H₂), 6.51 (5-H₂), 6.33 (4-H₂), 2.65 (Ph), 3.2-2.0 (m)(3',4', 5'-H of pyridyl ring), 3.2-2.0 (br) (2 x NH).

(b) Reaction with hydroxylamine hydrochloride:--
Following the reaction of 4-benzyl-2-imino-6-phenyliminopiperazine with hydroxylamine hydrochloride, the 6(2-pyridyl)-analogue (279 mg.) gave the same dioxime (IIIb) (163 mg., 70%), m.p. and mixed m.p. 197° (decomp.). The identity was further confirmed by the i.r. spectrum.

**Attempted condensation of aromatic amines with N-benzyliminodiacetonitrile:**

(a) Reaction between N-benzyliminodiacetonitrile (Ib) and m-phenylenediamine: (a) The dinitrile (Ib) (1.85 g.) and m-phenylenediamine (0.54 g.) were added to a suspension of sodamide in benzene under nitrogen. Following the procedure for the preparation of 4-benzyl-2-imino-6-phenyliminopiperazine, a pale yellow product was obtained, which unlike the imidine (VIIIb) gave very broad i.r. absorption similar to that of the polymeric material obtained in the preceding experiment.

(β) Changing the benzene solvent to the basic solvent NN-dimethylaniline led to the same polymeric product.

(γ) An attempt to condense the dinitrile (Ib) (1.85 g.) with molten m-phenylenediamine (2.16 g.) in the presence of sodamide (1 g.) was abortive. The same polymeric product was obtained.

(b) Reaction between N-benzyliminodiacetonitrile and p-phenylenediamine: (α) When the dinitrile (Ib) (3.7 g.), p-phenylenediamine (1.08 g.) and sodamide (2 g.) were heated to 50°-60° for 2 hr. under nitrogen, ammonia was evolved. Cooling of
the reaction solution afforded a crystalline compound. This was unreacted p-phenylenediamine and no reaction product was obtained.

(β) Repeating the above reaction using benzene as solvent led to exactly the same result.

(c) Reaction between N-benzylinodiacetonitrile (Ib) and 2,6-diaminopyridine: A similar attempt to condense the dinitrile (Ib) (1.85 g.) with 2,6-diaminopyridine (2.18 g.) led to most of the diamine being recovered.

(2) Compounds from N-acetylaminodiacetonitriles (Ic and Id):

Attempted reactions of N-benzylinodiacetonitrile (Ic):

(a) With ammonia: The dinitrile (Ic) (3 g.) in methanol (30 ml.) containing liquid ammonia (15 ml.) was heated at 120°-130° in a sealed tube overnight. Next day, evaporation of the solution under reduced pressure afforded a brown product (1.5 g.) (m.p. 114°-115°). After recrystallisation of the product from hot water (charcoal), it had m.p. 129°, undepressed in admixture with benzamide. The i.r. spectrum was the same as that of benzamide.

(b) Sodamide: Reaction of the dinitrile (Ic) with sodamide in formamide (cf. pp.69) gave intractable material only.

Attempted reaction of N-acetylaminodiacetonitrile (Id):

(a) With ammonia: The dinitrile (Id) (2.54 g.) in methanol (25 ml.) was allowed to react with liquid ammonia (15 ml.) at 100° in a sealed tube overnight. Evaporation of the solution
under reduced pressure afforded intractable material.

(b) With sodamide:- The dinitrile (Id) with sodamide in formamide gave intractable material.

4-Benzoyl-2,6-dihydroxyiminopiperazine (IIc):

(a) Formation:- A hot solution of the dinitrile (Ic)\textsuperscript{14} (1.99 g., 0.01 mol) in dioxan (5 ml.), methanol (2 ml.) and water (3 ml.) was treated with hydroxylamine hydrochloride (2.76 g., 0.04 mol) and sodium carbonate (1.06 g., 0.01 mol) dissolved in water (5 ml.) and dioxan (2 ml.). The solution was heated under reflux for 0.5 hr. during which 4-benzoyl-2,6-dihydroxyiminopiperazine (IIc) separated (1.7 g., 70%), m.p. 198° (decomp.) (from aqueous methanol) (Found : C, 53.4; H, 5.0; N, 22.8. C\textsubscript{11}H\textsubscript{12}N\textsubscript{4}O\textsubscript{3} requires C, 53.2; H, 4.8; N, 22.6%); m/e 248; ν\textsubscript{max.} 3350 (s) (1-NH), 3140 (w)(OH), 1675 (s)(C=N), 1642 (s)(CO), 1503 (w), 1278 (s), 1235 (w), 1142 cm\textsuperscript{-1}; λ\textsubscript{max.} 232 nm., 19.4 \times 10\textsuperscript{-3} ε ; τ (CF\textsubscript{3}CO\textsubscript{2}H) 4.94 (s)(2 ×CH\textsubscript{2}), 2.43 (s)(Ph).

This dioxime (IIc) gave a greyish violet colour in aqueous ethanol with iron(III)chloride.

(b) Hydrolysis:- The dioxime (0.248 g.) was heated under reflux in 3N. hydrochloric acid (3ml.) for 1.25 hr., the solution was cooled and benzoic acid was collected (0.11 g., 90%), identical (i.r. spectrum) with authentic material. Evaporation of the filtrate afforded 2,6-dioxopiperazine hydrochloride (0.15 g., 100%) which after recrystallisation from methanol had m.p. 277°-278° (decomp.) undepressed by, and i.r.
spectrum the same as, authentic material (see later).

4-Benzoyl-6-hydroxyimino-2-oxopiperazine (Vc):

The dioxime (IIIC) (0.496 g.) was dissolved in a warm mixture of methanol (5 ml.), dioxan (10 ml.) and water (5 ml.). To the cooled solution, 10% sodium nitrite (4 ml.) was added, followed by 3N. hydrochloric acid (4 ml.). Next day, the solution was evaporated under reduced pressure, affording 4-benzoyl-6-hydroxyimino-2-oxopiperazine (0.18 g., 40%), m.p. 183°-184° (decomp.) from aqueous methanol (Found: C, 56.85; H, 4.8; N, 17.9. \(\text{C}_{11}\text{H}_{11}\text{N}_{3}\text{O}_{3}\) requires C, 56.65; H, 4.7; N, 18.0%). m/e 233; \(v_{\max}\) 3150 (br)(OH, NH), 1650 (s)(br)(C=N, C=O), 1600 (w), 1505, 1410 (w), 1350, 1325 (s), 1282, 1258, 1230, 1182 (w), 1135 (s) cm\(^{-1}\); \(\lambda_{\max}\) 220 (inf1.) nm., 10.2 \(10^{-3}\) \(\epsilon\). The monoxime (Vc) in aqueous methanol gave a yellowish orange colour with iron(III)chloride.

4-Acetyl-2,6-dihydroxyiminopiperazine (IIId):

(a) Formation :- Hydroxylamine hydrochloride (11.2 g.) and sodium carbonate (4.24 g.) were dissolved in warm water (10 ml.) and methanol (30 ml.), and N-acetyliminodiacetonitrile (Id) (5.48 g.) was added. After the solution had been refluxed for 15 mins. 4-acetyl-2,6-dihydroxyiminopiperazine (IIId) (3.7 g., 50%) separated as needles, m.p. 202°-204° (decomp.) (from aqueous methanol) (Found: C, 38.6; H, 5.5; N, 30.2. \(\text{C}_{6}\text{H}_{10}\text{N}_{4}\text{O}_{3}\) requires C, 38.7; H, 5.4; N, 30.1%); m/e 186; \(v_{\max}\) 3420 (1-NH), 3200 (br)(s)(OH), 1670 (s)(C=N), 1630 (s)(C=O), 1302(w),
1255 (s), 1195 (w) cm⁻¹; λ max. 234 nm., 15.0 × 10⁻³ε; r(CF₃CO₂H)
7.58 (s) (Me), 4.98 (d)(6)(2×CH₂). It gave a grey violet colour
in aqueous ethanol with iron(III)chloride.

(b) Hydrolysis:— (a) The preceding dioxime (0.744 g.)
was suspended in methanol (10 ml.), water (10 ml.) and dioxan (10
ml.) and 10% sodium nitrite (8 ml.) was added, followed by 3N.
hydrochloric acid (5 ml.). Next day, evaporation of the solution
afforded 4-acetyl-2,6-dioxopiperazine (VIIa) (0.4 g., 64%) as
flakes, m.p. 155⁰-156⁰, from methanol. (Lit. m.p. 167⁰-168⁰, ref.
9). (Found : C, 46.2; H, 5.2; N, 17.8. Calc. for C₆H₅N₂O₃ C,
46.15; H, 5.1; N, 17.9%); v max. 3190 and 3080 (w)(NH), 1730 and
1702 (s)(imide CO), 1650 (4-CO) cm⁻¹; m/e 156.

(b) The dioxime (IIId) (0.186 g.) was heated under reflux with
3N. hydrochloric acid (3 ml.) for 1 hr. Evaporation of the solution
and recrystallisation of the residue from aqueous methanol gave
2,6-dioxopiperazine hydrochloride (VIIa') (0.11 g., 73%), m.p. and
mixed m.p. 278⁰-279⁰ (decomp.).

N-Benzoyliminodiacetamidoxime (IVc):

(a) Formation:— The dinitrile (Ic)(3.98 g.) solution
(25 ml. methanol, 10 ml. water and 80 ml. dioxan) and hydroxyl-
amine hydrochloride (5.36 g.) with sodium carbonate (4.24 g.) in
water (18 ml.) were mixed together and kept at 25⁰ for 27 hr.
during which ammonia was evolved. The solid obtained after eva-
poration of the above mixture was triturated with methanol and
the solution filtered. Addition of ether precipitated N-benzoyl-
iminodiacetamidoxime (2.65 g., 50%) which was recrystallised
from aqueous methanol as needles, m.p. 169°-170° (decomp.)
(Found : C, 41.9 ; H, 4.7 ; N, 21.9 . C$_{18}$H$_{24}$N$_8$O$_{10}$ requires C,
42.2; H, 4.7; N, 21.9%; m/e 265; v max. 3455 (s), 1581 (w),
1556 (s), 1318, 1290, 1275 (s), 1163, 1010 (s), 970, 948, 920,
800 (s) cm$^{-1}$ ; r (D$_2$O) 2.45 (s)(Ph), 5.31 (s)(2 x CH$_2$).
With dilute iron(III)chloride, it gave a brown colour.

(b) Cyclisation :- Crystalline dioxime (IIIc) was
isolated when the above amidoxime (IVc) (0.4 g.) was heated
under reflux with hydroxylamine hydrochloride in aqueous metha-
nol. This dioxime had m.p. 197° (decomp.) (from aqueous methanol)
and mixed m.p. 198°-199°(decomp.) and the correct i.r. spectrum.

N-Acetyliminodiacetamidoxime (IVd):

(a) Formation:- Following the method of preparation
of iminodiacetamidoxime (IVA), the dinitrile (Id) (2.74 g.) in
methanol (15 ml.) was mixed with hydroxylamine (from the hydro-
chloride 5.36 g. and sodium carbonate 4.24 g.) in water (18 ml.)
and the solution kept for 48 hr. at room temperature. Recrystall-
isation of the product (3.85 g., 96%) from aqueous methanol
gave N-acetyliminodiacetamidoxime (2.5 g., 62.5%) as granular
crystals, m.p. 165°-171° (decomp.) (Found : C, 35.0 ; H, 6.3 ;
N, 33.8 . C$_6$H$_{13}$N$_5$O$_3$ requires C, 35.5; H, 6.4; N, 34.5%); m/e
203; v max. 3400 (s) and 3300 (s)(NH$_2$), 3140-2200 (br)(OH), 1663
(s)(CO), 1638 (C=N), 1600, 1253 (s), 1000, 968, 930, 735 cm$^{-1}$.
The amidoxime (IVd) gave a brown colour with iron(III)chloride.

r (D$_2$O) 5.91 (s)(2 x CH$_2$), 7.83 (s)(CH$_3$).

(b) Cyclisation:- The amidoxime (IVd) (0.4 g.) with
hydroxylamine hydrochloride (0.7 g.) afforded the dioxime (IIIId)(0.29 g.), identified by m.p. and mixed m.p. (203°-205° decomp.) and the i.r. spectrum comparison.

**N-Benzyliminodiacetamidoxime (IVb):**

(a) Formation: The crystalline product (2.65 g., 51%) was deposited when a mixture of the dinitrile (Ib)(3.7 g.) in methanol (60 ml.) containing hydroxylamine hydrochloride (5.36 g.) was kept with sodium carbonate (4.24 g.) in water (18 ml.) at 25° overnight. From aqueous methanol, N-benzyliminodiacetamidoxime crystallised, m.p. 171°-172° (decomp.) (Found: C, 51.2; H, 6.7; N, 27.1. C₁₁H₁₇N₅O₂.H₂O requires C, 50.8; H, 6.9; N, 26.9%); m/e 251; v max. 3430 (s) and 3330 (s)(NH₂), 3300-2400 (br)(OH), 1662 (s) and 1648 (w)(C=N), 1600, 1240, 992, 742 (s), 698 (s) cm⁻¹. It gave a reddish brown colour with iron(III)chloride; r (D₂O/CF₃CO₂H) 2.6 (s)(Ph), 6.34 (s)(CH₂), 6.57 (s)(2 x CH₂).

(b) Cyclisation: Following the previous cyclisation, N-benzyliminodiacetamidoxime (0.4 g.) was heated under reflux with hydroxylamine hydrochloride solution in methanol to afford 4-benzyl-2,6-dihydroxyiminopiperazine (IIIb) (0.17 g., 50%) as colourless needles. Recrystallised material (from aqueous methanol) had m.p. 196° (decomp.) undepressed by authentic material, and the correct i.r. spectrum.

(3) Compounds from iminodiacetonitrile (Ia):
Attempted reaction of iminodiacetonitrile:

(a) With ammonia: Analogously to the N-acyl-dinitriles (Ic and Id), when iminodiacetonitrile (Ia) in liquid ammonia was heated in a sealed tube only tar was formed and none of the desired product could be detected.

(b) With sodamide: 2,6-diformyliminopiperazine (IIa):

Iminodiacetonitrile (Ia) (1.9 g.) was dissolved in formamide (40 ml.) under nitrogen, and sodamide (2 g.) was added cautiously. Next day, the solution was concentrated under reduced pressure (0.1 mm.) on a steam bath to ca. 25 ml. and then kept under nitrogen for 7 days. The solid was collected and washed with dioxan and ether, and recrystallised from methanol to give needles.

m.p. 196°-198° (decomp.) (Found: C, 42.7; H, 4.8; N, 33.1. C₆H₅-N₄O₂ requires C, 42.8; H, 4.8; N, 33.3%). m/e 168; λ max. 249.5, 347 nm., 18.3, 17.65 10⁻³; ν max. 3400 (1-NH), 3380-3000 (4-NH, bonded NH), 1670 (s) and 1630 (s) (C=N, C=O), 1565, 1273 (s), 1065, 1025, 990 (w), 835 (w), 792 (w), 745 cm⁻¹.

Iminodiacetamidoxime (IVA):

(a) Formation: Ammonia was evolved when a mixture of iminodiacetonitrile (9.5 g.), methanol (80 ml.), hydroxylamine hydrochloride (26.8 g.) and sodium carbonate (4.24 g.) in water (90 ml.) was left for 42 hr. at 25°. The solution when evaporated somewhat, gave salt, and the filtrate on further evaporation under reduced pressure afforded iminodiacetamidoxime (IVA) (8.25 g., 51%), m.p. 138° (decomp.) after recrystallisation from aqueous
methanol (lit. m.p. 126°-127° (decomp.), ref. 11) (Found : C, 29.65; H, 6.8; N, 43.5. Calc. for C₄H₁₁N₅O₂ C, 29.8; H, 6.8; N, 43.5%); m/e 161; v max. 3398 (s) and 3310 (NH₂), 3205 (s)(NH) 3080-2400 (br)(OH), 1678 (s) and 1660 (s) (C=N), 1606, 1103, 980, 930 (s) cm⁻¹. With iron(III) chloride, the compound gave a brown colour, which changed to olive green on further addition of the reagent and finally to turquoise; r(D₂O) 6.79 (2 x CH₂).

(b) Cyclisation: The above amidoxime (IVa)(1.61 g.) and hydroxylamine hydrochloride (2.8 g.), when boiled in aqueous methanol (40 ml.) for 20 min. and cooled, afforded a product (33%) whose i.r. spectrum was identical with a molecular complex of the dioxime (IIla) i.e. (IIla') (see later): the mixed m.p. was undepressed.

2,6-Dihydroxyiminopiperazine (IIla):

(a) Formation: Hydroxylamine solution from the hydrochloride (5.6 g.), sodium carbonate (4.24 g.) and water (10 ml.) was heated with iminodiacetonitrile¹⁴,¹⁵ (3.8 g.) in methanol (15 ml.) under nitrogen at 70° overnight. Polymeric matter was removed and the solution treated with charcoal. Evaporation of the filtrate under reduced pressure then gave the product (0.8 g., 14%) which crystallised from aqueous methanol as flakes, m.p. 225° (decomp.) (Found : C, 33.5; H, 5.6; N, 38.7. C₄H₈N₄O₂ requires C, 33.3; H, 5.6; N, 38.9%); m/e 144; v max. 3410 (1-NH), 3280 (4-NH), 3100 (br)(OH), 1670 (s)(C=N), 1540, 1500, 1445, 1405 (w), 1335, 1300, 1200 (w), 1109 cm⁻¹; λ max. 234 nm., 15.8
The dioxime (IIIa) with iron(III)chloride in aqueous methanol gave a reddish brown colour.

(b) Hydrolysis:—To the preceding dioxime (1.44 g.) in methanol (35 ml.), dioxan (12 ml.) and water (25 ml.), 10% sodium nitrite (20 ml.) was added and then 3N. hydrochloric acid (20 ml.). After 3 hr., the solution was treated with charcoal and evaporated to give 2,6-dioxopiperazine hydrochloride (1.16 g., 77%), m.p. 278° (decomp.) from aqueous methanol (Found: C, 31.9; H, 4.7; N, 18.9; C_4H_7CIN_2O_2 requires C, 31.9; H, 4.65; N, 18.6%); v max. 3300-2300 (NH and NH^+), 1725 (s)(br) and 1685 (CO), 1560 (w), 1542, 1445, 1400 (s), 1350, 1300, 1280 (s), 1238 (s)(br), 1183 (s) cm^{-1}.

(c) Benzylation:—To the dioxime (IIIa) (1.44 g., 0.01 mol) suspension in pyridine (20 ml.), benzyl chloride (3.8 g., 0.03 mol) was added. Next day, the pyridine was evaporated under reduced pressure and the residue poured into water. Recrystallisation of the precipitated 4-benzyl-2,6-dihydroxyiminopiperazine (IIIb) from aqueous ethanol gave crystals (0.4 g., 15%) m.p. and mixed m.p. 196° (decomp.) and correct i.r. spectrum.

(d) Acetylation:—Similar interaction of the dioxime (IIIa) in pyridine with acetic anhydride for 48 hr. and evaporation gave a syrup which crystallised after addition of methanol. The dioxime (IIIb)(40%) thus obtained had m.p. and mixed m.p. 204° (decomp.) and the correct i.r. spectrum.

(e) Benzoylation:—Analogous benzoylation of the dioxime (IIIa), but for 13 days, afforded (by work up as after benzylation) a solid (0.5 g., 10%) which gave no colour with
iron(III) chloride. Recrystallisation from 96% ethanol produced 4-benzoyl-2,6-dibenzoyloxyiminopiperazine (IIIC1) as clusters of needles, m.p. 172° (with darkening from 170°) (Found: C, 65.7; H, 4.5; N, 12.3. C25H20N4O5 requires C, 65.8; H, 4.4; N, 12.3%)
m/e 456; \( \nu_{\max} \) 3430 (1-NH), 1740 (s)(ester CO), 1660 and 1638 (s) (C=N and amide CO), 1600, 1585 (w), 1405, 1318, 1247 (s)(br) cm\(^{-1}\).

**Salt formation by 2,6-dihydroxyiminopiperazine:**

(a) **Hydrochloride** (IIIA1): To aqueous methanolic hydrochloric acid (0.75 N., 10ml.), the dioxime (IIIs) (0.5 g.) was added. After 10 min., with occasional shaking, the hydrochloride monohydrate had formed (0.54 g., 83%), m.p. 185° (decomp.) raised to 190° (decomp.) by recrystallisation from aqueous methanol (Found: C, 24.0; H, 5.6; N, 27.5. C4H11ClN4O3 requires C, 24.2; H, 5.5; N, 28.2%); \( \nu_{\max} \) 3400 (NH imide), 3210 (br)(OH), 2670 and 2440 (HN\(^+\)), 1680 and 1642 (w)(C=N), 1280, 1028 (s), 1000 (s), 950, 939 (s), 908 cm\(^{-1}\).

(b) **Molecular complex with hydroxylamine hydrochloride**

2,6-Dihydroxyiminopiperazine (IIIA) (0.29 g.) in a minimum of aqueous methanol was heated under reflux with hydroxylamine hydrochloride (0.28 g.) for 1 hr. On cooling the solution, a crystalline complex of the dioxime and hydroxylamine hydrochloride (IIIA11) was afforded, m.p. 161° (decomp., with evolution of gas) (Found: C, 25.8; H, 5.7; N, 33.55. C4H6N4O2; \( \frac{1}{2} \) NH2OH.HCl. \( \frac{1}{2} \)H2O requires C, 25.6; H, 5.9; N, 33.55%).
$v$ max. 3397 (NH), 3210 (br)(OH), 2700-2000 (br)(NH$^+$), 1672 (s) and 1640 (C-N), 1241, 1202, 1025 (s), 1000 (s), 990, 950, 938 (s), 904 cm$^{-1}$.

Dissociation of the complex (IIIa''): Recrystallisation of the above complex (IIIa'') from boiling aqueous methanol afforded 2,6-dihydroxyiminopiperazine (IIIa) as flakes, m.p. 224° (decomp.) and mixed m.p. 225°-226° (decomp.). It gave the correct i.r. spectrum.

(4) **Compounds from N-cyanomethyliminodiacetonitrile (Ie):**

2,6-Diiminopiperazine-4-acetonitrile (IIe):- A solution of the trinitrile (Ie) (8.04 g.) in warm formamide (60 ml.) was mixed with a solution of sodamide (7.3g.) in formamide (60 ml.) and stirred under nitrogen in the absence of light for 6 hr. After being kept at 0° for 100 hr., the product was collected and washed briefly with formamide, ethanol, ethylacetate, and dry ether. It formed colourless crystals (4.43 g., 44%), m.p. 180° (char). (Found : C, 47.5; H, 6.1; N, 46.1. $C_6H_9N_5$ requires C, 47.7; H, 6.0; N, 46.35%); m/e 151 (9%), 124 (3%), 111 (4%), 83 (78%), 68 (11%), 42 (100%); $v$ max. 3450-3000 (s)(NH), 1668 and 1626 (s) (C=N), 1570 (s)(br), 1365 (s), 1345 (s), 1315 (w), 1292 (w), 1278, 1260 (w), 1200, 1170, 1157 (s), 1138 (w), 1115 cm$^{-1}$; $\lambda$ max. 250.5 nm., 18.0 $10^{-3}$ε.

The picrate crystallised from ethanol as yellow needles, m.p. 193°-195° (decomp.) (Found : C, 37.9; H, 3.35; N, 29.4. $C_{12}H_{12}N_8O_7$ requires C, 37.9; H, 3.2; N, 29.5%).
6-Imino-2-oxopiperazine-4-acetamide (VIIe):

When the imidine (IIe)(0.84 g.) was warmed with water (5 ml.), ammonia was evolved. After 10 min., the solution was chilled and the product collected (0.5 g., 58%), recrystallisation from hot water gave needles, m.p. 212° (decomp.) (Found: C, 42.2; H, 6.1; N, 33.0. C_{6}H_{10}N_{4}O_{2} requires C, 42.35; H, 5.9; N, 32.9%). m/e 170 (10.8%), 153 (3.2%), 126 (86.5%), 112 (29.7%), 99 (25.4%), 71 (32.4%), 42 (100%), ν max. 3390 (s) and 3190 (s) (NH_{2}), 3310 (1-NH), 1660 (br)(s)(2 CO), 1520 (s), 1410, 1340 (s), 1308, 1247, 1202 (w), 1160 (w), 1150, 1150, 1132 (s) cm^{-1}. ν (CF_{3}CO_{2}H) 6.08 (s), 5.89 (s), 5.51 (s) (each CH_{2}), 2.2 (br) (CONH_{2}), Λ max. 238 nm., 15.3 \times 10^{-3} ε.

Tris(amidoximinomethyl)amine (IVe):

Hydroxylamine hydrochloride (5.56 g.) and sodium carbonate (2.12 g.) were dissolved in water (20 ml.), tri-(cyanomethyl)amine^{22} (Ie)(2.68 g.) in ethanol (100 ml.) was added and the solution heated under reflux. After 15 min. the solution was cooled and the product (3.8 g., 81%) collected m.p. 172° (decomp.) (from aqueous methanol) (lit. m.p. 112°, ref. 12) (Found: C, 31.1; H, 6.6; N, 42.2. Calc. for C_{6}H_{15}N_{7}O_{3} C, 30.9; H, 6.4; N, 42.1%). m/e 233; ν max. 3470 and 3380 (s)(NH_{2}), 3300, 3160 (w) and 3050 (sh)(bonded NH_{2} and OH), 1670 (s)(C=N), 1610, 1585 (s), 1350 (w), 1340, 1256 (w), 1238; τ (D_{2}O) 6.86 (s)(3 × CH_{2}). A reddish brown colour was given with iron(III)chloride in aqueous ethanol.
**Tris(N-acetylamidoximinomethyl)amine (IVe')**:

A suspension of trisamidoxime (IVe) (2.33 g., 0.01 mol) in acetic anhydride (6.12 g., 0.06 mol) and pyridine (20 ml.) was kept at 25° for 27 hr. The product was filtered off, washed with ethanol and dried (2.26 g., 63%), and recrystallised from water to afford flakes, m.p. 156° (decomp.) (Found: C, 40.3; H, 5.9; N, 27.3; C₁₂H₂₁N₇O₆ requires C, 40.1; H, 5.85; N, 27.3%); m/e 359; ν max. 3475 (s)(NH), 3340 (br)(OH), 1760 (s)(C=O), 1660-1600 (br)(C=N), 1220 (br), 1008 (s), 970, 910 (s), 883 cm⁻¹.

It gave a reddish brown colour with iron(III)chloride in aqueous solution.

(5) **Compounds from o-cyanobenzylcyanide (If):**

1,3-Dihydroximino-12,3,4-tetrahydroisoquinoline (Homophthalimide dioxime ) (IIIf):

o-Cyanobenzylcyanide (If)²³,²⁴ (1.42 g., 0.01 mol) in methanol (16 ml.) with hydroxylamine hydrochloride (5.6 g., 0.08 mol) and sodium carbonate (0.8 g.) in 40% aqueous methanol (40 ml.) was heated under reflux for 1.5 hr. The cyclic dioxime (IIIf) which separated was filtered off, washed with water and methanol and dried (yield, 0.97 g., 51%, m.p. 220°-225°(decomp.).

After recrystallisation from aqueous methanol, the m.p. was 223°-225° (decomp.) (Found: C, 56.8; H, 4.8; N, 21.8. C₉H₇N₃O₂ requires C, 56.5; H, 4.7; N, 22.0%). m/e 191; ν max. 3380 (2-NH), 3280 and 2705 (br)(OH), 3030 (ring H), 1666 (s) and 1604 (w) (3-imidoxime), 1644 (s) and 1578 (w) (1-imidoxime), 1140, 973,
924 (s), 770 and 721 cm$^{-1}$, $\lambda_{\text{max.}}$ 238 nm., 16.7 $10^{-3}$ and 269 nm., 7.3 $10^{-3}$; $\tau$ (DMSO) 6.215 (s)(CH$_2$), 2.1-2.75 (complex) (5,6,7-H's), 2.17 (dd)(8-H), 1.41 (br)(NH), 0.015 (s)(3-NOH), -0.7 (s)(1-NOH). It gave a reddish brown colour with iron(III)-chloride.

The same cyclic dioxime (IIIf) was obtained in progressively smaller yield when the above reaction was repeated with the following changes:

(a) $\beta$-cyanobenzylcyanide (0.01 mol) was refluxed with hydroxylamine hydrochloride (0.04 mol) and sodium carbonate (0.4 g.) for 45 min.,

(b) 30 min., and (c) 20 min. In the last case, the yield of the dioxime (IIIf) was 20% only.

(d) When the reaction time was 10 min. unreacted dinitrile (If) was recovered almost quantitatively.

(b) Hydrolysis:- Homophthalimide dioxime (IIIf) (0.4 g.) was heated under reflux with 3N. hydrochloric acid (4 ml.) for 2 hr. The solution after charcoal treatment and cooling gave homophthalimide (0.25 g., 79%). It had m.p. 235°, the same as reported, and the correct i.r. spectrum.

1-Amino-3-hydroxyaminoisoquinoline$^{24}$ (XVII):

Elvidge et al.$^{24}$, obtained 1-amino-3-hydroxyaminoisoquinoline (XVII)(in 78%) from the reaction of the dinitrile (If) (1.42 g., 0.01 mol) and hydroxylamine (1.32 g., 0.04 mol) after the reaction solution had been heated under reflux for 4 hr.
(a) Formation: The same product (XVII) was also obtained in the following cases where the reaction conditions were even milder:

(a) The dinitrile (If) (1.42 g., 0.01 mol) in methanol (18 ml.) with hydroxylamine (1.32 g., 0.04 mol) or (0.33 g., 0.01 mol) at room temperature for 20 hr; yields were 84 and 75% respectively.

(b) The dinitrile (If) (1.42 g.), hydroxylamine hydrochloride (5.6 g., 0.08 mol) and sodium carbonate (0.4 g.) in 60% aqueous methanol at room temperature for 18 hr; yield 60%.

The identity of the product (XVII) thus obtained was checked by its m.p. and i.r. and p.m.r. spectra. The product (XVII) gave a turquoise blue colour with iron(III)chloride in addition.

(b) Hydrolysis: 1-amino-3-hydroxyamino-isoquinoline (XVII)(0.35 g.) was boiled with 3N. hydrochloric acid (4 ml.) for 1 hr. The solution after charcoal treatment and cooling afforded crystalline homophthalimide (0.2 g., 62.5%) which had m.p. 234°-235° and the correct i.r. spectrum.
PART II

PYRAZINE N-OXIDES FROM IMINODIACETONITRILE.
INTRODUCTION
Hydroxylamine has been used as a reagent in acidic and basic medium to obtain a variety of aromatic N-oxides. The classes of product relevant to the present work are 1. aromatic N-oxides, 2. 2-amino derivatives of aromatic N-oxides and 3. 2,6-diamino derivatives of aromatic N-oxides.

1. Aromatic N-oxides from 1:5-dialdehydes and hydroxylamine.

Glutaconic aldehyde and hydroxylamine when heated in methanol in acidic medium give the dioxime as an intermediate which undergoes cyclisation with liberation of one mole of hydroxylamine, and pyridine 1-oxide is formed.

\[
\text{CHO} \quad \text{CHONa} \quad \text{NH}_2\text{OH} \quad \text{HCl} \quad \text{MeOH (HCl)} \quad \text{NH}_2\text{OH} \quad \text{OH}
\]

Eq. 9

Similarly, Schöpf and Koch, obtained isoquinoline N-oxide.
Parisi et al. obtained 4-hydroxyaminopyridine 1-oxide by allowing a mixture of γ-pyrone and hydroxylamine to stand at 20°C for a few days. They assumed that there was intermediary formation of the monoxime of a 1,5-dicarbonyl compound which must have undergone intramolecular condensation with cyclisation.

The above reactions show that either a monoxime or a dioxime of a 1,5-dialdehyde in the presence of hydroxylamine cyclise to give aromatic N-oxide.

2. 2-Amino derivatives of aromatic N-oxides.

Sharp and Spring condensed an α-aminonitrile with an α-oximinoketone in the presence of N-methylmorpholine to get 2-amino-3,5-dialkylpyrazine 1-oxides.
Analogously, Newbold et al. synthesized 2-amino-3,6-dialkylpyrazine 1-oxides from α-oximinoaldehydes and α-aminonitriles.

Later, Taylor and Lenard selected rather different α-amino-nitriles to condense with α-oximinoketones and obtained 2-amino-3,5-disubstituted pyrazine 1-oxides (where R=CH₃ or Ph and R'=CN, CONH₂ or COOEt in Eq. 12).

Unsubstituted monoaminopyrazine 1-oxides described in the literature by different chemists are shown on the next page. Thus, Elina et al. prepared 2-aminopyrazine 1-oxide and 3-aminopyrazine 1-oxide which resulted from 3-chloropyrazine 1-oxide when treated with ammonia and was also obtained by Terao from 2-carbamoylpyrazine.
3. 2,6-Diamino aromatic N-oxide from the reactions of a dinitrile with hydroxylamine.

Shaw synthesised 2,6-diamino-s-triazine 1-oxide derivatives by the reaction of alkyl and aryl dicyanoamidine salts derived from amidines or imido esters, with hydroxylamine. (Eq.15).

In contrast to the reaction (Eq.15), o-cyanobenzylcyanide (Ig) with hydroxylamine (favourably in basic media) gave the aromatised hydroxyamino product (XVII) (Chapter 2(V)) rather than a diamino N-oxide as shown in Eq.15.

This anomaly can be explained by assuming that the dicyanoamidine salt in acidic medium reacts with hydroxylamine to
give an amino-hydroxy group (β) rather than amidoxime group. Thence the hydroxyamino group attacks the adjacent nitrile function and gives the N-oxide derivative (Eq. 15). In the case of α-cyanobenzylcyanide (If), the cyclisation takes place through the more basic amino group of the amidoxime intermediate attacking the nitrile function. This is followed by aromatisation to the product (XVII). It has already been found (Chapter 2V) that the dinitrile (If) with hydroxylamine under a variety of alternative reaction conditions failed to give an N-oxide product (XII). Likewise neither glutaronitrile and its α-phenyl analogue nor N-substituted iminodiacetonitriles (Ib-Id) give any N-oxide product. No attempts have been described in the literature of reactions of iminodiacetonitrile with
hydroxylamine affording aromatic products. Reactions of this kind are described in a later section of this thesis.
DISCUSSION
(i) 2-Amino-6-hydroxyaminopyrazine 1-oxide (IX):

When iminodiacetonitrile (Ia) was heated with hydroxylamine under reflux overnight, 2,6-dihydroxyiminopiperazine (IIIa) was formed in poor yield (10%) accompanied by a large amount of insoluble resinous material (pp. 31). In contrast, the N-acyl-dinitriles (Ic and Id) gave their corresponding dioximes (IIIC and IIId) quantitatively in 0.5 hr. It was observed that the latter reactions were exothermic (pp. 27) but not the former. The above difference may arise because the dinitriles (IIIC and IIId) (having \(-\text{CO-N<} \) bond) are neutral whilst the dinitrile (Ia) is basic.

This consideration led us to re-examine the reaction of iminodiacetonitrile (Ia) with hydroxylamine applying some modifications. For example, hydroxylamine hydrochloride was added to make the reaction solution less basic than in the previous case (pp. 31), in the hope that a good yield of the dioxime (IIIa) would then be obtained.

A hot aqueous methanolic solution of hydroxylamine and its hydrochloride (2:6 moles) was added slowly to a refluxing...
methanolic iminodiacetonitrile (1 mole) solution under nitrogen. With an exothermic reaction a yellow brown product (A) (41%) started to separate and this was complete after 1 hr. After removal of the product (A), the filtrate was charcoaled and then set aside to cool while nitrogen was bubbled through for 1 hr. Unexpectedly another pale yellow product (B) precipitated (20.5%). This modified reaction, thus gave two products with a total yield of 61.5%.

\[
\text{Iminodiacetonitrile (Ia)} \rightarrow \text{Product (A)} + \text{Product (B)}
\]

\[
41\% \quad 20.5\%
\]

Eq. 16

Identification of the product (A):

The product (A) was identified as a molecular complex (IIIa') of the dioxime (IIIa) with hydroxylamine hydrochloride by comparison of its i.r. spectrum and melting point with that of the material made from the two constituents. Further, the product (A) upon recrystallisation afforded the free base (IIIa) analogously to the authentic complex (IIIa') (pH 31).

Identification of the product (B):

As with 1-amino-3-hydroxyaminoisoquinoline (XVII) product (B) was recrystallised from aqueous methanol as pale
yellow needles and was sensitive to prolonged exposure. The product (B) was insoluble in water, chloroform, carbon tetrachloride, benzene, dioxan and pyridine, and was soluble in methanol and dimethylsulphoxide. Similarly to aromatic hydroxyamino compounds e.g. 2-hydroxyaminopyridine, 1-amino-3-hydroxyaminoisoquinoline etc., product (B) gave a blue colour with a little iron(III)chloride. Addition of an excess of iron(III)chloride changed the blue colour to a turquoise, greenish blue. The product (B) also reduced Fehling's solution and gave a silver mirror with Tollens's reagent (cf. 3-hydroxyaminopyridine). The mass spectrum of the product (B) gave m/e 142, a molecular weight lower by two than that of the dioxime (IIIa), and elemental analysis indicated a molecular formula C₄H₆N₄O₂.H₂O. It appeared that the product (B) was an aromatised compound having either the structure (XIII) or (IX) in each case as a hydrate. The aromatic nature of the product (B) was supported by its u.v. absorption maximum (Fig.14) at 338 nm.

Initially, the structure (XIII) was proposed for the compound (B) because it explained the properties described above. Nevertheless, the structure (XIII), being symmetrical, failed to
explain the appearance of two lines of equal intensity in the aromatic region of the p.m.r. spectrum (Fig. 4). To account for this, the unsymmetrical structure (IX) was proposed. In agreement the p.m.r. spectrum (Fig. 4) shows, also, two broad peaks, each of intensity corresponding to 2 protons, one from the amino group and one from the NHOH group. Further support for the structure (IX) is given by the i.r. spectra (Fig. 3 and 6). Strong peaks at 1200 and 838 cm\(^{-1}\) are suggestive of N→O stretching frequencies as reported for pyrazine N-oxides.

The product (B) was further characterised as its picrate.

As mentioned before, analysis of the product (B) suggested that it was a mono hydrate which was also the case with 1-amino-3-hydroxyaminoisoquinoline. Thermogravimetric analysis of the product (B) gave a loss of 11.0% of its weight when heated from 90° to 105°. As the calculated loss is 11.25%, the presence of a molecule of water in the product (B) seems well demonstrated.

The anhydrous product (B'), thus obtained, gave the correct elemental values for C\(_4\)H\(_6\)N\(_4\)O\(_2\). The i.r. spectrum is shown in Fig. 6. The p.m.r. spectrum of the product (B') showed a band (Fig. 7) which on expansion appeared as a quartet (J = 1.08 c/s) in agreement with meta-coupling between two non-equivalent aromatic protons.

From the foregoing evidence, it is clear that the product (A) is a molecular complex (III\(a''\)) and the product (B) is 2-amino-6-hydroxyaminopyrazine 1-oxide monohydrate (IXa),
Fig. 5

Weight loss: 11.0%.

$\text{C}_4\text{H}_8\text{N}_4\text{O}_2\text{H}_2\text{O}$ requires $11.25\%$.

$\text{H}_2\text{O}$ loss: 11.25%.
Fig. 6

Fig. 7
hence the above reaction can be represented as follows:

\[ \text{CN} \text{CN} \quad \rightarrow \quad \text{Ia} \rightarrow \text{IIIa}^{11} \quad + \quad \text{IXa} \quad \text{Eq.17} \]

Mechanism of formation of the product (IX):

This is considered in two parts.

(a) Cyclisation and formation of the 2-amino-6-hydroxyamino-1-oxide group:

Initially, it was thought that the dinitrile (Ia) reacted with hydroxylamine (2 moles) and formed the acyclic bisamidoxime (IVa).

\[ \text{CN} \text{CN} \quad \rightarrow \quad 2 \text{NH}_2\text{OH} \rightarrow \quad \text{Ia} \rightarrow \text{IVa} \quad \text{Eq.18} \]
The bisamidoxime (IVa) then cyclised with a loss of ammonia and formed the intermediate (IXb) (Eq.18). This on subsequent dehydrogenation would then afford the product (IX) (cf. mechanism (b)). However, the proposal was ruled out as it has been shown (pp.31) that the bisamidoxime (IVa) with hydroxylamine under the same reaction conditions gives only a complex (IIIa') indicating that the bisamidoxime (IVa) is not the intermediate responsible for the formation of the aromatised product (IX).

Another possible intermediate was the monoamidoxime-monoritrile (Ia') believed to be formed by the partial reaction of hydroxylamine with one of the two nitrile groups of iminodiacetonitrile (Ia). This intermediate (Ia') might then undergo intramolecular cyclisation to give intermediate (Xb) (Eq.19), for which there are precedents.

If then the imino group of this cyclic intermediate (Xb) (Eq.19)
reacts with hydroxylamine it would then give (see Eq. 20) the same intermediate (IXb) as proposed before (Eq. 18).

![Reaction equation]

It appears however from Shaw's reaction that conversion of the intermediate (Xb) to (IXb) (Eq. 20) is unlikely because Shaw, in fact, obtained the 2,6-diamino 1-oxide derivative.

It has been known that carbonyl compounds in acidic form media add hydroxylamine to an intermediary compound:

![Intermediary compound]

An analogous intermediate can be proposed for addition to the nitrile group, the imino group of which then reacts further to give a dihydroxyamidine or hydroxyamidoxime.

![Additional reaction equations]

Thus Eq. 21 is proposed:
The intermediate (Ia''') cyclises to the intermediate (IXb) through intramolecular attack on the nitrile group by either the hydroxyimino or hydroxyamino group.

These last proposals (Eq.21,22) are supported by the following evidence:

(i) The analogous carbonyl reaction\textsuperscript{45}.

(ii) The known capacity\textsuperscript{46} of the aliphatic imino group to react with hydroxylamine to form the hydroxyimino compound and

(iii) The many examples\textsuperscript{35,36,41,47} of internal cyclisation of the hydroxyimino group with the nitrile function to form an exocyclic imino compound which tautomermes to the amino N-oxide system.

Hence the last mechanism is most favoured.
(b): Dehydrogenation and aromatisation of the intermediate (IXb) to the final product (IX):

The aromatisation mechanism can be represented as a coupled oxidation-reduction, hydroxylamine being reduced as shown below:

This mechanism is favourable as the N→O function present at the para position to the 4-NH group (Eq. 23, IXb) presumably makes the NH more acidic and hence the proton is easily removable by the nucleophilic attack of hydroxylamine. A pair of electrons then enters the ring followed by the transfer of $H^\Theta$ from the 5-position to hydroxylamine, to yield ammonia and water, and the ring attains aromaticity.

Hence the complete reaction mechanism which explains formation of the aromatised product (IX) is the sum of the equations 21, 22, and 23.
Although most of the properties of the N-oxide (IX) have been discussed previously, the effects of acid and alkali on this N-oxide (IX) are worthy of discussion.

In sulphuric acid, this N-oxide (IX) decomposes immediately i.e. it is unstable, whilst in nitric acid it undergoes oxidation vigorously without giving any tractable product. However, a dilute solution of either strong alkali or weak alkali, affects the N-oxide (IX) instantly giving a deep yellow colour reminiscent of pseudo-acids e.g. o- and p-nitrophenols. The red to yellow colour given by o- and p-nitrophenols in alkaline solution is due to the quinonoid form as shown below (Eq. 24 and 25). Addition of acid removes the red or yellow colour.

\[
\begin{align*}
\text{P-Nitrophenol} & \xrightarrow{\text{OH}^-} \text{Colourless} & \xleftarrow{\text{H}^+} \text{P-Nitrophenol} \\
\text{Benzenoid} & \quad \text{Yellow colour} \\
\text{Quinonoid} & \\
\end{align*}
\]

\[
\begin{align*}
\text{o-Nitrophenol} & \xrightarrow{\text{OH}^-} \text{Yellow} & \xleftarrow{\text{H}^+} \text{o-Nitrophenol} \\
\text{Benzenoid} & \quad \text{red colour} \\
\text{Quinonoid} & \quad \text{Eq. 25}
\end{align*}
\]
By analogy with equation 24, the present compound (IX) can be tautomerase in rather similar fashion (Eq. 26) and this may well explain the production of a yellow colour with alkali.

![SAM_0118.png](attachment:SAM_0118.png)

Unlike the quinonoid form of α- and p-nitrophenols, the quinonoid form of the N-oxide (IX) carries a single positive charge after losing a pair of electrons (Eq. 26). This would seem to explain why addition of acid to the yellow alkaline solution does not regenerate the colourless N-oxide (IX). Further to this, when the yellow alkaline solution of the N-oxide (IX) is allowed to stand, the colour turns to brown and finally to black with a precipitation of a black polymeric material having no characteristic m.p., insoluble in most solvents and showing generalised light absorption. The quinonoid form thus appears to polymerise readily.

Although support exists from several literature sources 11,41,45,47 for the foregoing reaction mechanism for the formation of 2-amino-6-hydroxyaminopyrazine 1-oxide (IX), the postulated intermediate, monoamidixime-monomonitrile (Ia') has never been
isolated. An attempt was therefore made to prepare this intermediate.

Initially it was hoped to prepare the amidoxime from substituted acetonitriles, $X-CH_2-CN$, where $X=\text{Cl, OH, or NH}_2$ as shown below:

$$X-CH_2-CN + \text{NH}_2\text{OH} \rightarrow X-CH_2-CN\text{NH}_2\text{OH} \quad \text{Eq.27}$$

It was then intended to condense this amidoxime with the appropriate acetonitrile to get the expected monoamidoxime-monoritrile (Ia').

$$X'(CH_2)NH \text{ON} \quad + \quad X'(CN) \rightarrow \quad X'(CH_2)NH \text{CN} \quad \text{Ia'}$$

When $X=\text{Cl or OH}; X'=\text{NH}_2$ and $X=\text{NH}_2; X'=\text{Cl or OH}$. Eq.28

When chloroacetonitrile or glycolonitrile (HO.CH$_2$.CN) was reacted with hydroxylamine at room temperature only, intractable material was obtained. However, aminoacetonitrile with hydroxylamine at room temperature deposited a pale yellow product. Unfortunately this product was a polymer of aminoacetamidoxime instead of the required aminoacetamidoxime.

The following evidence supports the polymeric structure:
(i) It does not melt or decompose but chars.
(ii) It is insoluble in most solvents except dimethylsulphoxide.
(iii) It gives a pure blue colour with iron(III) chloride showing the presence of an amidoxime group.
(iv) The i.r. spectrum shows no nitrile absorption, but shows a broad OH band at 3200-2600 cm\(^{-1}\), C=N at 1678 cm\(^{-1}\) and a single sharp NH peak at 3355 cm\(^{-1}\) instead of multiple peaks expected for aminoacetamidoxime.
(v) The p.m.r. spectrum in d\(_5\)-dimethylsulphoxide supports the polymer structure as it shows two one-proton broadened peaks at 3.69\(\tau\) and 1.19\(\tau\) assignable to imino and oxime protons. These peaks disappear when the spectrum is rerun after the solution of the polymer has been shaken with D\(_2\)O.
Pyrazines and pyrazine 1-oxides from iminodiacetonitrile:
(ii) 2,6-Diaminopyrazine 1-oxide:

Catalytic reduction of 2-amino-6-hydroxysminopyrazine 1-oxide (IX) using Adam's catalyst (PtO₂) in acetic acid in an atmosphere of hydrogen resulted in uptake of one molecular equivalent of hydrogen and afforded a product having m.p. 280°-282° (decomp.) (64% yield).

Uptake of just one molecular proportion of hydrogen by the N-oxide (IX) indicated that each oxygen atom in the molecule (IX) is in a different environment. Thus reduction of either NHOH or of N-oxide group had occurred.

The mass spectrum gave m/e 126 and the elemental analysis gave the molecular formula C₄H₆N₄O for which either of the two structure (X) or (XIV) can be given.

![Structures X and XIV](image)

The structure (X) for the above reduction product was accepted as it was unanimously supported by the following evidence:

(i) It is reported that the most likely group to reduce under the reaction condition used is NHOH but not the N-oxide group.²⁷,⁴⁸

(ii) Analogously to 1-oxides of 2-aminopyridine and 2-amino-4-pyrazine derivatives,³⁵,³⁶ the reduction product gave a pure blue
colouisation with iron(III)chloride which was discharged on addi-
tion of hydrochloric acid. For the structure (XIV) the colour
expected with iron(III)chloride would be turquoise blue (pp.44).
(iii) The i.r. spectrum of the reduction product (Fig.8) showed
undoubtedly the presence of N-oxide stretching frequencies at
1225 and 841 cm.\(^{-1}\). Such absorption would not be given by the
structure (XIV). The u.v. light absorption, also suggestive of
the structure (X), is included in (Fig.14).
(iv) The p.m.r. spectrum (Fig.9) showed two peaks, one at 2.67\(\tau\)
and another at 3.4\(\tau\) (br) equivalent to 2 and 4 protons respect-
ively. These signals account for the ring protons and amino
group protons respectively. This result proved the symmetrical
structure (X) and hence that the reduction product is 2,6- di-
aminopyrazine 1-oxide (X).

The chemical shift of 3.4\(\tau\) for NH\(_2\) protons in 2,6-di-
aminopyrazine 1-oxide (X) indicated that in the precursor (IX),
the signal at 3.18\(\tau\) is assignable to the amino group protons
whilst that at lower field arises from the hydroxyamino group.

(iii) 2,6-Diacetamidopyrazine 1-oxide:

The 2,6-diacetyl derivative (XI) was obtained (in
100% yield) when 2,6-diaminopyrazine 1-oxide (X) was kept in
acetic anhydride (excess) at room temperature for 38 hr. This
derivative (XI) gave no specific colouration with iron(III)-
chloride which showed that acetylation had occurred on both amino
groups of the N-oxide (X). The i.r. spectrum (fig. 10) showed
strong N→O stretching absorption at 1230 cm$^{-1}$ which suggested that the N→O function was unaffected by the acetylation reaction. The p.m.r. data from the spectra (fig. 12 and 13) of the diacetyl derivative (XI) are tabulated.

**TABLE XXVII**
The p.m.r. results of 2,6-diacetamidopyrazine 1-oxide (XI).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Chemical shift (τ) and assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH$_3$</td>
</tr>
<tr>
<td>d$_6$-DMSO</td>
<td>7.7</td>
</tr>
<tr>
<td>CF$_3$CO$_2$H</td>
<td>7.4</td>
</tr>
</tbody>
</table>

**TABLE XXVIII**
Chemical shift (τ) of β-proton of 2,6-diacetamidopyrazine 1-oxide (XI) and 2,5-dimethylpyridine 1-oxide (xiv) in different solvents.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Solvent</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ppm.</td>
</tr>
<tr>
<td>XI</td>
<td>d$_6$-DMSO</td>
<td>0.93</td>
</tr>
<tr>
<td>xiv$^{49}$</td>
<td>CDCl$_3$</td>
<td>2.95</td>
</tr>
</tbody>
</table>

In acidic medium (CF$_3$CO$_2$H), the N-oxide will be in the conjugate acid form, and the overall electron density on
the ring will be diminished. Thus the chemical shift of the aromatic protons moves from 0.93 $\tau$ (d$_6$-DMSO) down to 0.24 $\tau$, a shift difference of 0.69 ppm. A similar shift (0.7 ppm) difference for the $\beta$-proton of 2,5-dimethylpyridine 1-oxide, upon protonation, has been reported by Okamoto et al.$^{49}$

(iv) 2,6-Diacetamidopyrazine (XVI):

Smooth deoxygenation of 2,6-diacetamidopyrazine 1-oxide (XI) by sodium dithionite (cf. ref. 50) afforded 2,6-diacetamidopyrazine (XVI) (82% yield). The i.r. spectrum of the deoxygenated product (XVI) (Fig. 11) showed an absence of N=O frequency and the spectrum as a whole was identical to that of the authentic sample obtained from 2,6-dihydroxyiminopiperazine (IIIa) as discussed later.

Aromatisation of 2,6-dihydroxyiminopiperazine (IIIa):

Attempts to aromatise 2,6-dihydroxyiminopiperazine (IIIa) using hydroxylamine in acidic media and using hydrogen peroxide catalysed by ferrous chloride$^{51}$ were abortive as only starting material was recovered. However, palladium-on-charcoal was found promising some extent.

When the dioxime (IIIa) and 10% palladium-on-charcoal catalyst were refluxed in o-dichlorobenzene, separation of water was observed and known$^{52}$ 2,6-diaminopyrazine (XV) was obtained in a very poor yield as a result of dehydrogenation, aromatisation and reductive dehydration of the dioxime (IIIa).
Dehydrogenation and aromatisation:

\[
\begin{align*}
\text{IIIa} & \quad \text{Pd/C} & \quad \text{XIII} \\
\text{HOHN} & \quad \text{NH} & \quad \text{HON} \\
\text{NOH} & \quad \text{NH} & \quad \text{NOH} \\
\end{align*}
\]

Reductive dehydration:

\[
\begin{align*}
\text{XIII} & \quad + 4\text{H} & \quad \text{XV} \\
\text{HOHN} & \quad \text{N} & \quad \text{H} \\
\text{N} & \quad \text{NH} & \quad \text{H} \\
\text{OH} & \quad \text{OH} & \quad \text{OH} \\
\end{align*}
\]

Because of the following, the yield of 2,6-diaminopyrazine was low:

1. It was observed that during the above reaction, a considerable amount of the dioxime (IIIa) appeared to be decomposing to black tar.
2. The aromatised intermediate (XIII) would be very unstable at the reaction temperature, and
3. Hydrogen evolved during dehydrogenation was half that required for the reductive dehydration of the intermediate (XIII) to give the diaminopyrazine.

It is reported\(^5\) and also experienced that 2,6-diaminopyrazine is sensitive to oxidation, and no attempts were made to purify and identify it as such, but it was converted into its stable diacetyl derivative (XVI).

When crude 2,6-diaminopyrazine was treated with excess
acetic anhydride overnight, it afforded 2,6-diacetamido-
pyrazine (XVI) which was purified by sublimation and identified
by the i.r. spectrum.
EXPERIMENTAL
(1) Formation of 2-amino-6-hydroxyaminopyrazine 1-oxide mono hydrate (IXa) and a molecular complex of 2,6-dihydroxyimino-piperazine. hydroxylamine hydrochloride (IIIa'').

A hot solution of hydroxylamine hydrochloride (111.2 g., 1.6 mole) and sodium carbonate (21 g., 0.2 mole) in methanol (120 ml.) and water (80 ml.) was dropped slowly into a boiling solution of iminodiacetonitrile (38 g., 0.4 mole) in methanol (160 ml.) under nitrogen. When half the solution had been added, an exothermic reaction took place, the solution turned dark in colour, and separation of a crystalline solid began (and increased gradually). After removal of external heating, the rest of the hydroxylamine solution was added (ca. 0.5 hr.) during which much solid separated. (If the exothermic reaction is rapid, an ice-bath can be used to control the reaction, but the mixture must not be allowed to cool below 50° during the addition). After 1.5 hr. (from the initial addition), the crystalline solid (IIIa'') was filtered off, washed with methanol and dried (yield, 27 g., 41%) and identified by the comparison of its i.r. spectrum with authentic sample. An attempt
to recrystallise the material (IIIa') from aqueous methanol (charcoal) afforded colourless crystals of 2,6-dihydroxyimino-piperazine (13.1 g., 22.7%), m.p. 224°-225° (decomp.) and mixed m.p. 226° (decomp.), and having the correct i.r. spectrum.

The above filtrate, (after removal of the complex (IIIa'')), after charcoal treatment (twice) and passage of nitrogen through it for 1 hr. gave pale yellow needles (11.65 g., 20.5%) m.p. 155° (decomp.): repeated recrystallisation from aqueous methanol furnished colourless 2-amino-6-hydroxyamino-pyrazine 1-oxide. monohydrate, m.p. 161° (decomp.) (Found: C, 29.8; H, 5.0; N, 35.0. \( \text{C}_4\text{H}_3\text{N}_4\text{O}_3 \) requires C, 30.0; H, 5.0; N, 35.0%); m/e 142; \( \nu \text{max.} \) 3520 (s) and 3430 (s)(NH, NH2), 3250 (br) and 3100 (NHOH), 2700 (br)(bonded OH), 1653, 1663 (s) and 1582 (br)(ring), 1501, 1246 (s), 1200 (s) (N=O), 1166 (w), 1146 (w), 1059 (w), 1010, 900-800 (br), 717 (br) cm\(^{-1}\); \( \lambda \text{max.} \) 235, 285, 338 nm., 24.3, 2.9, 5.5 \( 10^{-3} \epsilon \); \( \tau (\text{DMSO}) \) 3.18 (br)(NH2), 2.44 and 2.49(ring H's), 0.88 (br)(NHOH). With dilute alkali it gave a bright yellow colour which darkened gradually, and finally a black solid separated. With a drop of dilute iron(III)chloride, it gave a blue colouration which turned to turquoise on addition of more iron(III)chloride solution (cf. 2-hydroxyaminopyridine\(^{27} \)). It also gave a silver mirror with Tollens' reagent and reduced Fehling's solution rapidly (cf. ref. 42).

(b) The picrate monohydrate crystallised from methanol as yellow needles and had m.p. 158° (decomp., darkening from 155°)
(found: C, 30.8; H, 2.9; N, 25.6. \( \text{C}_{10}\text{H}_{11}\text{N}_{7}\text{O}_{11} \) requires C, 30.8; H, 2.8; N, 25.2%).

(c) Dehydration of 2-amino-6-hydroxyaminopyrazine 1-oxide monohydrate: The monohydrate (IXa)(145 mg.) loses 18 mg. (12.4% ; calculated 11.25%) of its weight when heated from 90° to 105° on the thermogravimetric balance giving anhydrous 2-amino-6-hydroxyaminopyrazine 1-oxide (IX)(127 mg.), m.p. 160°(decomp.) (Found: C, 33.3; H, 4.3; N, 39.4. \( \text{C}_{4}\text{H}_{6}\text{N}_{4}\text{O}_{2} \) requires C, 33.8; H, 4.3; N, 39.4%); \( \nu \text{ max.} \) 3440 (w) and 3360 (w) (NH2), 3295 and 3160 (NH and NH2), 2640 (br)(OH), 1642 (s), 1585 (sh) and 1566 (br)(ring), 1510, 1301, 1241, 1200 (s)(N=O), 1147, 1061, 921 (br), 839 (s) cm\(^{-1}\).

**Attempted preparation of chloroacetamidoxime:**

Chloroacetonitrile (7.55 g.) and hydroxylamine (6.6 g.) in 50% aqueous methanol (200 ml.) were kept at room temperature overnight. The solution was evaporated and the material obtained was extracted with methanol. When the concentrated \( \text{ethanolic} \) solution was added to an excess of acetone, a pink product was precipitated. When filtered off, even under nitrogen, it turned into tar immediately.

**Attempted preparation of hydroxacetamidoxime:**

Following the above procedure but using glycolonitrile instead of chloroacetonitrile, no tractable product was isolated.

**Attempted preparation of aminoacetamidoxime:** (A polymer of aminoacetamidoxime): Aminoacetonitrile hydrochloride (18.5 g.), hydroxylamine hydrochloride (25.6 g.) and sodium carbonate (31.8 g.)
in water (170 ml.) were kept overnight under nitrogen. Next day
a pale yellow polymeric product was deposited in 50% yield. This
polymer, purified by reprecipitation from dimethylsulphoxide
with water, had m.p. 180° (charring and darkening from 170°)
(Found: C, 33.3; H, 5.55; N, 38.9. (C₂H₄N₂O)ₙ requires
C, 33.3; H, 5.55; N, 38.9.
ν max. 3355 (NH), 3200-2600 (br) (OH),
1678 (s) (C=N), 1085, 1017, 930, 898 and 838 cm⁻¹; δ(DMSO) 6.36
(s) (CH₂), 3.69 (br) (NH) and 1.19 (br) (=NOH). With iron(III)chloride
it gave a pure blue colour.

2,6-Diaminopyrazine 1-oxide (X):
2-Amino-6-hydroxyaminopyrazine 1-oxide hydrate (IXa)
(6.4 g., 0.04 mole), glacial acetic acid (200 ml.) and platinum
(0.56 g) oxide catalyst was shaken together in an atmosphere of hydrogen
(cf. ref. 53). In 0.75 hr., the uptake of hydrogen was 1110 c.c.
(calculated: 960 c.c. required by the compound + 110 c.c. by
the catalyst = 1070 c.c.). The catalyst was filtered off and the
filtrate evaporated. The residue was dissolved in methanol (200
ml.) and the solution was treated with charcoal, and concentrated
in a rotatory film evaporator to afford a colourless product
(3.2 g., 64%), m.p. 280°-282° (decomp.). Recrystallisation from
water gave needles of 2,6-diaminopyrazine 1-oxide (X) m.p. 294°-
295° (decomp.) (Found: C, 38.05; H, 4.8; N, 44.1. C₄H₆N₄O
requires C, 38.1; H, 4.8; N, 44.4%); m/e 126; ν max. 3360 and
3250 (sh) (NH), 3160 and 3090 (br) (NH and bonded NH), 1608 (s),
1561 and 1541 (ring), 1260, 1225 (s) (N=O), 841 (s), 818 (s), 736,
712 (br) cm⁻¹. It was stable in concentrated sulphuric acid and
alkali, and with iron(III)chloride gave a deep, pure blue colouration which did not fade on standing but was discharged by a drop of dilute hydrochloric acid (cf. ref. 27). \( \tau (\text{DMSO}) 3.4 \text{ (br)(2 x NH}_2\text{)}, 2.67 \text{ (2 x ring H's); } \lambda_{\text{max.}} 230.5, 282, 336 \text{ nm.}, 21.7, 2.2, 9.6 \times 10^{-3} \varepsilon. \)

2,6-Diacetamidopyrazine 1-oxide (XI):

2,6-Diaminopyrazine 1-oxide (X)(0.63 g.) was suspended in acetic anhydride (20 ml.). After 38 hr., the 2,6-diacetyl derivative (XI) was filtered off, washed with ethanol and dried (1.05 g., 100%), m.p. 264°-265° (decomp.). Recrystallisation from boiling aqueous methanol gave needles, m.p. 272°-273°(decomp.) (Found : C, 45.65; H, 4.7; N, 26.8. \( \text{C}_8\text{H}_10\text{N}_4\text{O}_3 \) requires C, 45.7; H, 4.7; N, 26.7%); \( m/e 210; \) \( \nu \text{ max. } 3270 \text{ (s)(NH)}, 3120 \text{ (w)}, 1692 \text{ (s)(CO)}, 1570 \text{ (s)(br)}, 1558 \text{ (sh)}, 1500 \text{ (w)}, 1336 \text{ (s)}, 1297 \text{ (s)}, 1276 \text{ (w)}, 1230 \text{ (s)(NO)}, 1142, 1060, 958, 885, 861 \text{ (s)}, 802 \text{ (w)}, 700 \text{ (br)} \text{ cm}^{-1}; \) \( \lambda_{\text{max.}} 252, 277 \text{ (infl.)}, 327 \text{ nm.}, 32.6, 10.3, 8.9 \times 10^{-3} \varepsilon; \) \( \tau \) \( (\text{d}_6-\text{DMSO}) 7.7 \text{ (s)(2 x CH}_3\text{)}, 0.93 \text{ (s)(2 x ring H's)}, -0.46 \text{ (br)(2 x NH)}; \) \( \tau (\text{CF}_3\text{CO}_2\text{H}) 7.4 \text{ (s)(2 x CH}_3\text{), 0.24 (2 x ring H's).} \)

2,6-Diacetamidopyrazine (XVI):

(a) By deoxygenation of 2,6-diacetamidopyrazine 1-oxide:- 2,6-diacetamidopyrazine 1-oxide (XI) (105 mg.) and sodium dithionite (0.21 g.) were heated under reflux in 70% (v/v)(12 ml.) aqueous ethanol (cf. ref. 50) for 20 min. gave 2,6-diacetamidopyrazine (XVI)(80 mg., 82%). It sublimed above 300° without melting or decomposing. It was insoluble in water, alcohols, acetic acid,
dimethylsulphoxide, chloroform, carbontetrachloride (Found: C, 49.6; H, 5.1; N, 28.9. C$_6$H$_{10}$N$_4$O$_2$ requires C, 49.5; H, 5.15; N, 28.9%). v max. 3300 (s)(NH), 3160 (w), 3100 (w), 1678 (s) (CO), 1566, 1280, 1260, 1240 (s), 1190, 1157 (s), 1122, 1040, 1010 (s), 960, 881, 810 cm$^{-1}$; λ max. 216.5, 244 (inf), 312.5 nm., 26.8, 6.95, 12.9 $10^{-3}$ ε.

(b) By acetylation of 2,6-diaminopyrazine: A suspension of 2,6-dihydroxyiminopiperazine (1 g.) and 10% palladium-on-charcoal (0.2 g.) in o-dichlorobenzene (100 ml.) was heated under reflux, under nitrogen, for three hours. The hot reaction solution was filtered off and the filtrate upon cooling precipitated deep yellow 2,6-diaminopyrazine which was filtered off, washed with o-dichlorobenzene, dry ether and dried (0.1 g.). To this 2,6-diaminopyrazine excess of acetic anhydride was added. Next day, a yellow precipitate of 2,6-diacetamidopyrazine was collected and purified by sublimation (190°-200°/ 0.2 mm.). Its identity was checked by the comparison of its i.r. spectrum with authentic sample.
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REFERENCES

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Repeated elemental analysis for the product obtained as a result of the reaction of N-benzoyliminodiacetonitrile (Ic) with hydroxylamine showed that the product had the composition $C_{18}H_{24}N_8O_{10}$. That the product was nevertheless essentially the expected bisamidoxime (IVc) was indicated by its conversion into the cyclic dioxime (IIIC) (pp. 27) in 55% yield. A possible explanation is that the reaction product is a molecular complex comprising the bisamidoxime, benzonitrile dinitrate monohydrate. However, the p.m.r. and mass spectra showed presence of only the amidoxime (IVc).