Synthesis and Thermolysis of Some Aromatic and Heterocyclic Amidoxime Derivatives

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ليلى أحمد طيب
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AIM OF THE WORK
Aim of the Work

In the past thirty years organic thermochemistry has developed rapidly and led to a wealth of novel reactions and applications that can be of great significance.

The present work has been devoted to study of thermal fragmentation of aromatic and heterocyclic amidoximes I-XI alone and/or in the presence of naphthalene and tetralin as radical scavengers. The main feature of these thermolyses is the homolysis of the N-O and C-N bonds initiating different free radical reactions.

On the other hand, these studies have been led to the formation of novel synthesis of a variety of heterocyclic compounds like; benzimidazole derivatives as the major products (45-70 \%) in addition to benzoazoles, carbazoles and triazine as the minor products.

Moreover, these target compounds I-XI have been found a number of significant biological activities and uses in the polymer field and as prodrugs.

Also, the biological effects and other useful uses of amidoxime derivatives I-XI have prompted us to clarify the behavior of these compounds when subjected to high temperatures 220-250\°C and reinvestigation such reactions in an effort to gain further information about more generalized thermolytic mechanism to account for the identified products.
I addition to the aimed synthetic value of the work, mechanistic studies and environmental applications are also targeted.
English Summary

The present study aims to preparation of some aromatic and heterocyclic amidoxime derivatives I-XIII containing pyridine and furan moieties which have antibacterial and antifungal as cited in literature.

Moreover, these compounds I-XIII are synthetically useful as precursors for various heterocyclic compounds. Also, the amidoxime functional group can serve as a prodrug unit for amidines.

Also, this study aims to investigate the effect of heat on these target compounds I-XIII which are widely used as biological activities and other useful as mentioned before.

On the other hand, this different usefulness for these compounds I-XIII have prompted us to clarify the behaviour of these compounds when subjected to high temperatures and reinvestigated such reactions in an effort to gain further information about more generalized thermolytic mechanism.

Firstly, study of thermal fragmentation and rearrangement of some aromatic amidoxime derivatives (I-III) as follows:

When N-p-chlorophenylbenzamide oxime I was heated at 220-250°C under nitrogen atmosphere for 5 h, it gave benzonitrile 17, benzoic acid 41, p-chlorophenol 155, p-chloroaniline 153, 3,6-dichloro-9H-carbazole 158, 2-amino-5-chlorophenol 156 as minor products in addition to N-(4-chlorophenyl) benzamide 157 and 5-chloro-2-phenyl-1H-benzimidazole 159 as major product (45.2%). Therefore this method was considered as a novel synthesis for 5-chloro-2-phenyl-1H-benzimidazole 159.
Analogous results were also obtained in the thermal fragmentation of \(N\)-\(p\)-chlorophenylbenzamide oxime I on thermolysis in the presence of naphthalene as a radical scavenger under the same conditions produced \(\alpha\)- and \(\beta\)-naphthols 76 and 77, respectively (16\%) in addition to the same products as mentioned previously.

Also, when \(N\)-\(p\)-chlorophenylbenzamide oxime I on heating under reflux at boiling anhydrous tetralin ca. 210\(^\circ\)C as hydrogen donor for 8 h formed \(\alpha\)-tetralone 78, 1-hydroxytetralin 81 and 1,1-bitetralyl 79 in addition to the same products as mentioned before.

Similarly, \(N\)-\(p\)-nitrophenylbenzamide oxime II undergoes thermolysis under the same conditions led to the formation of benzonitrile 17, benzoic acid 41, \(p\)-nitrophenol 162, \(p\)-nitroaniline 160, 3,6-dinitro-9H-carbazole 164, 6-nitro-2-phenylbenz[d]oxazole 165, as the minor products in addition to \(N\)-(4-nitrophenyl)benzamide 163 and 5-nitro-2-phenyl-1H-benzimidazole 167 as major product (46.1\%), therefore this method was considered as a novel synthesis for 5-nitro-2-phenyl-1H-benzimidazole 167.

Thermolysis \(N\)-\(p\)-methoxyphenylbenzamide oxime III on heating under the same conditions gave benzonitrile 17, benzoic acid 41, \(p\)-anisidine 168, phenol 74a, 3,6-dimethoxy-9H-carbazole 171, 6-methoxy-2-phenylbenz[d]oxazole 172 as the minor products in addition to \(N\)-(4-methoxyphenyl)benzamide 170 and 5-methoxy-2-phenyl-1H-benzimidazole 173 as major product (52.6\%), therefore this method was considered as a novel synthesis for 5-methoxy-2-phenyl-1H-benzimidazole 173.
Secondly, study of thermal fragmentation and rearrangement of some heterocyclic benzamidoxime derivatives containing pyridine and furan moieties (IV-X) as follows:

When \(N\)-phenylnicotinamide oxime IV (\(N\)-phenyl-3-pyridylamide oxime) was heated at 220-250°C under nitrogen atmosphere for 5h produced aniline 71a, phenol 74a, nicotinic acid 176, nicotinonitrile 177, 9H-carbazole 179, 2-(pyridin-3-yl)benz[d]oxazole 180 as the minor products in addition to \(N\)-phenylnicotinamide 178 and 2-(pyridine-3-yl)-1H-benzimidazole 181 as major product (60.5%), therefore this method was considered as a novel synthesis for 2-(pyridine-3-yl)-1H-benzimidazole 181.

Also, \(N\)-phenylnicotinamide oxime IV on thermolysis in the presence of naphthalene as a radical scavenger under the same conditions produced \(\alpha\)- and \(\beta\)-naphthols 76 and 77, respectively (18%) beside the same products as mentioned before.

Attention has been given also to thermal fragmentation of \(N\)-phenylnicotinamide oxime IV on heating under reflux in boiling anhydrous tetralin ca. 210°C as hydrogen donor for 8 h afforded \(\alpha\)-tetralone 78, 1-hydroxytetralin 81 and 1,1-bitetralyl 79 in addition to the same products as mentioned previously.

Thermolysis of \(N\)-p-methylphenylnicotinamide oxime V was heated under the same conditions yielded \(p\)-toluidine 75b, \(p\)-cresol 74b, nicotinic acid 176, nicotinonitrile 177, 3,6-dimethyl-9H-carbazole 185, 2-amino-5-methylphenol 183 as the minor products in addition to \(N\)-(4-methylphenyl) nicotinamide 184 and 5-methyl-2-(pyridine-3-yl)-1H-benzimidazole 186 as major product (62.1%), therefore this method was considered as a novel synthesis for 5-methyl-2-(pyridine-3-yl)-1H-benzimidazole 186.
Similarly, \( N-p \)-chlorophenyl\nicotinamide oxime \textbf{VI} was heated under the same conditions gave rise to \( p \)-chloroaniline 153, \( p \)-chlorophenol 155, nicotoinic acid 176, nicotinonitrile 177, 3,6-dichloro-9H-carbazole 158, 2-amino-5-chlorophenol 156 as the minor products in addition to \( N-(4 \)-chlorophenyl\nicotinamide 188 and 5-chloro-2-(pyridine-3-yl)-1H-benzimidazole 189 as major product (60.0%), therefore this method was considered as a novel synthesis for 5-chloro-2-(pyridine-3-yl)-1H-benzimidazole 189.

Also, thermal fragmentation of \( N \)-phenyl-2-furamide oxime \textbf{VII} under the conditions used formed aniline 71a, 2-furonitrile 195, 2-furoic acid 192, furil 193, 2-furamide 194, phenol 74a, 9H-carbazole 179 and 2-(furan-2-yl)benz[d]oxazole 196 as the minor products in addition to \( N \)-phenyl-2-furamide 197 and 2-(furan-2-yl)-1H-benzimidazole 198 as major product (37%), therefore this method was considered as a novel synthesis for 2-(furan-2-yl)-1H-benzimidazole 198.

Similar results were also obtained on thermal fragmentation of \( N \)-phenyl-2-furamide oxime \textbf{VII} in the presence of naphthalene as a radical scavenger under the same conditions produced \( \alpha \)- and \( \beta \)-naphthols 76 and 77, respectively (20%) beside the same products as mentioned previously.

Analogous results were also obtained in the thermal fragmentation of \( N-p \)-methylphenyl-2-furamide oxime \textbf{VIII} under the conditions used formed \( p \)-toluidine 75b, 2-furonitrile 195, 2-furoic acid 192, \( p \)-cresol 74b, 3,6-dimethyl-9H-carbazole 185 and 6-methyl-2-(furan-2-yl)benz[d]oxazole 201 as minor products in addition to \( N-(4 \)-methylphenyl\)-2-furamide 200 and 5-methyl-2-(furan-2-yl)-1H-benzimidazole 202 as major product (47.5%), therefore this method was considered as a novel synthesis for 5-methyl-2-(furan-2-yl)-1H-benzimidazole 202.
Similarly, \( N-p \)-chlorophenyl-2-furamide oxime \( \text{IX} \) under the same conditions formed \( p \)-chloroaniline \( 153 \), 2-furonitrile \( 195 \), 2-furoic acid \( 192 \), \( p \)-chlorophenol \( 155 \), 3,6-dichloro-9H-carbazole \( 158 \) and 6-chloro-2-(furan-2-yl)benz [d]oxazole \( 204 \) as the minor products in addition to \( N-p \)-chlorophenyl-2-furamide \( 205 \) and 5-chloro-2-(furan-2-yl)-1H-benzimidazole \( 206 \) as major product (40\%), therefore this method was considered as a novel synthesis for 5-chloro-2-(furan-2-yl)-1H-benzimidazole \( 206 \).

Also, thermolysis of \( N \)-2-pyridylbenzamide oxime \( \text{X} \) was heated at 220-250°C under nitrogen atmosphere for 5 h gave benzoic acid \( 41 \), benzonitrile \( 17 \), 2-hydroxypyridine \( 209 \), 2-aminopyridine \( 207 \), 9H-pyrrolo[2,3-b:5,4-b’]dipyridine \( 211 \), 2,4,6-triphenyl-1,3,5-triazine \( 19 \), 2-phenyl-1H-oxazo[4,5-b]pyridine \( 212 \) as the minor products beside \( N \)-(pyridin-2-yl) benzamide \( 210 \) and 2-phenyl-1H-imidazo[4,5-b]pyridine \( 213 \) as major product (52\%), therefore this method was considered as a novel synthesis for 2-phenyl-1H-imidazo[4,5-b]pyridine \( 213 \).

**Thirdly: Preparation and thermal fragmentation and rearrangement of benzamidoxime derivatives containing naphthalene ring (XI-XIII) as follows:**

Attention has been given also to thermal fragmentation of \( N-\alpha \)-naphthylbenzamide oxime \( \text{XI} \) when heated under the same conditions led to the formation of benzoic acid \( 41 \), benzonitrile \( 17 \), \( \alpha \)-naphthylamine \( 214 \), \( N-(\alpha \)-naphthyl)benzamide \( 216 \), 2-phenyl[naphth[1,2-d]oxazole \( 217 \) as the minor products in addition to 2-phenyl-1H-naphth[1,2-d]imidazole \( 218 \) as major product (38\%), therefore this method considered as a novel synthesis for 2-phenyl-1H-naphth[1,2-d]imidazole \( 218 \).
Also, preparation of $N$-$\alpha$-naphthylnicotinamide oxime $\text{XII}$ through heating of anhydrous aluminum chloride, 3-cyanopyridine and $\alpha$-naphthylamine in the presence of 1,1,2,2-tetrachloroethane as solvent giving $N$-$\alpha$-naphthylnicotinamidine $219$ which reacts with hydroxylamine hydrochloride in water to form the compound $\text{XII}$. Moreover, when thermolysis of this compound $\text{XII}$ under the conditions used several times, unfortunately, we didn’t get the expected products as mentioned previously.

Furthermore, preparation of $N$-$\alpha$-naphthyl-2-furamide oxime $\text{XIII}$ through heating of anhydrous aluminum chloride, 3-cyanofuran and $\alpha$-naphthylamine in the presence of 1,1,2,2-tetrachloroethane as solvent giving $N$-$\alpha$-naphthyl-2-furamidamidine $220$ which reacts with hydroxylamine hydrochloride in water to form the compound $\text{XIII}$. Moreover, when thermolysis of this compound $\text{XIII}$ under the conditions used several times, unfortunately, we didn’t get the expected products as mentioned previously.

The mechanism invoked for the rationalization of the products of thermolysis assumes the intermediacy of free radicals originating from homolysis of the N-O and C-N bonds of aromatic and heterocyclic benzamidoximes followed by the common reactions of free radicals involving H-abstraction, coupling, fragmentation, isomerization, dimerization, disproportionation and cyclization to give the identified products.

Isolation of the products was achieved by fractional distillation under reduced pressure and column chromatography using gradient elution technique.
The nature of products were assigned by preparation of reference compounds and derivatives whenever possible, together with elemental analyses, thin-layer chromatography (TLC), infrared spectroscopy (IR), proton nuclear magnetic resonance (\(^1\)H-NMR), carbon nuclear magnetic resonance (\(^{13}\)C-NMR), mass spectroscopy (MS) and gas chromatography coupled with mass spectroscopy (GC/MS).
ABBREVIATIONS
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIBN</td>
<td>Azoisobutynitrile</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling points</td>
</tr>
<tr>
<td>CsF</td>
<td>Cesium fluoride</td>
</tr>
<tr>
<td>Ca.</td>
<td>Approximately</td>
</tr>
<tr>
<td>cyclizn.</td>
<td>Cyclization</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1-Carbonyldiimidazole</td>
</tr>
<tr>
<td>$^{13}$C-NMR</td>
<td>Carbon nuclear magnetic resonance</td>
</tr>
<tr>
<td>dimern.</td>
<td>Dimerization</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-diisopropylethylamine</td>
</tr>
<tr>
<td>DCC</td>
<td>Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet doublet</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>et.al</td>
<td>And others</td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Eq.</td>
<td>Equation</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionization</td>
</tr>
<tr>
<td>Fig.</td>
<td>Figure</td>
</tr>
<tr>
<td>Fn.</td>
<td>Furan</td>
</tr>
<tr>
<td>FVP</td>
<td>Flash vacuum pyrolysis</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>¹H-NMR</td>
<td>Proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>HRP</td>
<td>Horseradish peroxidase</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>GLC</td>
<td>Gas liquid chromatography</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>G</td>
<td>Gram</td>
</tr>
<tr>
<td>GC/MS</td>
<td>Gas chromatography with mass spectroscopy</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-Hydroxybenzotriazole hydrate</td>
</tr>
<tr>
<td>Lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectroscopy</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point in °C</td>
</tr>
<tr>
<td>mmp</td>
<td>Mixed melting point</td>
</tr>
<tr>
<td>min.</td>
<td>Minute</td>
</tr>
<tr>
<td>m/e</td>
<td>Mass- to- charge ratio</td>
</tr>
<tr>
<td>NOS</td>
<td>NO-Synthases</td>
</tr>
<tr>
<td>NADPH</td>
<td>Nicotinamide adenine dinucleotide phosphate-oxidase</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>Sodium borohydrate</td>
</tr>
<tr>
<td>NMP</td>
<td>N-Methyl pyrrolidone</td>
</tr>
<tr>
<td>nm</td>
<td>Nanometer</td>
</tr>
<tr>
<td>Py.</td>
<td>Pyridine</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>Pt</td>
<td>Platinum</td>
</tr>
<tr>
<td>Rₚ</td>
<td>Rate of flow</td>
</tr>
<tr>
<td>R.T.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>STP</td>
<td>Static (sealed-tube) pyrolysis</td>
</tr>
<tr>
<td>soln.</td>
<td>Solution</td>
</tr>
<tr>
<td>SDS</td>
<td>Sodium dodecyl sulfate</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>Torr</td>
<td>is a non-SI unit of pressure with the ratio of 1 to 760 standard atmosphere, i.e. ~ = 1 mmHg</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBTU</td>
<td>N,N,N',N'-tetramethyl-(O)-benzotriazole uranium tetrafluoroborate</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>v/v</td>
<td>Volume to volume ratio for a solution</td>
</tr>
<tr>
<td>(\nu)</td>
<td>Frequency</td>
</tr>
<tr>
<td>vol.</td>
<td>Volume</td>
</tr>
<tr>
<td>(\delta)</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>(\Delta)</td>
<td>Heat</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>naph.</td>
<td>Naphthalene</td>
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</table>
INTRODUCTION
INTRODUCTION

Chemistry of Amidoxime Derivatives

Amidoximes are an interesting class of compounds. They can serve as starting materials for the synthesis of valuable heterocyclic compounds and are also useful building blocks for a number of heteroarenes including imidazoles [1], benzimidazoles [2], pyrimidines [3], quinazolines [4], 4H-1,2,4-thiadiazines [5], 1,2,4-benzothiadiazines and benzothiazoles [6], 4,5-dihydro-1,2,4-oxadiazoles [7], 4H-[1,4,2]diazaphospholes [8], 4H-1,3-oxazin-4-ones [9] and 2,5-dihydro-1,2,4,6-thiatriazines [10]. Moreover, they are used as the key intermediates for an important route for amidines synthesis [11].

In addition to this usefulness, this class of compounds possesses pronounced biological activity. The details of such activities have been recently reviewed [12].

Furthermore, several \(N\)-arylbenzamidines have interesting biological properties, including inhibitor activity towards tyrosine kinases [13] and nitric oxide synthetase [14] and as selective \(D_1\) dopamine receptor antagonists [15]. Antimicrobial [16] and antiphrastic properties have also been reported.

Also, amidoximes-containing molecules have found a number of significant uses in the polymers fields and as potential drugs in a wide range of therapeutic areas [17].

Another interesting feature concerning amidoximes is that they can be used as produrg unit for amidines [18].
1. Synthesis of amidine Derivatives

1.1. Preparation of Amidines from Cyanides

Amidines and their N-monosubstituted derivatives 3 were prepared by heating the ammonium or alkyl or aryl-ammonium salt of an aromatic or aliphatic sulphonic acid 2 with a cyanide 1 at 180-300°C [19], eq. 1. α-Naphthamidine and o-substituted benzamidines can be prepared in this way as follows:

\[
\text{R}^1\text{C} = \text{N} + \text{R}^1\text{S}_2\text{CF}_2 \xrightarrow{\Delta} \text{R}^1\text{N} = \text{C} = \text{N} + \text{R}^1\text{S} = \text{CF}_2 \xrightarrow{\Delta} \text{R}^1\text{N} = \text{C} = \text{N} \quad \text{eq. 1}
\]

1.2. Preparation of Amidines from Cyanides, Aluminium Chloride, and Ammonia or Amines

Amidines and N-substituted amidines 5 can be prepared from cyanides 1, aluminium chloride, and ammonia or an amine. The method gives good yields of NN-dialkyl-amidines as in eq. 2, which are obtained in poor yield by the ammonium sulphonate method [20].

\[
\text{R}^1\text{C} = \text{N} + \text{AlCl}_3 \xrightarrow{\Delta} \text{R}^1\text{C} = \text{N} + \text{NHXY} \xrightarrow{\Delta} \text{R}^1\text{C} = \text{N} + \text{NHXY} \xrightarrow{\Delta} \text{AlCl}_3 \quad \text{eq. 2}
\]

1.3. Preparation of Substituted Amidines from Ketoxime Sulphonates and Ammonia or Amines.

Amidines are produced in good yield when ketoxime sulphonates 6, undergo Beckmann rearrangement in presence of ammonia or amines. When N-phenylbenzimidobenzene sulphonate 7 is heated
alone it yields benzenesulphonic anhydride 8 and \(N\)-benzoyl-\(NN'\)-diphenylbenzamidine 9 [21] as outlined in Scheme 1 as follows:

![Scheme 1](image)

Similarly, thermal decomposition of acetoxime benzene sulphonate affords a complicated mixture containing benzene- sulphonic anhydride, \(NN'\)-dimethylacetamidine, and 4-methylimino-1,2,6-trimethyl-1,4-dihydro-pyrimidine 10 [21]; Scheme 1.

1.4. Preparation of Amidines from Cyanides, Ammonia or an Amine, and an Ammonium or Substituted ammonium Salt.

Amidines and their \(N\)-substituted derivatives can be prepared by heating a cyanide, ammonia or a primary or secondary amine, and the corresponding ammonium or substituted ammonium salt, especially a sulphonate, at a suitable temperature within the range 150-220°C [22], Scheme 2.
1.5. Preparation of Amidines from Substituted Amides, a Sulphonyl Chloride and an Amine.

Amidines 13 are prepared by the reaction of amines with imidosulphonates 12, produced \textit{in situ}, from \textit{N}-monosubstituted amides 11 and sulphonyl chlorides in presence of pyridine [23] as in eq. 3.

\[
\text{R-CN + NHXY} \rightarrow \text{R-C} \text{NHXY} \rightarrow \text{R-C} \text{NHXY} + \text{NHXY}
\]

\[
\text{R-CN} + \text{ArSO}_3 \rightarrow \text{R-C} \text{NHXY} \rightarrow \text{R-C} \text{NHXY} + \text{ArSO}_3
\]

\[X, Y = \text{H, R}^{'}, \text{H, CH}_3 , \text{H, C}_2\text{H}_5 \]

1.6. Preparation of Substituted Amidines from Ammonium or Substituted Ammonium Salts and \textit{N}-Acylbenzene sulphonalkyl amides or \textit{Acyl benzenesulphonanilides}

When a carboxylic acid 14 was heated with a sulphondialkyl amide 15 a carbondialkyl amide 11 was produced, and it was found that the acids and \textit{N}-monosubstituted sulphonamides (2 moles) afforded \textit{N,N}-disubstituted amidinium sulphonates 16 [24]. It was suggested that the reaction takes place in consecutive steps as shown in Scheme 3.
1.7. Preparation of N-Arylbenzamidines from Benzonitriles and Anilines in the Presence of AlCl$_3$

The preparation of N-arylbenzamidines 18 was accomplished by the reaction of benzonitrile 17 and substituted anilines in the presence of AlCl$_3$ as a Lewis acid catalyst at 200°C beside 2,4,6-triphenyl-1,3,5-triazine 19 could also produced from this reaction [25], Scheme 4.

\[
\begin{align*}
R-CO-NH-R + R^3-SO_2-NH-R &\rightarrow R-CO-NH-R + R^3-SO_2-OH \\
R-CO-NH-R + R^3-SO_2-NH-R + R^3-SO_2-OH &\rightarrow R-CO-NH-R + R^3-SO_2-OH
\end{align*}
\]

\[
R-CO-NH-R + R^3-SO_2-NH-R + R^3-SO_2-OH \rightarrow R-CO-NH-R + R^3-SO_2-OH
\]

\[
R - R' = CH_3, Ph
\]

Scheme 3

1.8. Preparation of Amidines by Photolysis

Newman [26] found that photochemical decomposition of 3,5-diphenyl-1,2,4-oxadiazole 20 occurred in ether to give N-benzoylbenzamidine 21; eq. 4.
2. Synthesis of Amidoximes

This is the most used process for the preparation of amidoximes:

2.1. Action of Hydroxylamine on Nitriles

The experimental procedure recommended by Tiemann [27] including liberating a hydroxylamine from its hydrochloride using sodium carbonate, adding an equivalent amount of nitrile and enough alcohol and keeping the mixture at 60-80°C for few hours to obtain amidoxime 22 as in eq. 5.

\[
\text{R-CN} + \text{NH}_2\text{OH} \rightarrow \text{R-C} = \text{N-OII} \quad \text{eq. 5}
\]

2.2. Action of Hydroxylamine on Amides or Thioamides

Although hydroxylamine, as a rule, does not react with amides, the only reported instance is that for the preparation of the two amidoximes 23 and 24 [28].
Some aromatic amidoximes 22 have been prepared by the action of hydroxylamine on thioamides 25, as in eq. 6.

\[
\begin{align*}
R\text{S} & + \text{NH}_2\text{OH} \rightarrow R\text{NH}_2\text{OH} + \text{H}_{2}\text{S} && \text{eq. 6}
\end{align*}
\]

Hydroxylamine was liberated from its hydrochloride by an equivalent amount of aqueous sodium carbonate. The thioamide was then introduced and ethanol added until the mixture became clear followed by reflux for few hours and the amidoxime 22 was isolated [29].

2.3. Reduction of Nitrosolic and Nitrolic Acids

Wieland and Bauer [30] prepared benzamidoxime 27 by reduction of nitrosolic acids 26 with hydrogen sulfide as eq. 7.

\[
\begin{align*}
\text{NO} & + 2\text{H}_2\text{S} \rightarrow \text{NH}_2\text{OH} + \text{H}_2\text{O} + \text{S}_8 && \text{eq. 7}
\end{align*}
\]

Also, an apparently general method was described for the preparation of the monoamidoximes 29, by catalytic reduction of nitrolic acids 28 [31], eq. 8.
2.4. *Action of Ammonia on Hydroximic Acid Chlorides (Chloroximes)*

*N*-Hydroxybenzimidoyl chloride 30 (Hydroximic acid chlorides), which was formed by direct chlorination of benzaldoxime, reacts easily with ammonia to yield benzamidoxime 27 as in eq. 9. This procedure was used by Werner [32] to prepare benzamidoxime, *o*-chlorobenzamidoxime and terephthalamidoxime [33].

\[
\begin{align*}
\text{N-OH} & \quad \text{Cl} \\
\text{C} & + 2\text{NH}_3 \\
\text{30} & \longrightarrow \text{N-OH} \\
\text{NH}_2 & \\
\text{27} & \\
\end{align*}
\]

**eq. 9**

2.5. *Reduction of Oxyamidoximes*

Ley and Ulrich [34] reported the synthesis of benzoxyamidoxime 31 by reaction of hydroximic acid chlorides 30 with hydroxylamine. Compound 31 was then reduced with sulfur dioxide to give the corresponding amidoxime 27 as in Scheme 5.

\[
\begin{align*}
\text{N-OH} & \quad \text{Cl} \\
\text{C} & + \text{NH}_2\text{OH} \\
\text{30} & \longrightarrow \text{N-OH} \\
\text{NH}_2\text{-OH} & \\
\text{31} & \\
\text{SO}_2 & \\
\text{N-OH} & \quad \text{NH}_2 \\
\text{27} & \\
\end{align*}
\]

**Scheme 5**
2.6. Action of Hydroxylamine on Iminoethers

This reaction was reported by Pinner [35] and Lossen [36], who obtained benzamidoxime 27 by treating ethyl iminobenzoate 32 with hydroxylamine; eq. 12.

\[
\text{eq. 12}
\]

Since benzonitrile is the starting material for the synthesis of the iminoether, this reaction was not considered as a practical method for the synthesis of amidoximes.

2.7. Action of Hydroxylamine on Amidine Hydrochlorides

Pinner [35] reported that benzamidoxime 27 was prepared by treating benzamidine hydrochloride 33 with hydroxylamine; eq. 13.

\[
\text{eq. 13}
\]

This reaction has no practical interest, since amidines generally are obtained from nitriles, thioamides, or iminoethers.

2.8. Action of Ammonia on Oximinoethers

An alcoholic solution of ammonia and ethyl benzhydroxamic acid 32 was heated in a pressure bottle for 8 hrs at 175°C, to yield benzamidoxime 27 [37] as in eq. 14.

\[
\text{eq. 14}
\]
2.9. Action of Formamidoxime on Aromatic Aldehydes

Conduché et al. [38] reported that formamidoxime 35 can react with aromatic aldehydes 34, leading to the formation of mandel amidoxime 36. Compound 36 is the only example that has been prepared by this method as in eq. 15.

\[
\begin{array}{c}
\text{CHO} \\
\text{34}
\end{array} + \begin{array}{c}
\text{N-OH} \\
\text{H} \quad \text{H} \quad \text{N} \quad \text{NH}_2
\end{array} \rightarrow \begin{array}{c}
\text{CH} \\
\text{35}
\end{array} \quad \begin{array}{c}
\text{OH} \\
\text{36}
\end{array} \quad \text{eq. 15}
\]

2.10. Action of Ammonia on Glyoxime Peroxides

Treatment of phenyl glyoxime peroxide 37 with ammonium hydroxide, an oxime containing amidoxime 38 [39] was produced; eq. 16.

\[
\text{Ph(C}_2\text{N}_2\text{O}_2)\text{H} + \text{NH}_2\text{OH} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{37}
\end{array} \quad \begin{array}{c}
\text{N-OH} \\
\text{HO-} \\
\text{NH}_2
\end{array} \quad \text{eq. 16}
\]

Another example was the reaction of dibenzoylglyoxime peroxide 39 with ammonium hydroxide that gives the corresponding amidoxime 40 and benzoic acid 41 [40]; eq. 17.

\[
\begin{array}{c}
\text{39}
\end{array} + \begin{array}{c}
\text{NH}_2\text{OH}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{39}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{C} \\
\text{39}
\end{array} \quad \begin{array}{c}
\text{C} \\
\text{N} \\
\text{39}
\end{array} \quad \begin{array}{c}
\text{N-OH} \\
\text{NH}_2
\end{array} \quad \begin{array}{c}
\text{Ph-C} \\
\text{39}
\end{array} \quad \text{eq. 17}
\]
2.11. **Rearrangement of α-Hydroxylamino Oximes to Cyclic Amidoximes by the Action of Sodium Borohydride.**

Tkachev *et. al* [41] reported the reductive Beckmann fragmentation of α-amino oximes under the action of sodium borohydride in acetonitrile medium. α-Hydroxylamino oximes 42 were found to undergo unknown rearrangement to give cyclic amidoximes 43; eq. 18.

![Equation 18](image)

2.12. **Synthesis of Arylamidoximes from Arylnitriles and Hydroxylamine**

A simple and easy synthesis of ten arylamidoximes 27 from arylnitriles 17 and hydroxylamine hydrochloride at room temperature, in the presence of sodium bicarbonate [42] is outlined in eq. 19.

![Equation 19](image)

\[ \text{Ar} = \text{Ph, } \alpha\text{-tolyl, } m\text{-tolyl, } p\text{-tolyl, } p\text{-ClC}_6\text{H}_4\text{H}_5, m\text{-ClC}_6\text{H}_4\text{H}_5, p\text{-BrC}_6\text{H}_4\text{H}_5, p\text{-ClCH}==\text{C}_6\text{H}_5, p\text{-AcC}_6\text{H}_5 \]

2.13. **Reactions of Monothiooxamides with O-Methylhydroxyl amine**

It was reported [43] that *N*-phenyl-2-morpholino-2-thiooxoacetamide 44 is converted into a mixture of the methoxy derivative of hydroxamic...
acid 45 and dimethoxyamidine 46 upon treatment with methoxy hydroxylamine as shown in Scheme 6.

![Scheme 6](image)


It has been reported [44] that O-vinylamidoximes 47 are synthesized from the reaction of amidoximes 27 and acetylene in superbase systems (KOH/DMSO, KOH/NMP, NaOH/CsF/NMP) in a preparative yield of up to 80%; eq. 20.

![Equation 20](image)

2.15. Synthesis of Heterocyclic Amidoximes

Thermolysis of 6-amino-1,2-dihydro-3H-quinazolines 48 gives the quinazoline oximes 49 as a sole product [45]; eq. 21.
Also, 6-bromomethyl-4-phenylpyrimidine 1-oxide 50 was reported to react readily with hydroxylamine hydrochloride in NaOH solution at room temperature with the formation of the oxime of 6-formyl-4-phenylpyrimidine 1-oxide 51 [46] as in eq. 22.

Few reports have been devoted to the synthesis of pyridazine amidoximes [47]. Pyridazine-3-amidoxime 54 was obtained from the corresponding ester 52 upon treatment with NH₃/NH₂OH system or by the reaction of the amide 53 with hydroxylamine (Scheme 7).

The reaction of the dinitrile 55 with hydroxylamine in ethanol was found to give the dioxime 56 with a 50% yield [48]. This compound is
converted into 57, the product from partial hydrolysis of one oxime group upon treatment with NaNO₂/H₂O/HCl system [48], Scheme 8.

![Scheme 8](image_url)

1,3,5-Triazine amidoximes were synthesized from the corresponding nitriles and hydroxylamine hydrochloride in a water–alcohol solution of sodium bicarbonate [49]. The amidoximes 59 were obtained from the imines 58 and hydroxyl amine hydrochloride [50]; eq. 23.

![eq. 23](image_url)

In the reaction of 4,5-dimethylpyrimidine 60 with EtONO only the activated methyl group at position 4 is nitrosated, and this leads to the formation of 5-methylpyrimidine-4-aldoxime 61 as a sole product [51]. However, the reaction of 1,4,6-trimethyl pyrimidin-2-one 62 with an excess of sodium nitrite to give 4,6-bis(hydroxyiminomethyl)-1-methylpyrimidine 63 [52], Scheme 9.
In a water–alcohol solution of sodium carbonate N-cyano- methyl-o-phenylenediamine 64 was found to react with hydroxylaminehydrochloride to give 2-hydroxyimino-1,2,3,4-tetrahydroquinoxaline 65 via initial formation of and subsequent cyclization [53], eq. 24.
3. Properties and Chemical Reactivities of Amidoximes

3.1. Organic Complexes

Amidoximes can form with chloral bimolecular complexes, which are insoluble in water and soluble in organic solvents. They have sharp melting points and may be used for the identification of amidoximes [54].

\[ \text{N-Phenylbenzamidoxime also can form a complex with chloral} \]
However, oxamidedioxime was reported to react with chloral to give a product \( C_8H_6N_4O_4Cl_2 \) whose structure has not been elucidated [56]. Moreover, trichloroacetic acid yields with an aqueous solution of adipamidedioxime a crystalline precipitate, soluble in alcohol [33] which has not been established definitely whether it is a salt or a molecular complex. Also, the uranyl complex \([\text{UO}_2 (\text{acetamidoxime})_4] (\text{NO}_2)_2\) and \([\text{UO}_2 (\text{benzamidoxime})_4] (\text{NO}_3)_2.xS \) (S= nitromethane or 1,2-dichloroethane, \( x < 1 \) ) were prepared by the reaction uranyl nitrate with the corresponding amidoxime in ethanolic solution, and characterized by thermal analysis and infrared spectroscopy [57].

3.2. Thermal Decomposition

Generally, amidoximes are decomposed when heated in the neighborhood of their melting points. However, benzamidoxime 27, mp \( 80^\circ\text{C} \), was stable up to \( 170^\circ\text{C} \). At this temperature it decomposes, yielding several products which were identified as nitrogen, nitrous oxide, ammonia, water, benzonitrile 17, benzamide 66, 3,5-diphenyl-1,2,4-oxadiazole 20, 3,5-diphenyl-1,2,4-triazole 67 and 2,4,6-triphenyl-1,3,5-triazine 19 [58]; Scheme 10.
Also, the thermal decomposition of \( p \)-phenylsulfonyl benzamidoxime \( 68 \) yields \( p \)-phenylsulfonylbenzamide \( 69 \) and 3,5-diphenylsulfone-1,2,4-oxadiazole \( 70 \) [33], Scheme 11.
3.3. **Thermal Fragmentation of N-Arylbenzamidoxime and O-Phenylsulfonyloxime Derivatives (STP)**

Gaber *et al.* [59] have reported that thermal fragmentation of *N*-arylbenezamide oximes 71a,b (Ar = Ph, *p*-tolyl) under nitrogen gives rise to benzanilide 78 and benzimidazole derivatives 72 as the major products, in addition to benzonitrile 17, arylamines 75, phenols 74, benzoic acid 38, and 2-phenylbenzoxazole 73. In the presence of naphthalene as radical scavenger, *N*-phenylbenzamide oxime gave α- and β-naphthols 76 and 77 in addition to the previous products. Also, heating *N*-phenylbenzamide oxime 71a under reflux in boiling tetralin lead to the formation of 1-hydroxytetralin 81, α-tetralone 80, and 1,1'-bitetralyl 79 as the major products as outlined in Scheme 12.

![Scheme 12](attachment:image)

Analogous results are obtained on heating *N*-arylbenezamide *O*-phenyl sulfonyloximes 82 in the presence of isoquinoline 83 as a radical trap which formed 1-phenylisoquinoline 84 in addition to benzonitrile 17, aniline 75a, diphenylamine 85, benzenesulfonic acid 86, diphenyl sulfone
and 2-phenylbenzimidazole 72a. The isolated products have been interpreted in terms of a free radical mechanism involving the homolysis of N–O and/or C–N bonds [60]; Scheme 13.

![Scheme 13](image)

3.4. Flash Vacuum Pyrolysis of N-Phenylbenzamide Oxime and Related Compounds (FVP)

Recently, Gaber et. al [61] have reported that flash vacuum pyrolysis (FVP) of N-phenylbenzamide oximes 71a-c at 650°C/0.01 Torr lead to the formation of imino-oxadiazole 88 as the major product in addition to N,N',N''-triphenylguanidine 89, 2-phenylbenzimidazole 72a and its derivatives 72b and 72c, 3,5-diphenyl-1,2,4-oxadiazole 20 and its derivatives 90 and 91 which are probably formed by intermolecular cycloaddition of benzonitrile oxide 92 and the diphenylcarbodiimide 93, an
unexpected process to take place under FVP conditions as shown in Scheme 14.

Scheme 14

3.5. Thermal Transformation of Arylamidoximes in the presence of Phosphorous Ylides

It has been reported that the unexpected formation of 3-aryl-5-arylamino-1,2,4-oxadiazoles took place through an aryl migration from the carbon atom to the nitrogen atom of the amidoximes, when arylamidoximes reacted thermally with ethoxycarbonylmethylene (triphenyl)phosphorane. 3,5-Diaryl-1,2,4-oxadiazoles, 3-aryl-5-methyl-1,2,4-oxadiazoles and 3,4-diaryl-1,2,5-oxadiazoles-N-oxide, nitriles, ureas and amides were also isolated suggesting aryl-
3.6. Hydrolysis

Many amidoximes, which form soluble salts with dilute mineral acids and alkalis at room temperature are hydrolyzed completely when heated in the same media [63] into amides and hydroxylamine and under more drastic conditions the amides are hydrolyzed into the corresponding acids 14 as in eq. 25.

\[ \text{eq. 25} \]

At 200°C, a solution of ammonium hydroxide can affect hydrolysis of benzamidoxime 27 into benzamide 66 and ammonium benzoate 96 [64]. Oxamidedioxime 97 is hydrolyzed by concentrated hydrochloric acid into oxalic acid 98, ammonia, and hydroxylamine [65]; Scheme 16.
3.7. Reduction

The reduction of benzamidoxime 27 with sodium amalgam produces ammonia and benzaldoxime 102; most of the amidoxime remains unchanged [66]; eq. 26.

Phenylglyoxalamidoxime 103 has been reduced by hydrogen and palladium/charcoal catalyst to phenylethanolamine 104 [67]; eq. 27.

Amidines 105 can be prepared by reduction of the corresponding amidoximes 27 in the presence of Raney nickel at 60-80°C [68]; eq. 28.
3.8. Oxidation

Oxidizing agents such as potassium ferricyanide, chlorine, or bromine in acetic acid, and iodine in aqueous bicarbonate react with benzamidoxime \(27\) to yield a product \(C_{14}H_{13}N_3O\) which corresponds to an aminodihydrooxadiazole \(106\) [69]; eq. 29.

3.8.1. Oxidation of Arylamidoximes by Hydrogen Peroxide and Horseradish Peroxidase in Water

The oxidation of arylamidoximes \(X-C_6H_4-C(NH_2)=N-OH (X = H, Me, Cl, NO_2, MeO) \(27\) by \(H_2O_2\) in the presence of horseradish peroxidase (HRP) under mild conditions (phosphate buffer pH 7.4, room temperature) to yield the corresponding amides \(66\) and nitriles \(17\) as well as dimeric products of open structures as O-(arylimidoyl)arylamidoximes \(107\) or aminodihydrooxadiazole \(108\) in 30-70 % yields [70]; Scheme 17.
3.8.2. Oxidation of Arylamidoximes by Various Chemical and Biomimetic Systems

Oxidation of 4-chlorobenzamidoxime 109 by various chemical systems leads to the corresponding amide 66 and nitrile 17, and to three dimeric compounds; O-(4-chlorobenzoyl)-4-chlorobenzamidoxime 110, 3,5-(chlorophenyl)-1,2,4-oxadiazole 111 and O-(chlorobenzimidoyl)-4-chlorobenzamidoxime 112 in greatly variable amounts according to the type of the oxidizing agent. Monoelectronic oxidants, such as Pb(OAc)$_4$ and Ag$_2$CO$_3$, selectively led to 4-chlorobenzonitrile, whereas hydroperoxides such as H$_2$O$_2$ and $t$-BuOOH only led to 4-chlorobenzamide. Other oxidants as $m$-chloroperbenzoic acid and Br$_2$ gave more complex mixtures [71]; Scheme 18.

\chem{\begin{align*}
\text{Oxidation} \quad & \quad \text{H}_2\text{O}_2 \\
\text{27} \quad & \quad \text{66} \quad \text{17} \\
\text{107} \quad & \quad \text{or} \quad \text{108}
\end{align*}}

($X=\text{H, }4\text{-CH}_3, 4\text{-NO}_2, 4\text{-CH}_2\text{O, }3\text{-NO}_2$)
It has been reported that microsomal liver cytochromes P450 catalyze the oxidative cleavage of the C=NOH bond of many amidoximes and guanidoximes, and NO synthases (NOS) catalyze the oxidation of $N^ω$-hydroxy-L-arginine 113 (NOHA) with formation of citrulline 114 and nitrogen oxides [72]; Scheme 19.
3.9. Cyclization

3.9.1. Synthesis of New Thiophene, Furan and Pyridine Substituted 1,2,4,5-Oxadiazaboroles

Nine new 3,4,5-trisubstituted 1,2,4,5-oxadiazaborates 117 were prepared by the cyclocondensation reaction of N-substituted thiophene, furan and pyridine carboxamidoximes 115 with phenylboronic acid 116 in refluxing toluene in good yields [73]; Scheme 20.
3.9.2. Synthesis of 3-aryl-5-(n-propyl)-4,5-dihydro-1,2,4-oxadiazoles

The synthesis of 3-aryl-5-(n-propyl)-4,5-dihydro-1,2,4-oxadiazoles 118a–f has been achieved in a facile manner by the reaction of an appropriate arylamidoxime 27 with butyraldehyde. Oxidation of 118a–f individually using MnO$_2$ in CH$_2$Cl$_2$ or sodium hypochlorite in THF/H$_2$O furnished 3-aryl-5-propyl-1,2,4-oxadiazoles 119a-f in good to excellent yields [74], Scheme 21.

\[ \text{Scheme 21} \]

3.9.3. Synthesis of 4,5-dihydro-1,2,4-oxadiazolines from N-unsubstituted amidoximes

4,5-Dihydro-1,2,4-oxadiazolines 120 can be synthesized from aromatic and aliphatic amidoximes 22 by cyclocondensation with aldehydes and ketones [75], Scheme 22.
3.9.4. Synthesis of 3-Aryl-1,2,4-Oxadiazines

An easy and simple synthesis of 3-aryl-trans-5,6-dihydroxy-5,6-dihydro-1,2,4-oxadiazines 123a–e instead of the expected products 122a–e from the reaction of arylamidoximes 27 with glyoxal 121 [76] is shown in Scheme 23.
3.9.5. Synthesis of 1,2,4-Oxadiazoles

The synthesis of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-ones 126a–k from the reaction of methyl levulinate 124 with arylamidoximes 27 to give the intermediate 125 followed by thermal cyclodehydration to generate 126. The reaction was carried out in a microwave oven without any solvent in much shorter time and in yields comparable with conventional heating [77]; Scheme 24.

Moreover, synthesis of 1,2,4-oxadiazoles 128 have been prepared using carboxylic acids 13 which were activated with 1,1'-carbonyl-diimidazole (CDI) as a reagent and then treated with O-acylbenzamidoximes 127 in DMF with additional CDI at 115°C for 6 h. The use of CDI facilitates parallel purification of the oxadiazole products by simple liquid-liquid extraction and filtration [78]; Scheme 25.
Furthermore, it was reported that an existing synthetic route involved the coupling of amidoximes 22 with carboxylic acid 14 in the presence of $O$-benzotriazol-$N,N,N',N'$-tetramethyluroniumtetrafluoroborate (TBTU), 1-hydroxybenzotriazole hydrate (HOBt) and excess $N,N$-diisopropyl ethylamine (DIPEA) followed by in situ thermal cyclization at 110 °C gave 3,5-disubstituted-1,2,4-oxadiazoles 128 [79]; Scheme 26.

Also, the reaction chloroacetamidoxime 129 with cyanoguanidine 130 in the presence of Lewis acids affords 3-chloro-5-guanidino-1,2,4-oxadiazoles 131 via the elimination of the amino group from the amidoxime fragment. 1,2,4-Oxadiazoles bearing the imidazole or pyrimidine moiety were also synthesized using the same approach [80]; eq. 30.
Also, synthesis of 3-aryl-5-decapentyl-1,2,4-oxadiazoles 134a–f from arylamidoximes 27a–f and palmitic acid 132 in the presence of 1,3-dicyclocelhexylcarbodiimide (DCC) via initial formation of aroyloxy-amidines 133a-f and subsequent thermal cyclization at 110°C [81]; Scheme 27.

**Scheme 27**

An efficient method for the synthesis of 3,5-diphenyl-1,2,4-oxadiazole 20 was reported through a one pot reaction of benzonitrile 17 with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with benzoyl chloride under solvent-free conditions using microwave irradiation [82]; eq. 31.
Thus, tetrabutylammonium fluoride (TBAF) was found to be a mild and efficient catalyst for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles 128. Using 0.1–1.0 equivalents of TBAF in THF for 1-24 h at room temperature, alkanoyl- and aroyloxyamidines 133, obtained from 22 by acylator at 0°C, were converted in high yield to the corresponding 3,5-disubstituted-1,2,4-oxadiazoles 128 [83]; Scheme 28.

![Reaction scheme](image)

**Scheme 28**

Furthermore, 3-R-5-R’-1,2,4-oxadiazoles 128 are prepared in good yield by one pot reaction of amidoximes 27 with acyl chlorides in pyridine solution [84]; Scheme 29.

![Reaction scheme](image)

**Scheme 29**

### 3.9.6. Synthesis of 1,2,4-Thiadiazoles

The reaction of carbon disulfide with amidoximes 27 in alkaline alcoholic solution produces 5-mercapto-1,2,4-thiadiazoles 135. In boiling ethanol, benzamidoximes gives with an excess of CS₂ the thiobenz-
amidoxime salt of the thioloxime of benzoyl dithiocarbamic acid 136. Dilute hydrochloric acid hydrolyzes this compound into thiobenzamidine hydrochloride 137 [85]; Scheme 30.

![Scheme 30](image)

**Scheme 30**

### 3.9.7. Synthesis of 1,2,3,5-Oxathiadiazoles

3,4-Disubstituted-2-oxides 138 are prepared in good yields by cyclization of \(N\)-alkyl- and \(N\)-arylamidoximes 71 with thionyl chloride in the presence of pyridine or triethylamine [86]; Scheme 31.

![Scheme 31](image)

**Scheme 31**

<table>
<thead>
<tr>
<th>( R )</th>
<th>( R' )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( m-ClC_6H_5 )</td>
<td>Ph</td>
</tr>
<tr>
<td>( p-ClC_6H_5 )</td>
<td>Ph</td>
</tr>
<tr>
<td>( p-MeOC_6H_5 )</td>
<td>CH_3</td>
</tr>
<tr>
<td>( p-CH_3C_6H_5 )</td>
<td>Ph</td>
</tr>
<tr>
<td>Ph</td>
<td>(CH_3)_2C</td>
</tr>
<tr>
<td>CH_3</td>
<td>( p-ClC_6H_5 )</td>
</tr>
</tbody>
</table>
3.9.8. Cyclization and Rearrangement of N-Arylbenzamidoximes by Reaction with Nitrile Oxides

Reaction of N-aryl benzamidoximes 71 with nitrile oxides 92 and 139 in refluxing toluene at 100°C mainly leads to 1,2,4-oxadiazole 4-oxides 140-143 and benzotriazines 144. A facile 5-exo-trigonal cyclization and an unusual [3,5] rearrangement are postulated to account for the observed results [87]; Scheme 32.

\[
\begin{align*}
\text{Ar}^+\text{CNO}^+ & \quad \text{Ar}^-\text{N}^+\text{O}^- \\
\text{NH} & \quad \text{HO} \\
\text{X} & \quad \text{Z} & \quad \text{Y} & \quad \text{Ar} \\
71 & \quad 140-143 & \quad 144
\end{align*}
\]

<table>
<thead>
<tr>
<th>71, 144</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Ar</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>b</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4-MeC₆H₄</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>4-MeC₆H₄</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>C₆H₅</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>4-MeC₆H₄</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>C₆H₅</td>
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<tr>
<td>h</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>4-MeC₆H₄</td>
</tr>
</tbody>
</table>

92, Ar’ = C₆H₅ 
139, Ar’ = 4-MeC₆H₄ 
140, Ar = Ar’ = C₆H₅ 
141, Ar’ = Ar = 4-MeC₆H₅ 
142, Ar = C₆H₅; Ar’ = 4-MeC₆H₄ 
143, Ar = 4-MeC₆H₄; Ar’ = C₆H₅

Scheme 32

3.9.9. Cycloaddition of Nitrile Oxides to Amidoximes

The nitrile oxides were generated in situ by adding the hydroximoyl chlorides 30 to N,N-diethylamidoximes 146 and triethylamine in benzene. The primary cycloadducts spontaneously aromatize with loss of diethylamine affording the 1,2,4-oxadiazoles-4-oxides 96. The latter compound undergoes deoxygenation with triethylphosphite in boiling benzene to give the oxadiazoles 128 [88]; Scheme 33.
3.9.10. Synthesis of Benzimidazoles from N′- Aryl-N-Hydroxyamidines

Partridge and Turner [90] have reported that 2-substituted benzimidazoles 72 can be prepared by treatment of an N′-aryl-N-hydroxyamidine 71 with benzenesulphonyl chloride in the presence of base under anhydrous conditions to give o-benzenesulfonyl-N-substituted benzamidine 147 followed by thermal cyclization; Scheme 34.

3.9.11. Beckmann Transformation of Amidoximes

Tiemann [91] reported that amidoximes 22 have been converted into unsymmetrical ureas when treated with benzenesulfonyl chloride and then with water forming its O-benzenesulfonyl derivative 148 which undergoes a Beckmann transformation into an O-benzenesulfonylisourea 149.
Subsequent hydrolysis yielded the asymmetrical urea 150; Scheme 35.
4. Application of Amidoximes

4.1. Chemotherapeutic Properties of Amidoximes

Several papers have been published concerning the anti-bacterial activity of amidoximes, compared with amidines. *p*-Sulfamidobenzamidoxime, for example has a slightly superior activity over the corresponding amidine on experimental typhus infections in mice [92, 93]. However, in most cases, the introduction of the oxygen atom decreases the anti-bacterial power of the amidines, together with their toxicity [94].

Lamb and White [95] have studied the trypanocide activity of several diamidoximes. Also, 2-methoxy-9-aminoacridine-6-amidoxime and 9-anilacridine-3-amidoxime are patented as products having pharmacological properties and useful in therapeutics [96]. Some halogenated phenols carrying an amidoxime group are active against *Mycobacterium tuberculosis, in vitro* [97].

4.2. Antimalarial Activity of Amidoximes

It has been reported that amidoxime and *O*-substituted derivatives of the bis-alkylamidine 1,12-bis(*N*,*N*-acetamidinyl) dodecane 151 were synthesized and evaluated as *in vitro* and *in vivo* antimalarial prodrugs. The bis-*O*-methylsulfonylamidoxime 152 derivatives show relatively potent antimalarial activity after oral administration [98]; Scheme 36.

![Scheme 36](image)
4.3. Anti-pneumocystis Activities of Aromatic Diamidoximes Prodrugs

Aromatic dicationic compounds, such as pentamidine, have potent antimicrobial activities. Clinical use of these compounds has been restricted, however due to their toxicity and limited oral activity.

A novel approach, using amidoxime derivatives as prodrugs, has recently been proposed to overcome these limitations. Although results were presented for amidoxime derivatives of only one diamidine, pentamidine, the authors in the original proposal claimed that amidoxime derivatives would work as effective prodrugs for all pharmacologically active diamidines. Nine novel amidoxime derivatives were synthesized and tested in this study for activity against *Pneumocystis carinii* in corticosteroid-suppressed rats. Only three of the nine compounds had significant oral anti-*Pneumocystis* activity. The bisbenzamidoxime derivatives of three direct pentamidine analogs had excellent oral and intravenous activities and reduced acute host toxicity. These compounds are not likely candidates for future drug development, however, because they have chronic toxic effects and the active amidine compounds have multiple sites susceptible to oxidative metabolism, which complicates their pharmacology and toxicology.

Novel diamidoximes from three other structural classes, containing different groups linking the cationic moieties, lacked significant oral or intravenous anti-*Pneumocystis* activity, even though the corresponding diamidines were very active intravenously. Both active and inactive amidoximes were readily metabolized to the corresponding amidines by cell-free liver homogenates. Thus, the amidoxime prodrug approach may provide a strategy to exploit the potent antimicrobial and other pharmacological activities of selected, but certainly not all, aromatic diamidines [99].
4.4. Miscellaneous uses of Amidoximes

It has been reported that many drugs containing an amidoxime function are biologically active and display antihypertensive, antibacterial, antitrypanocid, or cytostatic properties [17]. They are mainly used as NO generators in vivo, having neuromodulatory and neurotransmitory actions [100].

Also, cyclic amidoximes were reported to possess anamnestic and antihypoxive activity [101], hypotensive activity [102].

Furthermore, amidoximes are less basic than amidines and are not protonated under physiological conditions, enhancing intestinal absorption by diffusion [103]. Endogenous cellular reductases reduce amidoximes to amidines. In addition to two antithrombotic drugs, sibrafibran and ximelagatran, were developed using this principle of latentiation [104].
EXPERIMENTAL


**EXPERIMENTAL**

**Instruments and Techniques:**

The following instruments have been used in this experimental work:

1. **Melting Point Apparatus (MP):**
   All melting points were determined on Gallen-Kamp melting point apparatus.

2. **Infra-Red Spectrophotometer (IR):**
   FT-IR spectra were recorded using Perkin-Elmer 100 series at Faculty of Science, King Abdul-Aziz University, Jeddah.

3. **Proton Nuclear Magnetic Resonance spectrophotometer (\(^1\)H-NMR):**
   \(^1\)H-NMR spectra were carried out using 600 MHz Bruker, AVANCE III- Cryo Probes and TMS as an internal standard at Faculty of Science, King Abdul-Aziz University, Jeddah.

4. **Carbon Nuclear Magnetic Resonance spectrophotometer (\(^{13}\)C-NMR):**
   \(^{13}\)C-NMR spectra were carried out using 150 MHz Bruker, AVANCE III- Cryo Probes at Faculty of Science, King Abdul-Aziz University, Jeddah.

5. **Mass spectrophotometer (MS):**
   Direct MS spectra were carried out using quadruple MS (Electronic ionization mode EI mode with source temperature: 200°C), at 70 eV at Cairo University, EGYPT.

6. **Gas Chromatography/ Mass spectrophotometer (GC/MS):**
   GC/MS analysis were carried out using Perkin Elmer clarus 500 provided with Perkin Elmer clarus 500 MS detector using capillary column: DB-5 with length 30 m, internal diameter 0.25 mm, film thickness 0.25 µm with carrier gas Helium, initial temperature 80°C and final temperature 280°C, rate of heating 10°C/min and injector temperature 280 °C/min, and then programmed to 300°C at 3°C/min
and held isothermally for 10 min at Petroleum Research Institute, EGYPT.

7. Elemental analysis were performed on Perkin Elmer's 2400, Series II Microanalyzer at Faculty of Science, King Abdul-Aziz University, Jeddah.
1. Preparation of \(N-p\)-Substituted Phenylbenzamide Oxime I-III

1.1. Preparation of \(N-p\)-Chlorophenylbenzamide Oxime I

This procedure has been passed through two steps:

**Step 1: Preparation of \(N-p\)-chlorophenylbenzamidine 154**

To stirred benzonitrile 17 (4.99 ml, 0.05 mol) at *ca*. 20°C was added portion wise powdered anhydrous \(\text{AlCl}_3\) (13.34 g, 0.1 mol). The reaction mixture was then heated (*ca*. 100°C) until a homogenous melt was formed. To this was added \(p\)-chloroaniline 153 (6.37 gm, 0.05 mol) and the mixture was heated for 6 h and then allowed to cool down to *ca*. 20°C. The resultant solid mass was then crushed and slurred in 12.5% NaOH (40 mL). The resulting mixture was extracted with dichloromethane (DCM), washed with (H\(_2\)O) and dried over (Na\(_2\)SO\(_4\)). This compound 154 was obtained as colourless needles (89%), mp 115-116°C (cyclohexane: EtOH, 95:05 v/v); \(R_f = 0.86\) (t-BuOMe).

```
N \(\text{Cl}\) \(\text{H}_2\text{N}\)
17
N
```

**Step 2: Preparation of \(N-p\)-chlorophenylbenzamide oxime I**

\(N-p\)-Chlorophenylbenzamidine 154 (11.53 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline to brilliant-yellow with ammonia, and boiled for a further 10 min. The solid which was separated furnished the pure \(N-p\)-chlorophenylbenzamide oxime I, as colourless needles, yield 80%, mp 175-178°C.
IR (KBr, cm\(^{-1}\)): 3400 (OH), 3340 (NH), 3150 (CH aromatic), 1620 (C=C aromatic), 1390 (C-N), 1195 (C-O).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 7.41 (m, 3H), 7.34 (s, 1H, NH), 7.32 (m, 2H), 7.05 (dd, 2H, \(J = 3.0, 9.0\) Hz), 6.58 (dd, 2H, \(J = 3.0, 9.0\) Hz), 9.36 (br, 1H, OH); (fig. 1).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 151.5 (C=N-OH), 138.19 (C), 130.5 (C), 129.9 (C), 128.7 (2CH), 128.5 (2CH), 128.3 (2CH), 127.8 (C-Cl), 122.3 (2CH); (fig. 2).

MS (EI, 200\(^\circ\)C), \textit{m/e} (%): 246 (M\(^+\), 35), 228 (40), 214 (25), 127 (100), 104 (36), 77 (70), 51 (24); (fig. 3).

Elemental analysis calculated for C\(_{13}\)H\(_{11}\)ClN\(_2\)O: C, 63.29; H, 4.49; N, 11.36 %.

Elemental analysis found: C, 62.98; H, 4.60; N, 11.40 %. 
Thermal fragmentation of $N$-$p$-chlorophenylbenzamide oxime I

**General Procedure:**

In a 50 ml round bottom flask equipped with an efficient reflux condenser provided with a gas trap was placed of $N$-$p$-chlorophenylbenzamide oxime I (1g). The flask was heated under reflux at 220-250ºC for 5 h using a temperature controlled hot plate with thermocouple to the required temperature under nitrogen stream with a constant rate. The gases evolved were detected by chemical means (NH$_3$ by Nessler's reagent and nitrogen gas collected was detected by GLC). After decomposition was complete as judge by TLC monitoring the products were separated into neutral, phenolic and basic component as reported in a previous work [105]. The pyrolysate was dissolved in ether and shaken several times with ethanolic potassium hydroxide (Claisen's solution) to separate into neutral and phenolic components. The Claisen extract was acidified with 2M HCl and the liberated phenols were extracted with ether. Ether was evaporated in vacuo, phenolic compounds was separated into its constituents by fractional distillation under reduced pressure, whereupon the following compounds were obtained:

$p$-Chlorophenol 155 collected at bp 130-135ºC/ 5 Torr; mp 43-45ºC.

The remaining residue (non-distillable) was separated by column chromatography on Kieselgel 60 (0.040-0.063 mm) as follows:

2-Amino-5-chlorophenol 156 was eluted using light pet. ether (40-60ºC)-benzene as mixture (1:1 v/v), mp 152-154ºC (lit.[106]; mp 155-157ºC).

$^1$H-NMR (600MHz, CDCl$_3$) $\delta$ 6.70 (d, 1H, $^3$J = 8.3 Hz), 6.64 (m, 1H, Ph-H), 6.72 (d, 1H, $^4$J = 2.3 Hz).

Moreover, the neutral fractions were extracted with ether. Ether was evaporated in vacuo. Benzoic acid 41 was identified by preparative TLC using pet. ether (60-80ºC)-acetone (5:1 v/v), $R_f$ = 0.065; mp and mmp 120ºC.
The residue was digested in dilute HCl solution followed by extraction with ether to dissolve the neutrals. The amines hydrochlorides were made alkaline by sodium carbonate solution to free the amines. The amines fraction was subjected either to fractional vacuum distillation or by column chromatography as mentioned in specific experiments.

Amino fraction was separated into its constituents by fractional vacuum distillation as follows:

**Fraction (a):** Benzonitrile 17, collected at bp 41-45ºC/ 3 Torr; on hydrolysis gave benzoic acid, mp and mmp 120ºC.

**Fraction (b):** p-Chloroaniline 153, collected at bp 182-188ºC/ 6 Torr; mp 69-73ºC.

The non distillable residue was separated by column chromatography to separate the charred materials that remained on the column as follows:

**Fraction (a):** N-(4-Chlorophenyl)benzamide 157 was eluted using light pet. ether (60-80ºC)-benzene as eluent (1:1 v/v), as colorless crystals from ethanol: H2O; mp 192-193ºC (lit. [107], mp 188-190ºC).

1H-NMR (600 MHz, CDCl3) δ: 7.865 (d, 2H, J = 8.4 Hz), 7.84 (br, 1H, NH), 7.61 (d, 2H, J = 8.4 Hz), 7.57 (d, 1H, J = 7.8 Hz), 7.51 (d, 2H, J = 7.8 Hz), 7.34 (d, 2H, J = 4.8 Hz); (fig. 4).

13C-NMR (150 MHz, CDCl3) δ: 165.69 (C=O, amid), 136.44 (C), 134.57 (C), 132.08 (C-Cl), 129.5 (2CH), 129.22 (2CH), 128.87 (2CH), 126.98 (2CH), 121.36 (CH); (fig. 5).

MS (EI, 200ºC); (m/e %): m/e 231 (M+ 16), 105 (100), 77 (47), 51 (17); (fig. 6).

**Fraction (b):** 3,6-Dichloro-9H-carbazole 158 was eluted using light pet-ether (60-80ºC)-benzene (1:2 v/v) as eluent, mp 202-204ºC (lit. [108], mp 204-206ºC).

1H-NMR (600 MHz, DMSO-d6) δ: 10.92 (br, 1H, NH), 9.14 (d, 2H, H4,5), 8.22 (dd, 2H, H2,7), 7.36 (d, 2H, H1,8); m/e 236.
Fraction (c): 5-Chloro-2-phenyl-1H-benzimidazole 159 was eluted using 2% ether-pentane as eluent, as pale brown solid, mp 210-212°C (lit. [109], mp 206-210°C).

$^1$H-NMR (600 MHz, DMSO-$d_6$) $\delta$ 7.3 (d, 1H, $J = 9.0$ Hz), 7.4 (d, 2H, $J = 8.8$ Hz), 7.6-7.8 (t, 4H, $J = 6$ Hz), 8.2 (d, 1H, $J = 8.0$ Hz), 7.88 (s, 1H, NH); (fig. 7).

MS (EI, 200°C); (m/e %): 228 (M*, 100), 194 (28), 158 (32), 104 (11), 94 (32), 77 (38), 63 (20); (fig. 8).

Elemental analysis calculated for C$_{13}$H$_9$N$_2$Cl: C, 68.42; H, 3.95; N, 12.28 %. Found; C, 68.45; H, 3.91; N, 12.28 %.
Thermal fragmentation of \( N-p \)-Chlorophenylbenzamide Oxime I in the Presence of Naphthalene.

It was done as mentioned previously whereby \( N-p \)-chlorophenyl benzamide oxime I (1g) in naphthalene (0.5 g) as radical scavenger was heated for 5h. The contents of the flask were separated by chemical means into neutral, phenolic and basic components.

Fractionation of the phenolic products by distillation under reduced pressure gave the following fractions:

**Fraction (a):** \( \alpha \)-Naphthol 76, collected at bp 95-110ºC/ 6 Torr; mp and mmp 96 ºC.

**Fraction (b):** \( \beta \)-Naphthol 77, collected at bp 150-158ºC/6 Torr; mp and mmp 117-119ºC ; its benzoate and picrate derivatives mp 106ºC and 142 ºC; respectively.

Estimation of both \( \alpha \) and \( \beta \)-naphthols by GLC were in the ratio 1:6, respectively as 16% yield.
Thermal Fragmentation of \(N-p\)-Chlorophenylbenzamide Oxime I in the Presence of Tetralin.

The \(N-p\)-chlorophenylbenzamide oxime I (1g) was placed in a 100 ml three necked flask with a gas inlet and condenser and heated under reflux at boiling anhydrous tetralin (25 ml) (distillation over lithium aluminum hydride under nitrogen) bp ca. 210°C for 8h.

The pyrolysate was evaporated in vacuo then the resulting residue was extracted with ether and was evaporated to dryness then subjected to distillation under reduced pressure for separation of lower boiling products such as benzonitrile, \(p\)-chlorophenol and \(p\)-chloroaniline as mentioned and discussed before, whereas the following fraction were separated as follows:

**Fraction (a):** \(\alpha\)-Tetralone 78 was collected at bp 113-116°C/ 6 Torr; \(n^\text{D}_{20}\): 1.5679; m/e 146.

**Fraction (b):** 1-Hydroxytetralin 81 was collected at bp 102-105°C/ 2 Torr as pale yellow oil; \(n^\text{D}_{20}\): 1.5638; phenyl urethane derivative (ligroin), mp and mmp 120-122°C; m/e 148.

The remaining residue was subjected to further separation into its constituents by column chromatography using ether-pentane as eluent as discussed before.

**Fraction (c):** 1,1-Bitetralyl 79 eluted from column chromatography using 2% ether-pentane mixture; mp and mmp 113°C; on heating with elemental sulfur give bis-naphthylene [110]; m/e 262.
1.2. Preparation of \( \text{N-}p\text{-Nitrophenylbenzamide Oxime II} \)

This procedure has been passed through two steps:

**Step 1: Preparation of \( \text{N-}p\text{-nitrophenylbenzamidine 161} \)**

To stirred benzonitrile 17 (4.99 mL, 0.05 mole) at \( ca. \) 20 °C was added portionwise powdered anhydrous AlCl\(_3\) (13.34 g, 0.1 mole). The reaction mixture was then heated (\( ca. \) 100°C) until a homogenous melt was formed. To this was added \( p\)-nitroaniline 160 (6.906 gm, 0.05 mole) and the mixture was heated for 8 h and then allowed to cool to \( ca. \) 20°C. The resultant solid mass was then crushed and slurred in 12.5% NaOH (40 mL). The resulting mixture was extracted with dichloromethane (DCM), washed with (H\(_2\)O) and dried over (Na\(_2\)SO\(_4\)). This compound 161 was obtained as yellow needles (21%), mp 164.5-165°C (benzene); \( R_f = 0.74 \) (t-BuOMe).

\[
\begin{align*}
\begin{array}{c}
\text{CN} \\
17
\end{array} + 
\begin{array}{c}
\text{H}_2\text{N} \\
160
\end{array} 
& \xrightarrow{\text{AlCl}_3} 
\begin{array}{c}
\text{N} \\
161
\end{array} 
\end{align*}
\]

**Step 2: Preparation of \( \text{N-}p\text{-nitrophenylbenzamide oxime II} \)**

\( \text{N-}p\text{-Nitrophenylbenzamidine 161} \) (12.06 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline to Brilliant-yellow with ammonia, and boiled for a further 10 min. The solid which separated furnished the pure \( \text{N-}p\text{-nitrophenylbenzamide oxime II} \), as yellow needles, yield 25%, mp 82-83°C.
IR (KBr, cm\(^{-1}\)): 3472 (OH), 3320 (NH), 3077.19 (CH aromatic), 1591 (C=C aromatic), 1323.9 (C-N), 1251 (C-O).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 9.64 (br, 1H, OH), 7.98 (d, 2H, \(J = 9.0\) Hz), 7.61 (br, 1H, NH), 7.46 (m, 3H), 7.4 (d, 2H, \(J = 7.5\) Hz), 6.63 (d, 2H, \(J = 9.0\) Hz); (fig. 11).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 150.1 (C=NOH), 145.46 (C), 141.93 (C-NO\(_2\)), 130.6 (C), 130 (CH), 129.03 (2CH), 128 (2CH), 125 (2CH), 118.8 (2CH); (fig. 12).

MS (EI, 200°C), \(m/e\) (%): 257 (M\(^+\), 18), 241 (26), 209 (11), 194 (21), 138 (32), 105 (95), 77 (100), 64 (12), 51 (30); (fig. 13).

Elemental analysis calculated for C\(_{13}\)H\(_{11}\)N\(_3\)O\(_3\): C, 60.00; H, 4.31; N, 16.33 %. Found: C, 61.20; H, 4.29; N, 16.35 %. 
Thermal Fragmentation of \textit{N-p}-Nitrophenylbenzamide Oxime II

In 100 ml three necked flask, the \textit{N-p}-nitrophenylbenzamide oxime II was heated at 220-250\(^\circ\)C under nitrogen atmosphere for 5h as mentioned before.

The contents of the flask were dissolved in ether and shaken several times with Claisen's solution to dissolve the resulting phenol. The ethereal layer containing the neutral and basic products was shaken several times with dilute hydrochloric acid to extract the basic products (B), leaving the neutral products (A) alone in the ethereal layer, which was washed with water, dried over anhydrous MgSO\(_4\) and evaporated.

The Claisen' extract was concentrated to remove some of the methanol and then acidified with aqueous hydrochloric acid to liberate the phenolic products (C).

The phenolic products (C) were subjected to fractional distillation under reduced pressure whereby the following fractions were obtained:

\textbf{Fraction (a)}: \textit{p}-Nitrophenol \textbf{162}, collected at bp 188-195\(^\circ\)C/ 8 Torr; mp 114-116\(^\circ\)C.

The basic products (B) were distilled under reduced pressure to give the following fractions:

\textbf{Fraction (a)}: Benzonitrile \textbf{17} collected at bp 41-45\(^\circ\)C/ 3 Torr; on hydrolysis gave benzoic acid, mp and mmp 121\(^\circ\)C.

\textbf{Fraction (b)}: \textit{p}-Nitroaniline \textbf{160}, collected at 195-200\(^\circ\)C/ 6 Torr; mp and mmp 146-148\(^\circ\)C.

Quantitative separation of the remaining residue (non-distillable) of basic products by column chromatography using gradient elution technique as mentioned previously to give the following products as follows:

\textbf{Fraction (a)}: \textit{p}-Nitroaniline \textbf{160} (in part) was eluted using light pet. ether (60-80\(^\circ\)C) as eluent, mp and mmp 146-148\(^\circ\)C.
**Fraction (b):** *N-(p-Nitrophenyl)benzamide** 163 was eluted using pet. ether (60-80°C)-benzene (1:1 v/v) as eluent, as a pale yellow crystal, mp 197-199°C (lit. [108], mp 196-198°C); \( R_f = 0.69 \) (50:50 acetone/hexane).

IR (KBr, cm\(^{-1}\)): 3336.9, 1656.8, 1612.3, 1505, 1406, 1351.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.52 (m, 2H), 7.59 (m, 1H), 7.85 (m, 4H), 8.06 (br, s, 1H), 8.25 (d, 2H, \( J = 9.07 \) Hz).

MS calculated for \( C_{13}H_{10}N_2O_3 \) (M-H) 242.06, found 242.21; (fig. 14).

**Fraction (c):** *3,6-Dinitro-9H-carbazole** 164 was eluted using pet. ether (60-80°C)-benzene (1:2 v/v) as eluent, mp 296-300°C (lit. [111], mp and mmp 307-310°C).

IR (KBr pellet, cm\(^{-1}\)): (3421, 3345), 3019, (2922, 2848), 1618, 1583, 1517, 1339.

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \( \delta \) 11.10 (S, br, 1H, NH), 9.34 (d, 2H, H\(_{4,5}\), \( J = 2.3 \) Hz), 8.40 (dd, 2H, H\(_{2,7}\), \( J = 2.3 \) Hz, \( J = 8.9 \) Hz), 7.78 (d, 2H, H\(_{1,8}\), \( J = 8.9 \) Hz).

Elemental analysis calculated for (\( C_{12}H_7N_3O_4 \)): C, 56.03; H, 2.72; N, 16.34%. Found: C, 56.08; H, 2.74; N, 16.11%; m/e 257.

**Fraction (d):** *6-Nitro-2-phenylbenz[d]oxazole** 165 was eluted using 1% ether-pentane as eluent, mp 178-180°C (lit. [112], mp and mmp 180-182°C); m/e 240 (M\(^+\), 100), 194 (22).

**Fraction (e):** *5-Nitro-1,2-diphenylbenzimidazole** 166 was eluted using 2% ether-pentane as eluent, m.p 181-182°C (lit. [113], mp and mmp 182-184°C).

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \( \delta \) 7.1-7.2 (d, 2H, \( J = 8.8 \) Hz), 7.3 (t, 1H, \( J = 6.7 \) ), 7.3 (t, 1H, \( J = 6.7 \) Hz), 7.4-7.5 (m, 5H, Ph), 8.12-8.36 (m, 5H, Ph); m/e 315.

**Fraction (f):** *5-Nitro-2-phenyl-1H-benzimidazole** 167, eluted using 2% ether-pentane as eluent, mp 208-210°C (lit [114], mp and mmp 207-209°C).
$^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ 9.35 (br, 1H, NH), 8.23 (dd, 2H, $J = 8.8$, 2.2 Hz), 7.87 (d, 2H, $J = 6.8$ Hz), 7.51 (m, 3H, Ph), 7.10 (d, 1H, $J = 2.2$ Hz); (fig. 15).

MS (EI, 200ºC), m/e (%): 240 (M$^+$, 100), 210 (55), 166 (65), 139 (30), 63 (60); (fig. 16).

Elemental analysis calculated for (C$_{13}$H$_9$N$_3$O$_2$): C, 65.27; H, 3.77; N, 17.57 %. Found: C, 65.28; 3.79; N, 17.53 %. 
1.3. Preparation of \(N\text{-}p\text{-}Methoxyphenylbenzamide Oxime III\)

This procedure has been passed through two steps:

**Step 1: Preparation of \(N\text{-}p\text{-}Methoxyphenylbenzamidine 169\)**

To stirred benzonitrile 17 (4.99 mL, 0.05 mole) at \(ca. 20^\circ C\) was added portionwise powdered anhydrous \(\text{AlCl}_3\) (13.34 g, 0.1 mole). The reaction mixture was then heated (\(ca. 100^\circ C\)) until a homogenous melt was formed. To this was added \(p\text{-}anisidine 168\) (6.15 gm, 0.05 mole) and the mixture was heated for 4 h and then allowed to cool to \(ca. 20^\circ C\). The resultant solid mass was then crushed and slurried in 12.5 \% NaOH (40 mL). The resulting mixture was extracted with dichloromethane (DCM), washed with (H\(_2\)O) and dried over (Na\(_2\)SO\(_4\)). This compound 169 was obtained as colourless plates, mp 114-115\(^\circ\)C, yield 93 \%, (cyclohexane : EtOH, 95:05 v/v); \(R_f = 0.36\) (t-BuOMe).

\[
\begin{array}{c}
\text{CN} + \text{H}_2\text{N} \xrightarrow{\text{AlCl}_3} \text{NH} \\
17 \quad 168 \quad 169 \quad \text{OCH}_3
\end{array}
\]

**Step 2: Preparation of \(N\text{-}p\text{-}Methoxyphenylbenzamide Oxime III\)**

\(N\text{-}p\text{-}Methoxyphenylbenzamidine 169\) (11.313 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g., 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline to brilliant-yellow solution with ammonia, and boiled for a further 10 min. The solid separated furnished the pure benzamidoxime, as colourless needles, yield 30 \%, mp 157-159\(^\circ\)C.
IR (KBr, cm$^{-1}$): 3400 (OH, NH), 3050 (CH aromatic), 2910 (CH aliphatic), 1615 (C-N), 1080 (C-O).

$^1$H-NMR (600 MHz, CDCl$_3$) δ: 7.46 (dd, 2H, $J = 3.6, 1.8$ Hz), 7.34 (m, 1H, Ph-H), 7.28 (dd, 2H, $J = 4.8, 1.2$ Hz), 6.66 (s, 5H, Ph-H), 3.70 (s, 3H, O-CH$_3$); (fig. 18).

$^{13}$C-NMR (150 MHz, CDCl$_3$) δ: 155.67 (C=N-OH), 152.58 (C-O-CH$_3$), 132.73 (CH), 131.06 (C), 129.46 (C), 128.5 (2CH), 128.3 (2CH), 123.8 (2CH), 113.9 (2CH), 55.34 (CH$_3$); (fig. 19).

MS (EI, 200°C), m/e (%): 242 (M$^+$, 90), 208 (100), 224 (60), 108 (71), 122 (70), 95 (26), 77 (60); (fig. 20).
Thermal Fragmentation of \(N-p\)-Methoxyphenylbenzamide Oxime III

It was worked-up and heated under the same conditions and the pyrolysate was separated by chemical means as mentioned previously.

The phenolic components was separated by fractional vacuum distillation into the following fractions:

Fraction (a): Phenol 74a, collected at bp 70-75\(^\circ\)C/ 5 Torr; picrate derivative, mp and mmp 83\(^\circ\)C; phenyl urethane, mp and mmp 126\(^\circ\)C and further identified by chemical test [115].

Fractionation of the basic products by distillation under reduced pressure to give the following fractions:

Fraction (a): Benzonitrile 17 was separated as mentioned before.

Fraction (b): \(p\)-Anisidine 168, collected at bp 174-178\(^\circ\)C / 6 Torr; mp and mmp 57-59 \(^\circ\)C.

Quantitative separation of the basic products was done by column chromatography into the following fractions:

Fraction (a): \(N\)-(4-Methoxyphenyl)benzamide 170 was eluted using light pet. ether (60-80\(^\circ\)C)-benzene (1:1 v/v), mp 134-135\(^\circ\)C (lit [116], mp 133-135\(^\circ\)C).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 3.79 (s, 3H, OCH\(_3\)), 6.88 (d, 2H, \(J = 8.90\) Hz), 7.50 (m, 5H, Ph-H), 7.79 (Br, s, 1H), 7.84 (d, 2H, \(J = 7.5\) Hz).

MS calculated for C\(_{14}\)H\(_{13}\)NO\(_2\) (M+H) 228.09, found 228.26.

MS (EI, 200\(^\circ\)C), m/e (%): 227 (42), 105 (100), 77 (40), 50 (10); (fig. 21).

Fraction (b): 3.6-Dimethoxy-9H-carbazole 171 was eluted using pet, ether (60-80\(^\circ\)C)-benzene (1:2 v/v) as eluent, mp and mmp 131-133\(^\circ\)C (lit. [117], mp 133-135\(^\circ\)C).

\(^1\)H-NMR (600 MHz, acetone-d\(_6\)) \(\delta\) 7.63 (s, 2H, Ph -H), 7.35-7.37 (d, 2H, Ph -H), 6.98-7.00 (dd, 2H, Ph -H), 3.86 (s, 6H, 2OCH\(_3\)).
Elemental analysis calculated for (C₁₄H₁₃NO₂): C, 73.99; H, 5.77; N, 6.16 %. Found: C, 73.98; H, 5.16; N, 6.09 %; m/e 227.

**Fraction (c):** 6-Methoxy-2-phenylbenz[d]oxazole 172 was eluted using 1% ether-pentane as eluent, as white solid, mp 66-69°C (lit [118], mp 68-70°C); TLC (30 % ethyl acetate/ hexane), R_f = 0.55.

IR (KBr, cm⁻¹): 3069, 2999, 2935, 2835, 1453.

¹H-NMR (600 MHz, CDCl₃) δ: 8.21-8.19 (m, 2H), 7.65 (d, 1H, J = 8.7 Hz), 7.51-7.49 (m, 3H), 7.11 (d, 1H, J = 2.4 Hz), 3.87 (s, 3H).

MS (EI, 200ºC): m/e (%) 225 (M⁺, 10), 210 (20), 209 (100), 181 (22), 103 (30), 79 (38), 64 (10), 51 (16), (fig. 22).

**Fraction (d):** 5-Methoxy-2-phenyl-1H-benzimidazole 173 was eluted using 2% ether-pentane as eluent, as a pale yellow solid, mp 142-144°C (lit [90], mp 145-146°C).

IR (KBr, cm⁻¹): 3411, 3016, 2920, 2849, 1631, 1594, 1270.

¹H-NMR (600 MHz, CDCl₃) δ: 8.37 (d, 2H, J = 7.8Hz), 7.74 (br,1H, NH), 7.71 (d, 1H, J = 9.0 Hz), 7.66 (m, 3H), 7.29 (d, 1H, J = 2.4 Hz), 7.12 (dd, 1H, J = 6.6Hz, 2.4 Hz), 3.86 (s, 3H, OCH₃); (fig. 23).

¹³C-NMR (150 MHz, CDCl₃) δ: 158.5 (C-OCH₃), 147.7 (C), 133 (2C), 129.5 (2CH), 127.7 (2CH), 123 (C), 116.3 (CH), 114.7 (CH), 96.1 (CH), 55.9 (O-CH₃); (fig. 24).

MS (EI, 200ºC), m/e (%): 224 (M⁺, 100), 209 (95), 181 (35), 154 (18), 77 (20); (fig. 25).
2. Preparation of $N$-$p$-Substitutedphenyl Nicotinamide Oxime IV-VI

2.1. Preparation of $N$-Phenylnicotinamide Oxime IV

This procedure involved two steps:

**Step 1: Preparation of $N$-phenylnicotinamidine 175**

To stirred anhydrous AlCl$_3$ (6.667 gm, 0.05 mole) was slowly added a mixture of 3-cyanopyridine 174 (5.205 gm, 0.05 mole), aniline 71a (4.54 mL, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with NaOH (5 N). The resulting mixture was extracted with chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80°C). The resulting solid was recrystallized from benzene, yield 58.82 %; mp 106-108°C.

![Chemical Reaction](image)

**Step 2: Preparation of $N$-phenylnicotinamide oxime IV**

$N$-Phenylnicotinamidine 175 (9.86 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for further 10 min. The residue was treatment from petroleum ether (60-80°C). The solid which separated furnished the pure nicotinamidoxime, as beige crystals on recrystallization from benzene, mp 160-162°C, yield 39.2 %; $R_f = 0.102$ (acetone: pet. ether (60-80°C), 3:7 v/v).
IR (KBr, cm$^{-1}$): 3367 (OH), 3050 (CH aromatic), 1620 (C=C), 1378 (C-N), 1235 (C-O).

$^1$H-NMR (600 MHz, DMSO-d$_6$) $\delta$: 10.78 (s, 1H, OH), 8.57 (d, 1H, $J = 3$ Hz), 8.55 (d, 1H, $J = 6.6$ Hz), 8.5 (s, 1H), 7.67 (d, 1H, $J = 8.4$ Hz), 7.36 (s, 1H, NH), 7.35 (m, 1H), 7.09 (dd, 1H, $J = 7.2, 1.2$ Hz), 6.82 (s, 1H), 6.66 (dd, 2H, $J = 1.2, 7.8$ Hz); (fig. 27).

MS (EI, 200$^\circ$C), $m/e$ (%): 213 (M$^+$, 62), 196 (100), 181 (21), 93 (94), 77 (53), 51 (32); (fig. 28).

Elemental analysis calculated for C$_{12}$H$_{11}$N$_3$O: C, 67.59; H, 5.20; N, 19.71%. Found: C, 67.53; H, 5.27; N, 20.03%.
Thermal Fragmentation of N-Phenylnicotinamide Oxime IV

N-Phenylnicotinamide oxime IV (1g) was heated at 220-250°C in a 100 ml flask fitted with a reflux condenser and a gas trap under nitrogen atmosphere as discussed before.

Also, the pyrolysate was separated into neutral, phenolic, and basic products as mentioned previously.

The neutral products were separated through distillation under reduced pressure as follows:

- **Fraction (a):** Nicotinic acid 176 was identified by preparative TLC using pet. ether (60-80°C)-acetone (6:1 v/v), Rf = 0.85; mp 235°C.
  MS (EI, 100 ºC), m/e (%): 123 (M+, 100), 105 (50), 78 (48), 51(35).

- **Fraction (b):** Phenol 74a was collected as mentioned before and further identified by chemical test [115].

The basic products were separated by fractional distillation under reduced pressure to give the following fractions:

- **Fraction (a):** Aniline 71a, collected at bp 80-85°C/ 6 Torr; acetyl derivative mp and mmp 113-114°C.

- **Fraction (b):** Nicotininitrile 177, collected at bp 120-128°C/ 3 Torr; on hydrolysis gave nicotinic acid, mp and mmp 236°C.

Separation of the basic products by column chromatography afforded the following fractions:

- **Fraction (a):** N-Phenylnicotinamide 178 was eluted using light pet. ether (60-80°C)-benzene (1:1 v/v) as eluent, mp 122-124°C (lit. [119]; mp 123-125°C).

1H-NMR (600 MHz, CDCl₃) δ 7.27 (d, 1H, J = 8.2 Hz), 7.48 (d, 2H, J = 8.01 Hz), 7.07 (t, 1H, J = 7.76 Hz), 8.05 (d, 1H, J = 8.1 Hz), 7.56 (d, 1H, J = 4.82 Hz), 8.55 (d, 1H, J = 4.65 Hz), 8.91 (d, 1H, J = 4.82 Hz).

MS (EI, 200°C), m/e (%): 198 (45), 106 (100), 77 (60), 51(23); (fig. 29).
Elemental analysis calculated for (C\(_{12}\)H\(_{10}\)N\(_2\)O): C, 72.71; H, 5.08; N, 14.13 %.

**Fraction (b):** 9H-Carbazole 179 was eluted using pet. ether (60-80ºC)-benzene (1:2 v/v), mp 240-243ºC (lit. [120], mp 243-245ºC).

IR (KBr, cm\(^{-1}\)): 3410, 3040, 2951, 2916, 2846, 1621, 1599, 1489, 1445.

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \(\delta\): 4.12 (s, 1H, NH), 7.17 (t, 2H, H-3, \(J = 7.7\) Hz), 7.40 (t, 2H, H-2, \(J = 7.7\) Hz), 7.51 (d, 2H, H-1, \(J = 7.7\) Hz), 8.11 (d, 2H, H-4, \(J = 7.7\) Hz).


**Fraction (c):** 2-(Pyridin-3-yl)benz[d]oxazole 180 was eluted using 1 % ether-pentane as eluent, mp 113-114ºC; (lit. [121]; mp 113-115ºC).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 7.37-7.50 (m, 3H), 7.59-7.64 (m, 1H), 7.78-7.82 (m, 1H), 8.52 (dt, 1H, \(J = 8.2, 2.0\) Hz), 8.77 (dd, 1H, \(J = 4.8, 2.0\) Hz), 9.47-9.48 (m, 1H).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 110, 119.9, 125.2, 126.4, 127, 127.4, 128, 135, 139.9, 152, 135; (fig. 30).

MS (EI, 200ºC), m/e (%): 196 (100), 170 (22), 130 (15), 63 (28), 51 (8); (fig. 31).

Elemental analysis calculated for C\(_{12}\)H\(_8\)N\(_2\)O: C, 73.46; H, 4.11; N, 14.28 %.

**Fraction (d):** 2-(Pyridin-3-yl)-1H-benzimidazole 181 was eluted using 2 % ether-pentane as eluent, mp 241-243ºC (lit. [122]; mp 245-247ºC).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 10.75 (br, 1H, NH), 9.27 (d, 1H, \(J = 1.2\) Hz), 8.69 (dd, 1H, \(J = 3, 1.5\) Hz), 8.46 (dt, 1H, \(J = 7.8, 3.6\) Hz), 7.45 (m, 2H), 7.30 (m, 3H); (fig. 32).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 150.65 (C), 148.64 (C-Py), 147.09 (C), 134.49 (2CH-Py), 124.13 (CH-Py), 123.93 (2CH-Ph), 119.83 (CH-Py), 116.42 (CH-Ph), 111.06 (CH-Ph); (fig. 33).
MS (EI, 200°C), m/e (%): 195 (100), 169 (38), 143 (12), 118 (5), 97 (15), 63 (18), 51 (8); (fig. 34).

Elemental analysis calculated for C$_{12}$H$_9$N$_3$: C, 73.83; H, 4.65; N, 21.52 %. Found: C, 73.70; H, 4.58; N, 21.40 %.
2.2. Preparation of \( N-p \)-Methylphenylnicotinamide Oxime V

This procedure involved two steps:

**Step 1: Preparation of \( N-p \)-methylphenylnicotinamidine 182**

To stirred anhydrous AlCl\(_3\) (6.667 gm, 0.05 mole) was slowly added a mixture of 3-cyanopyridine 174 (5.205 gm, 0.05 mole), 4-methylaniline 75b (5.357 gm, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with NaOH (5 N). The resulting mixture was extracted by CHCl\(_3\) (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80\(^\circ\)C). The resulting solid was recrystallized from benzene, yield 74.35 %, mp 84-86\(^\circ\)C.

\[
\begin{align*}
\text{CN} & \quad \text{NH}_2 \\
\text{N} & \quad \text{NH} \\
\text{AlCl}_3 & \quad \text{Cl}_2\text{CH}-\text{CH}-\text{Cl} \\
174 & \quad 75b \\
\end{align*}
\]

**Step 2: Preparation of \( N-p \)-methylphenylnicotinamide oxime V**

\( N-p \)-Methylphenylnicotinamidine 182 (10.56 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The solid separated furnished the pure nicotinamidoxime V, as pale yellow crystals on recrystallization from benzene, mp 172-175\(^\circ\)C, yield 42.5 %; \( R_f = 0.130 \) (acetone : pet. ether (60-80\(^\circ\)C), 3:7 v/v).
IR (KBr, cm$^{-1}$): 3356 (NH, OH), 2740 (CH aliphatic), 1629 (C=C), 1385 (C-N), 1219 (C-O).

$^1$H-NMR (600 MHz, CDCl$_3$) δ: 9.95 (s, 1H, OH), 8.73 (d, 1H, $J = 3$ Hz), 8.58 (d, 1H, $J = 6.6$ Hz), 7.68 (dd, 1H, $J = 4.2$, 1.8 Hz), 7.26 (s, 1H, NH), 7.22 (m, 1H), 6.94 (d, 2H, $J = 8.4$ Hz), 6.61 (dd, 2H, $J = 4.8$, 1.8 Hz), 2.23 (s, 3H, CH$_3$); (fig. 36).

$^{13}$C-NMR (150 MHz, CDCl$_3$) δ: 150.2 (C=N-OH), 150 (C-Py), 149.2 (C-Py), 136.4 (C-Ph), 136 (C-CH$_3$), 133.2 (C-Py), 129.5 (2CH-Ph), 127.5 (C-Py), 123.1 (CH-Py), 122.3 (2CH-Ph), 20.7 (CH$_3$); (fig. 37).

MS (EI, 200°C), m/e (%): 227 (M$^+$, 91), 210 (95.6), 195 (26.5), 181 (20), 106 (79.4), 105 (48.5), 91 (100), 77 (67), 51 (35); (fig. 38).

Elemental analysis calculated for C$_{13}$H$_{13}$N$_3$O: C, 68.70; H, 5.77; N, 18.50 %. Found: C, 68.27; H, 5.72; N, 18.39 %. 
Thermal Fragmentation of N-p-Methylphenylnicotinamide Oxime V

It was heated and the pyrolysate were separated in neutral, phenolic and basic components as mentioned previously.

The phenolic products were separated into their constituents by distillation under reduced pressure and column chromatography to give the following fractions:

Fraction (a): p-Cresol 74b, collected at bp 60-65°C/ 6 Torr; benzoyl derivative mp and mmp 71-73°C.

Fraction (b): 2-Amino-5-methylphenol 183 was eluted from column chromatography using pet. ether (60-80°C), mp 158-160°C.

Nicotinic acid 176 and nicotinonitrile 177 were identified as mentioned before.

Fractionation of the basic products by distillation under reduced pressure gives the following fractions:

Fraction (a): p-Toluidine 75b, collected at bp 74-78°C / 3 Torr; mp and mmp 45-48°C; benzoyl derivative, mp 144-145°C.

Quantitative separation of the basic products was done by column chromatography into the following fractions:

Fraction (a): Identified as N-(4-methylphenyl)nicotinamide 184 was eluted using light pet. ether (60-80°C)-benzene (1:1 v/v) as eluent, mp 115-118°C (lit. [123], mp 114-116°C).

$^1$H-NMR (600 MHz, CDCl$_3$) δ: 7.32 (d, 1H, $J = 8.05$ Hz), 7.51 (d, 1H, $J = 8.16$ Hz), 7.16 (t, 1H, $J = 7.77$ Hz), 7.42 (d, 1H, $J = 8.16$ Hz), 7.48 (d, 1H, $J = 8.16$ Hz), 8.12 (d, 1H, $J = 8.11$ Hz), 7.63 (d, 1H, $J = 8.16$ Hz), 8.55 (d, 1H, $J = 4.78$ Hz), 8.90 (d, 1H, $J = 4.81$ Hz), 2.82 (s, 3H, CH$_3$).

MS (EI, 200°C), m/e (%): 212 (48), 106 (100), 78 (50), 51 (17); (fig. 39)

Fraction (b): 3,6-Dimethyl-9H-carbazole 185 was eluted using pet. ether (60-80°C)-benzene (1:2 v/v) as eluent, mp 217-219°C (lit. [124], mp 219-222°C).
$^1$H-NMR (600 MHz, DMSO-d$_6$) $\delta$: 11.10 (s, br, 1H, NH), 9.34 (d, 2H, H$_{4,5}$, $J = 2.3$ Hz), 8.40 (dd, 2H, H$_{2,7}$, $J = 2.3$, 8.9 Hz), 7.78 (d, 2H, H$_{1,8}$, $J = 8.9$ Hz), 2.51 (s, 6H, 2CH$_3$).

Elemental analysis calculated for C$_{14}$H$_{13}$N: C, 86.15; H, 6.07; N, 7.18 %.
Found: C, 86.19; H, 6.69; N, 7.12 %; m/e 195.

Fraction (c): 5-Methyl-2-(pyridin-3-yl)-1H-benzimidazole 186; eluted using 2 % ether-pentane as eluent, mp 220-222°C. (lit. [122], mp 221-223°C).

$^1$H-NMR (600 MHz, DMSO-d$_6$) $\delta$: 2.41 (s, 3H, CH$_3$), 7.03 (d, 1H, $J = 8.0$ Hz), 7.41-7.56 (m, 3H, Ph), 8.49 (dt, 1H, $J = 8.3$, 1.8 Hz), 8.65 (dd, 1H, $J = 8.1$, 1.6 Hz), 9.38 (dd, 1H, $J = 2.2$, 0.7 Hz), 12.98 (s, br, 1H, NH).

MS (EI, 200°C), m/e (%): 209 (100), 183 (15), 104 (20), 77 (18), 51 (10); (fig. 40).

Elemental analysis calculated for C$_{13}$H$_{11}$N$_3$: C, 74.62; H, 5.30; N, 20.08 %.
Found: C, 74.70; H, 5.20; N, 19.92 %.
2.3. Preparation of \(N-p\)-chlorophenylnicotinamide Oxime VI

This procedure involved two steps:

**Step 1: Preparation of \(N-p\)-chlorophenylnicotinamidine 187**

To stirred anhydrous \(\text{AlCl}_3\) (6.667 gm, 0.05 mole) was slowly added a mixture of 3-cyanopyridine 174 (5.205 gm, 0.05 mole), \(p\)-chloroaniline 153 (6.379 gm 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with \(\text{NaOH}\) (5 N). The resulting mixture was extracted by \(\text{CHCl}_3\) (100 ml). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80°C). The resulting solid 187 was recrystallized from benzene, yield 75%, mp 155-158°C.

![Chemical Reaction Diagram]

**Step 2: Preparation of \(N-p\)-chlorophenylnicotinamide oxime VI**

\(N-p\)-Chlorophenylnicotinamidine 187 (11.58 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The solid separated furnished the pure amidoxime, as brown crystals on recrystallization from benzene:ethanol (95: 05 v/v); mp 175-177°C, yield 39.5 %, \(R_f = 0.1219\) (acetone: petroleum ether (60-80°C), 3:7 v/v).
IR (KBr, cm\(^{-1}\)): 3399.15 (OH), 3281 (NH), 3103.7 (CH aromatic), 1596 (C=C aromatic), 1372 (C-N), 1092 (C-O).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 10.06 (br, 1H, OH), 8.78 (dd, 1H, \(J = 1.2, 0.6\) Hz), 8.61 (dd, 1H, \(J = 3, 1.8\) Hz), 7.65 (dd, 1H, \(J = 1.8, 4.2\) Hz), 7.37 (s, 1H, NH), 7.25 (m, 1H), 7.09 (dd, 2H, \(J = 4.2, 3\) Hz), 6.618 (dd, 1H, \(J = 4.8, 3\) Hz); (fig. 42).

MS (EI, 200°C), \(m/e\) (%): 247 (M\(^+\), 16), 230 (9.9), 127 (27), 104 (23.4), 75 (44.4), 63 (33.3), 51 (100); (fig. 43).

Elemental analysis calculated for C\(_{12}\)H\(_{10}\)ClN\(_3\)O: C, 58.19; H, 4.07; N, 16.97 %. Found: C, 57.94; H, 4.02; N, 16.89 %.
Thermal Fragmentation of N-p-Chlorophenynicotinamide Oxime VI

It was heated under the same conditions as mentioned previously then after the decomposition was completed; the products were separated into neutral, basic and phenolic components as in a previous work [105].

The phenolic products were fractionated under vacuum distillation and column chromatography to afford the following fractions:

**Fraction (a):** p-Chlorophenol **155**, collected at bp 130-135°C/ 6 Torr; mp 43-45°C.

**Fraction (b):** 2-Amino-5-chlorophenol **156** was eluted using pet. ether (60-80°C-benzene (1:1 v/v) as eluent, mp 152-154°C.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$: 6.7 (m, 1H, Ph-H), 6.64 (m, 1H, Ph-H), 6.72 (m, 1H, Ph-H).

Separation of the basic products into its constituents by distillation under reduced pressure and column chromatography gave the following fractions:

**Fraction (a):** Identified as p-chloroaniline **153**, collected at bp 182-188°C/ 6 Torr; mp and mmp 69-72°C.

**Fraction (b):** N-(4-Chlorophenyl)nicotinamide **188** eluted using pet. ether (60-80°C)-benzene (1:1 v/v) as eluent, mp 173-175°C (lit. [125], mp 174-176°C).

IR (KBr, cm$^{-1}$): 3217, 3132, 3061, 3035, 1718, 1695, 1530.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$: 9.08 (d, 1H, $J = 2.4$ Hz), 8.77 (dd, 1H, $J = 1.8$, 3.6 Hz), 8.21 (t, 1H, $J = 1.8$ Hz), 8.09 (br, 1H, NH), 7.61 (d, 2H, $J = 8.4$ Hz), 7.45 (t, 1H, $J = 4.8$ Hz), 7.35 (d, 2H, $J = 8.4$ Hz); (fig. 44).

$^{13}$C-NMR (150 MHz, CDCl$_3$) $\delta$: 163.8 (C-amide), 152.6 (CH-Py), 147.7 (CH-Py), 136 (C-Ph), 135.5 (CH-Py), 130.5 (C-Ph), 130 (C-Py), 129.2 (2CH-Ph), 123.8 (CH-Py), 121.6 (2CH-Ph); (fig. 45).

MS (EI, 200 °C), m/e (%): 232 (28), 106 (100), 78(50), 51 (20); (fig. 46).
**Fraction (c):** 3,6-Dichloro-9H-carbazole 158 was eluted using pet. ether (60-80°C)-benzene (1:2 v/v) as eluent, mp 202-204°C (lit. [108]; mp 202-205°C).

$^1$H-NMR (600 MHz, DMSO-d$_6$) $\delta$: 10.92 (s, br, 1H, NH), 9.14 (d, 2H, H$_{4,5}$), 8.22 (dd, 2H, H$_{2,7}$), 7.36 (d, 2H, H$_{1,8}$); m/e 236.

**Fraction (d):** Identified as 5-chloro-2-(pyridin-3-yl)-1H-benzimidazole 189 was eluted using 2% ether-pentane as eluent; mp 147-148°C (lit. [126]; mp 145-147°C).

$^1$H-NMR (600 MHz, CD$_3$OD) $\delta$ 9.14 (d, 1H, C'2-H), 8.58 (dd, 1H, C'6-H), 8.38 (d, 1H, C'4-H), 7.53 (m, 3H, C'5-H, C4-H, C7-H), 7.18 (dd, 1H, C 6-H).

MS (EI, 200°C), m/e (%): 229 (100), 203 (30), 193 (13), 177 (5), 114 (12), 78 (8), 63 (20), 51 (7); (fig. 47).

Elemental analysis calculated for C$_{12}$H$_8$N$_3$Cl: C, 62.76; H, 3.51; N, 18.30%. Found: C, 62.32; H, 3.60; N, 18.35%.
3. Preparation of \(N-p\)-Substituted Phenyl-2-Furamide Oxime VII - IX

3.1. Preparation of \(N\)-phenyl-2-furamidine oxime VII

This procedure involved two steps:

**Step 1: Preparation of \(N\)-phenyl-2-furamidine 191**

To stirred anhydrous \(\text{AlCl}_3\) (6.667 gm, 0.05 mole) was slowly added a mixture of 2-cyanofuran 190 (4.37 ml, 0.05 mole), aniline 71a (4.54 mL, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with \(\text{NaOH}\) (5 N). The resulting mixture was extracted with chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80 \(^\circ\)C). The resulting solid was recrystallized from benzene, yield 60 \%, mp 215-218\(^\circ\)C.

**Step 2: Preparation of \(N\)-phenyl-2-furamide oxime VII**

\(N\)-Phenyl-2-furamidine 191 (9.310 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The residue was treated with pet. ether (60-80\(^\circ\)C), and the crude product was subjected to column chromatography using n-pentane : diethyl ether (9:1 v/v), which gave \(N\)-phenyl-2-furamidine oxime VIII as a solid mp 125-128\(^\circ\)C, yield 21 \%, \(R_f = 0.231\) (acetone: pet. ether (60-80\(^\circ\)C), 3:7 v/v).
IR (KBr, cm$^{-1}$): 3646 (OH, NH), 3186 (CH aromatic), 1599.5 (C=C aromatic), 1342 (C-N), 1243.6 (C-O).

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$: 9.7 (s, 1H, OH), 7.37 (br, NH, 1H), 7.19 (d, 1H, $J = 7.2$ Hz), 7.21 (m, 3H), 6.75 (d, 2H, $J = 7.8$ Hz), 6.56 (d, 1H, $J = 3.6$ Hz), 6.38 (dd, 1H, $J = 3.6$, 1.8 Hz); (fig. 49).

MS (EI, 200°C), $m/e$ (%): 202 (M$^+$, 36.5), 185 (78), 156 (36.5), 118 (22), 103 (29.2), 93 (200), 77(35.4), 65 (29.2), 51 (19.5); (fig. 50).

Elemental analysis calculated for C$_{11}$H$_{10}$N$_2$O$_2$: C, 65.34; H, 4.98; N, 13.85 %.

Found: C, 65.22; H, 5.04; N, 13.90 %. 
Thermal Fragmentation of $N$-Phenyl-2-furamide Oxime VII

$N$-Phenyl-2-furamide oxime VII was heated at 220-250°C under nitrogen atmosphere as mentioned previously. The pyrolysate were separated into neutral, phenolic and basic components as discussed before.

The neutral products were separated by fractional distillation under reduced pressure and column chromatography to give the following fractions:

**Fraction (a):** Identified as 2-furoic acid 192, collected at bp 140-148°C / 6 Torr; mp 128-130°C.

MS (EI, 200°C), (m/e %): 112 (100), 95 (90), 44 (5); (fig. 51).

**Fraction (b):** Furil 193 was eluted using pet. ether (60-80°C) as eluent; mp 163-165°C.

Fractionation of the basic products was accomplished by distillation under reduced pressure to afford the following fractions:

**Fraction (a):** Aniline 71a, collected at bp 80-86°C/6 Torr; acetyl derivative mp and mmp 113-114°C.

**Fraction (b):** 2-Furamide 194; collected at bp 125-130°C/ 6 Torr; mp 138-140°C.

MS ((EI, 200°C), m/e % : 111 (100), 95 (95), 67 (8), 44 (13); (fig. 52).

**Fraction (c):** Identified as 2-furonitrile 195, collected at bp 85-92°C/ 6 Torr; on hydrolysis gave 2-furoic acid, mp 130-132°C.

MS ((EI, 200°C), m/e % : 93 (100), 66 (40), 65 (20); (fig. 53).

The remaining residue was separated into its constituents by column chromatography to give the following fractions:

**Fraction (a):** 9H-Carbazole 179 was separated as mentioned before.

**Fraction (b):** 2-(Furan-2-yl)benz[d]oxazole 196 was eluted using 1 % ether-pentane as eluent, mp 90-92°C (lit. [127], mp 88-90°C).

IR (KBr, cm$^{-1}$): 3108, 1643, 1525, 1449, 1390, 1308, 1238, 1155.
\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.02 (s, 1H), 7.26-7.34 (m, 2H), 7.57-7.54 (m, 2H), 7.72 (dd, 1H, \(J = 5.9, 3.1\) Hz), 8.21 (s, 1H); (fig. 54).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 109, 110, 120, 124, 125, 144.2, 144.3 (CH), 115, 142, 150, 158 (C); (fig. 55).

MS (EI, 200°C), m/e (%): 185 (50), 170 (5), 103 (10), 93 (100), 77 (30), 65 (18), 51 (10); (fig. 56).

Elemental analysis calculated for C\(_{11}\)H\(_7\)NO\(_2\): C, 71.35; H, 3.81; N, 7.56 %.

Found: C, 71.40; H, 3.78; N, 7.54 %.

**Fraction (c):** Identified as \(N\)-phenyl-2-furamide 197 was eluted using pet. ether (60-80°C)-benzene (1:1 v/v) as eluent; mp 122-123°C (lit. [128], mp 123-124°C).

IR (KBr, cm\(^{-1}\)): 3280, 3140, 3059, 1656, 1598, 1581, 1529.

MS (EI, 200°C), m/e (%): 187 (40), 130 (5), 95 (100), 77 (5), 65 (8), 51 (5); (fig. 57).

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \(\delta\): 10.13 (s, 1H, NH), 7.92 (s, 1H, Ar), 7.72-7.73 (m, 2H), 7.31-7.35 (m, 3H), 7.07-7.11 (m, 1H), 6.69-7.70 (m, 1H).

Elemental analysis calculated for C\(_{11}\)H\(_9\)NO\(_2\): C, 70.58; H, 4.85; N, 7.48.

Found: C, 70.67; H, 4.79; N, 7.53 %.

**Fraction (d):** 2-(Furan-2-yl)-1H-benzimidazole 198 was eluted using 2% ether-pentane as eluent, mp 285-287°C (lit. [129], mp 286-288°C).

IR (KBr, cm\(^{-1}\)): 3442, (NH), 3093, 1625 (CN), 1521, 1438.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 12.87 (s, 1H, NH), 8.07 (d, 1H, \(J = 1.19\) Hz), 7.47 (d, 2H, \(J = 1.50\) Hz), 7.15-7.19 (m, 3H), 6.78 (m, 1H).

MS (EI, 200°C), m/e (%): 184 (100), 156 (30), 129 (18), 102 (10), 92 (12), 77 (8), 63 (10), 51 (7); (fig. 58).

Elemental analysis calculated for C\(_{11}\)H\(_8\)N\(_2\)O: C, 71.73; H, 4.38; N, 15.21.

Found: C, 71.68; H, 4.39; N, 15.48 %.
3.2. Preparation of \(N\text{-}p\text{-}methylphenyl\text{-}2\text{-}furamide\) oxime VIII

This procedure involved two steps:

Step 1: Preparation of \(N\text{-}p\text{-}methylphenyl\text{-}2\text{-}furamidine\) 199

To stirred anhydrous AlCl\(_3\) (6.667 gm, 0.05 mole) was slowly added a mixture of 2-cyanofuran 190 (4.37 ml, 0.05 mole), \(p\text{-}toluidine\) 75b (5.35 gm, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with NaOH (5 N). The resulting mixture was extracted with chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the resulting solid was recrystallized from ethanol, yield 80%, mp 189-191°C.

\[
\text{H}_2\text{N} \quad \text{Cl}_2\text{CHCHCHCl}_2 \quad \text{Cl}_{\text{AlCl}_3} \quad \text{NH} \quad \text{CH}_3
\]

Step 2: Preparation of \(N\text{-}p\text{-}methylphenyl\text{-}2\text{-}furamide\) oxime VIII

\(N\text{-}p\text{-}Methylphenyl\text{-}2\text{-}furamide\) 199 (10.81 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The residue was treated with pet. ether (60-80°C), and the crude product was subjected to column chromatography using n-pentane:diethyl ether (9:1 v/v), which gave \(N\text{-}p\text{-}methylphenyl\text{-}2\text{-}furamide\) oxime as colourless needles, mp 158-160°C, \(R_f\) = 0.234 (acetone: pet. ether (60-80°C) 3:7 v/v).
IR (KBr, cm\(^{-1}\)): 3478 (OH), 3365 (NH), 2922 (CH aliphatic), 1638 (C=C aromatic), 1336 (C-N), 1245 (C-O).

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \(\delta\): 10.50 (s, 1H, OH), 8.24 (s, 1H, NH), 7.63 (dd, 1H, \(J = 2.4, 1.8\) Hz), 6.91 (d, 2H, \(J = 8.4\) Hz), 6.57 (m, 3H), 6.51 (dd, 1H, \(J = 3.0, 1.8\) Hz); (fig. 60).

\(^{13}\)C-NMR (150 MHz, DMSO-d\(_6\)) \(\delta\): 206.6 (C=NOH), 146.2 (C-Fn.), 143.5 (C-Fn), 141.8 (C-Ph), 138.6 (C-CH\(_3\)), 128 (2CH-Ph), 118.9 (2CH-Ph), 111.2 (CH-Fn), 110.6 (CH-Fn), 20.2 (CH\(_3\)); (fig. 61).

MS (EI, 200°C), \(m/e\) (%): 216 (M\(^+\), 68.2), 199 (94), 184 (26.8), 171 (17), 117 (36.58), 107 (100), 91 (41.5), 77 (56), 65 (37.8), 51 (22); (fig. 62).

Elemental analysis calculated for C\(_{12}\)H\(_{12}\)N\(_2\)O\(_2\): C, 66.65; H, 5.59; N, 12.96 \%. Found: C, 66.97; H, 5.48; N, 13.02 \%. 
Thermal Fragmentation of \( N-p \)-Methylphenyl-2-furamide Oxime VIII.

\( N-p \)-Methylphenyl-2-furamide oxime VIII (1g) was worked-up as mentioned previously whereby ammonia gas and water were detected as usual.

The pyrolysate were separated into neutral, phenolic and basic components as discussed before.

It is worthy to mention that 2-furoic acid 192, 2-furonitrile 195, \( p \)-cresol 74b and \( p \)-toluidine 75b were separated and identified as mentioned before, see the previous experimental work.

Quantitative separation of the basic fractions was done by column chromatography into the following fractions:

Fraction (a): \( N \)-(4-Methylphenyl)-2-furamide 200 eluted using pet. ether (60-80ºC)-benzene (1:1 v/v) as eluent, mp 108-110ºC (lit. [130], mp 109-110ºC).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \): 2.34 (s, 3H), 6.56 (dd, 1H, \( J = 3.4, 1.8 \) Hz), 7.17 (d, 2H, \( J = 8.2 \) Hz), 7.20 (d, 1H, \( J = 3.3 \) Hz), 7.50 (dd, 1H, \( J = 1.6, 0.7 \) Hz), 7.54 (d, 2H, \( J = 8.4 \) Hz), 8.03 (br, NH, 1H).

MS (EI, 200ºC), m/e (%): 201 (50), 144 (5), 108 (10), 95 (100), 77 (10), 67 (5), 51 (4); (fig. 63).

Fraction (b): Identified as 3,6-dimethyl-9H-carbazole 185 was eluted using pet. ether (60-80ºC)-benzene (1:2 v/v) as eluent, mp 217-219ºC and identified as mentioned previously.

Fraction (c): Identified as 6-methyl-2-(furan-2-yl)benz[d]oxazole 201 was eluted using 1% ether-pentene as eluent, mp 52-54ºC (lit. [131], mp 53-55ºC); m/e 199.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \): 7.64 (dd, 1H, \( J = 2.0, 0.5 \) Hz), 7.34 (m, 1H, 7.50 (dd, 1H, \( J = 0.5, 3.5 \) Hz), 7.13-7.17 (m, 1H), 6.95 (dd, 1H, \( J = 2.0, 3.5 \) Hz), 8.25 (d, 1H, \( J = 8.0 \) Hz), 2.48 (s, 3H); (fig. 64).
\^13C-NMR (150 MHz, CDCl\textsubscript{3}) \(\delta\): 158.8, 151.4, 145, 144.7, 139.5, 135.0, 119.5, 115, 111.1, 109.6, 21.7; (fig. 65).

**Fraction (d)**: 5-Methyl-2-(furan-2-yl)-1H-benzimidazole \textbf{202} was eluted using 2\% ether-pentane as eluent, mp 198-200\textdegree C (lit. [129], mp 200-202\textdegree C).

\(^1\)H-NMR (600 MHz, DMSO-d\textsubscript{6}) \(\delta\): 2.3 (s, 3H, CH\textsubscript{3}), 6.67 (dd, 1H, \(J = 3.4\) Hz), 7.83 (dd, 1H, \(J = 1.7\) Hz), 7.04 (dd, 1H, \(J = 3.4\) Hz), 7.11 (d, 1H, \(J = 8.12\) Hz), 7.63 (d, 1H, \(J = 8.18\) Hz), 7.65 (d, 1H, \(J = 4.0\) Hz).

MS (EI, 200\textdegree C), m/e (%): 198 (100), 169 (20), 104 (8), 77 (12), 51 (7); (fig. 66).
3.3. Preparation of \( N-p \)-chlorophenyl-2-furamide oxime IX

This procedure has been passed through two steps:

Step 1: Preparation of \( N-p \)-chlorophenyl-2-furamidine 203

To stirred anhydrous \( \text{AlCl}_3 \) (6.667 gm, 0.05 mole) was slowly added a mixture of 2-cyanofuran \( 190 \) (4.37 mL, 0.05 mole), \( p \)-chloroaniline \( 153 \) (6.37 gm, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with NaOH (5 N). The resulting mixture was extracted by chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80ºC). The resulting solid 203 was recrystallized from ethanol, yield 77 %, mp 98-100ºC.

\[
\begin{align*}
\text{O} & \quad \text{CN} \\
& \quad \text{Cl} \\
& \quad \text{H}_2\text{N} \\
\text{Cl} & \quad \text{CH-CH-Cl} \\
\text{AlCl}_3 
\end{align*}
\]

\( 190 \) \( 153 \) \( 203 \)

\[ \text{N-p-Chlorophenyl-2-furamidine} \]

\[ \text{N-p-Chlorophenyl-2-furamide} \]

Step 2: Preparation of \( N-p \)-chlorophenyl-2-furamide oxime IX

\( N-p \)-Chlorophenyl-2-furamide 203 (11.03 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The residue was treated with pet. ether (60-80ºC), and the crude product was subjected to column chromatography using n-pentane:diethyl ether (9:1 v/v), which gave \( N-p \)-chlorophenyl)-2-furamide oxime as a solid mp. 183-185ºC, \( R_f = 0.28 \) (acetone: petroleum ether (60-80ºC), 3:7 v/v).
\[ \text{NH} \begin{array}{c} \text{N} \\ \text{N} \end{array} \text{Cl} \xrightarrow{\text{NH}_2\text{OH, HCl}} \Delta, 10 \text{ min}, \text{H}_2\text{O} \rightarrow \text{NH} \begin{array}{c} \text{N} \\ \text{N} \end{array} \text{Cl} \]

$^1$H-NMR (600 MHz, CDCl$_3$) \( \delta \): 77.26 (br, 1H, NH), 7.16 (d, 2H, \( J = 2.4 \), 4.8 Hz), 7.69 (d, 2H, \( J = 1.8 \), 4.8 Hz), 6.55 (dd, 1H, \( J = 0.6 \), 3.0 Hz), 6.41 (dd, 1H, \( J = 1.2 \), 1.8 Hz), 7.39 (dd, 1H, \( J = 0.6 \), 1.2 Hz); (fig. 68).

MS (EI, 200°C), m/e (%): 236 (M$^+$, 73), 204 (29), 184 (12), 127 (100), 99 (27), 93 (29), 75 (27), 63 (18), 51 (9); (fig. 69).

Elemental analysis calculated for C$_{11}$H$_9$ClN$_2$O$_2$: C, 55.83, H, 3.83, N, 11.84 %. Found: C, 55.69, H, 4.01, N, 12.12 %.
Thermal Fragmentation of \( N-p \)-Chlorophenyl-2-Furamide Oxime IX

It was done as mentioned previously where by \( N-p \)-chlorophenyl-2-furamide oxime IX (1g) was heated at 220-250\(^\circ\)C under nitrogen atmosphere. The pyrolysate was separated into neutral, phenolic and basic components as discussed before.

It was worthy to mention that 2-furoic acid 192, 2-furonitrile 195, \( p \)-chlorophenol 155, \( p \)-chloroaniline 153 and 3,6-dichloro-9H-carbazole 158 were separated and identified as discussed before.

Quantitative separation of the basic products was done by chromatography into the following fraction:

Fraction (a): Identified as 6-chloro-2-(furan-2-yl)benzoxazole 204 was eluted using 1% ether-pentane as eluent, mp 136-138\(^\circ\)C (lit [132]; 135-137\(^\circ\)C).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \): 6.79 (dd, 1H, \( J = 3.45, 1.76 \) Hz), 8.01(dd, 1H, \( J = 8.0, 0.6 \) Hz), 7.21 (dd, 1H, \( J = 3.45, 0.92 \) Hz), 7.75 (dd, 1H, \( J = 8.07, 1.81 \) Hz), 8.11(dd, 1H, \( J = 8.07, 0.6 \) Hz), 7.92 (dd, 1H, \( J = 1.81, 0.6 \) Hz).

MS (EI, 200\(^\circ\)C), m/e (%): 220 (100), 219 (33), 204 (20), 129 (35), 127 (100), 111 (40), 94 (60), 93 (30), 75 (33); (fig. 70).

Fraction (b): Identified as \( N \)-(4-chlorophenyl)-2-furamide 205 was eluted using pet. ether (60-80\(^\circ\)C)-benzene (1:1 v/v) as eluent, mp 150-152\(^\circ\)C (lit. [133], mp 152-153\(^\circ\)C).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \( \delta \): 8.10 (br, 1H, NH), 7.61 (d, 2H, \( J = 8.2 \) Hz), 7.51 (d, 1H, \( J = 1.2 \) Hz), 7.34 (d, 2H, \( J = 8.4 \) Hz), 7.25 (d, 1H, \( J = 3.6 \) Hz), 6.57 (dd, 1H, \( J = 1.8, 3.6 \) Hz); (fig. 71).

\(^13\)C-NMR (150 MHz, CDCl\(_3\)) \( \delta \): 156 (C=O amide), 147.4 (C-Fn), 144.4 (CH, Fn), 136 (C-Ph), 129.1 (2 CH-Ph), 129.5 (C-Cl), 121 (2CH-Ph), 115.6 (C-Fn), 112.7 (C-Fn); (fig. 72).

MS (EI, 200\(^\circ\)C), m/e (%): 221 (M\(^+\), 28), 95 (100), 63 (6); (fig. 73).
Elemental analysis calculated for C$_{11}$H$_8$NO$_2$Cl: C, 59.61; H, 3.64; N, 6.32; Cl, 15.99%. Found: C, 59.58; H, 3.72; N, 6.52; Cl, 15.75%.

**Fraction (c):** Identified as 5-chloro-2-(furan-2-yl)benzimidazole was eluted using 2% ether-pentane as eluent; mp 202-203°C (lit. [134]; mp 200-202°C.

$^1$H-NMR (600 MHz, CDCl$_3$) $\delta$: 6.72 (dd, 1H, $J = 3.43, 1.75$ Hz), 7.80 (dd, 1H, $J = 1.75, 0.89$ Hz), 7.03 (dd, 1H, $J = 3.43, 0.89$ Hz), 7.39 (dd, 1H, $J = 8.06, 1.69$ Hz), 7.86 (dd, 1H, $J = 8.06, 0.85$ Hz), 7.83 (dd, 1H, $J = 1.69, 0.85$ Hz).

MS (EI, 200°C), m/e (%): 218 ($M^+$, 100), 189 (14), 155 (36), 109 (9), 63 (12), 51 (8); (fig. 74).
4. Preparation of \( N\)-(pyridin-2-yl)benzamide oxime X

This procedure has been passed through two steps:

**Step 1: Preparation of \( N\)-(pyridin-2-yl)benzamidine 208**

A mixture of 2-aminopyridine 207 (9.98 mL, 0.1 mole), benzonitrile 17 (9.98 mL, 0.1 mole), and powdered sodium (2.3 g, 1 atom) in dry benzene (100 mL) was refluxed for 27 consecutive hours. After addition of ethanol (10 mL), ionisable cyanide was extracted with dilute sodium hydroxide and recovered as silver cyanide (0.73 g, 5.5 %). Basic material was then collected in dilute hydrochloric acid and \( N\)-(pyridin-2-yl)benzamidine 208, was precipitated by sodium hydroxide, recrystallisation from ethanol, mp 94-98°C, yield 51.36 %.

\[
\begin{align*}
\text{CN} & \quad + \quad \begin{array}{c}
\text{N} \\
\text{H}
\end{array} & \xrightarrow{\text{NaOH benzeure}} & \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \quad \text{NH} \\
\text{H}
\end{align*}
\]

**Step 2: Preparation of \( N\)-(pyridin-2-yl)benzamide oxime X**

\( N\)-(Pyridin-2-yl)benzamidine 208 (19.72 g, 0.1 mole) was added to a solution of hydroxylamine hydrochloride (10.4 g, 1.5 mole) in water (90 mL). The suspension was boiled for 10 min, made just alkaline to brilliant-yellow solution with ammonia, and boiled for a further 10 min. The solid separated furnished the pure amidoxime, as pale yellow crystals, mp 186-188°C, on recrystallization from ethanol, yield 46.65 %, \( R_f = 0.221 \) (acetone: pet. ether (60-80°C), 3:7 v/v).
IR (KBr, cm\(^{-1}\)): 3476 (OH), 3364 (NH), 3110 (CH aromatic), 1641 (C=C aromatic), 1335 (C-N), 1256 (C-O).

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \(\delta\): 10.88 (s, 1H, OH), 8.71 (s, 1H, NH), 7.91 (d, 1H, \(J = 4.8\) Hz), 7.52 (m, 1H), 7.39 (dd, 1H, \(J = 4.2, 1.2\) Hz), 7.33 (m, 5H, Ph-H), 6.74 (m, 1H); (fig. 76).

\(^{13}\)C-NMR (150 MHz, DMSO-d\(_6\)) \(\delta\): 206.7 (C=NOH), 154.06 (C-Py), 147.26 (CH-Py), 137.27 (CH-Py), 133.72 (C-Ph), 128.6 (CH-Ph), 128 (2CH-Py), 126.9 (2CH-Ph), 115.7 (CH-Py), 111.9 (CH-Py); (fig. 77).

MS (EI, 200°C), \(m/e\) (%): 213 (M\(^+\), 35.29), 196 (13.23), 181 (31.61), 94 (36.76), 79 (27.9), 77 (100), 51 (12.92); (fig. 78).

Elemental analysis calculated for C\(_{12}\)H\(_{11}\)N\(_3\)O: C, 67.59; H, 5.20; N, 19.71 %. Found: C, 67.26; H, 5.53; N, 20.20 %.
Thermal Fragmentation of \( N\)-2-Pyridylbenzamide Oxime X

\( N\)-2-Pyridylbenzamide oxime X (1g) was placed in a 100 ml three necked flask fitted with a condenser and heated at 220-250ºC under nitrogen atmosphere as discussed previously.

Moreover, the content of the flask was separated into neutral and basic components as mentioned before.

The neutral products were separated by distillation under reduced pressure as follows:

Fraction (a): Benzonitrile \( 17 \), collected at bp 42-48ºC/ 3 Torr; on hydrolysis gave benzoic acid. mp and mmp 120ºC.

Fraction (b): Identified as benzoic acid \( 41 \) by preparative TLC using pet. ether (60-80ºC)-acetone (5:1 v/v) as eluent, \( R_f = 0.65 \); mp and mmp 120ºC and IR is coincident with that of authentic sample.

The basic products were fractionated under reduced pressure to give the following fractions:

Fraction (a): Identified as 2-aminopyridine \( 207 \), collected at bp 180-188ºC / 6 Torr; mp 54-58ºC; IR is coincident with that of an authentic sample.

Fraction (b): Identified as 2-hydroxypyridine \( 209 \), collected at bp 220-228ºC / 6 Torr; mp 105-107ºC.

The remaining residue was subjected to column chromatography whereby the following fractions were obtained:

Fraction (a): \( N\)-(Pyridin-2-yl)benzamide \( 210 \) was eluted using pet. ether (60-80ºC)-benzene (1:1 v/v) as eluent; mp 81-83ºC (lit. [135], mp 80-82ºC; \( R_f = 0.26 \) (30:70 acetone-n-hexane).

IR (KBr, cm\(^{-1}\) ): 3288. 3058, 1650, 1584, 1537, 1481, 1330.

\(^1\)H-NMR (600 MHz, CDCl\(_3\) ) \( \delta \): 6.95 (m, 1H), 7.41 (m, 2H), 7.49 (m, 1H), 7.68 (m, 1H), 7.88 (m, 2H), 9.39 (s, br, 1H), 8.01 (m, 1H), 8.37 (m, 1H).
MS (EI, 200°C), m/e (%): 198 (8), 169 (50), 105 (100), 77 (85), 51 (30); (fig. 79).

Fraction (b): 2,4,6-Triphenyl-1,3,5-triazine 19 was eluted using pet. ether (60-80°C)-benzene (1:2 v/v) as eluent, in the form of light yellow needles, mp 231-233°C (lit. [136], mp 230-232°C); Rf = 0.36 (9:1 v/v n-hexane-dichloromethane).

$^1$H-NMR (600 MHz, CDCl$_3$) δ: 8.79 (m, 6H), 7.63 (m, 9H); (fig. 80).

MS (EI, 200°C), m/e (%): 309 (30), 103 (100), 76 (20), 51 (10), (fig. 81).

Elemental analysis calculated for C$_{21}$H$_{15}$N$_3$: C, 81.53; H, 4.89; N, 13.58 %.

Found: C, 81.42; H, 4.77; N, 13.61 %.

Fraction (c): Identified as 9H-pyrrolo[2,3-b: 5,4-b']dipyridine 211 was eluted using pet. ether (60-80°C)-benzene (1:4 v/v); mp 229-23°C (lit. [137], mp 230-232°C).

Elemental analysis calculated for C$_{10}$H$_7$N$_3$: C, 70.95; H, 4.15; N, 24.85.

Found: C, 70.9; H, 4.15; N, 25.0 %.

Fraction (d): Identified as 2-phenyloxazolo[4,5-b]pyridine 212 was eluted using 1% ether-pentane, mp 125-127°C (lit. [138], mp 127-128°C; Rf = 0.56 (ethylacetate-pentane, 1:2 v/v).

$^1$H-NMR (600 MHz, CDCl$_3$) δ: 8.38 (dd, 1H, $J = 7.8, 1.5$ Hz), 7.55-7.62 (m, 3H), 7.36-7.41 (m, 1H); (fig. 82).

MS (EI, 200°C), m/e (%): 196 (100), 181 (20), 104 (18), 77 (60), 65 (70), 51 (60), (fig. 83).

Elemental analysis calculated for C$_{12}$H$_8$N$_2$O$_2$: C, 73.46; H, 4.11; N, 14.28.

Found: C, 73.46; H, 4.43; N, 14.18 %.

Fraction (e): 2-Phenyl-1H-imidazo[4,5-b]pyridine 213 was eluted using 2 % ether-pentane as eluent mp 288-290°C (lit. [139], mp 291-293°C).
$^1$H-NMR (600 MHz, DMSO-d$_6$) δ: 13.58 (br, 1H, NH), 8.35 (d, 1H, $J = 7.8$ Hz), 8.24 (d, 2H, $J = 4.2$ Hz), 8.03 (br, 1H, H-Py), 7.56 (m, 3H, H-Ph), 7.26 (dd, 1H, $J = 3.0$, 4.8 Hz); (fig. 84).

$^{13}$C-NMR (150 MHz, CDCl$_3$) δ: 153.6 (C), 149.2 (C-Py), 142.99 (CH-Py), 136.98 (C-Ph), 130.9 (C-Ph), 129.75 (C-Py), 129.75 (2CH-Ph), 127.8 (CH-Py), 126.98 (2CH-Ph); (fig. 85).

MS (EI, 200°C), m/e (%): 195 (M$^+$; 100), 104 (34.6), 92 (19.8), 65 (13.6), 51 (12.3); (fig. 86).

Elemental analysis calculated for C$_{12}$H$_9$N$_3$: C, 73.83; H, 4.65; N, 21.53
Found: C, 73.78; H, 4.58; N, 21.69 %.
5. Preparation of \(N-\alpha\)-Naphthyl heteroarylamide Oxime XI-XIII

5.1. Preparation of \(N-\alpha\)-Naphthylbenzamide Oxime XI

This procedure involved two steps:

**Step 1: Preparation of \(N-\alpha\)-naphthylbenzamidine 215**

A mixture of \(\alpha\)-naphthylamine 214 (14.31 gm, 0.1 mole), benzonitrile 17 (9.98 mL, 0.1 mole), and powdered sodium (2.3 g, 1 atom) in dry benzene (100 mL) was refluxed for 27 consecutive hours. After addition of ethanol (10 mL), ionisable cyanide was extracted with dilute sodium hydroxide and recovered as silver cyanide (0.73 g, 5.5%). Basic material was then collected in dilute hydrochloric acid and \(N-\alpha\)-naphthyl benzamidine 215 was precipitated by sodium hydroxide, recrystallization from ethanol gave colourless crystals, mp 150-152\(^\circ\)C, yield 77.4 %.

**Step 2: Preparation of \(N-\alpha\)-naphthylbenzamide oxime XI**

\(N-\alpha\)-Naphthylbenzamidine 215 (24.6 gm, 0.1 mole) was added to a solution of hydroxylamine hydrochloride (10.4 g, 1.5 mole) in water (90 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The residue was treated with pet. ether (60-80\(^\circ\)C). The solid separated furnished the pure amidoxime, as dark purple crystals on recrystallization from benzene, mp 184-186\(^\circ\)C, yield 30.29 %; \(R_f = 0.285\) (acetone: pet. ether (60-80\(^\circ\)C) 3:7 v/v).
IR (KBr, cm\(^{-1}\)): 3382 (OH), 3361 (NH), 3058 (CH aromatic), 1642 (C=C aromatic), 1363 (C-N), 1245 (C-O).

\(^1\)H-NMR (600 MHz, DMSO-d\(_6\)) \(\delta\): 10.66 (s, 1H, OH), 8.34 (d, 1H, \(J = 8.4\) Hz), 8.167 (s, 1H, NH), 7.87 (d, 2H, \(J = 8.4\) Hz), 7.55 (m, 2H), 7.34 (dd, 2H, \(J = 3.6, 1.2\) Hz) 7.22 (m, 4H), 6.56 (d, 1H, \(J = 7.2\) Hz) (fig. 88).

\(^{13}\)C-NMR (150 MHz, CDCl\(_3\)) \(\delta\): 152.2 (C=NOH), 135.7 (C-naph), 133.9 (C-Ph.), 131.6 (C-Ph), 128.9 (CH-Ph), 128.1 (CH-naph), 127.9 (2CH-Ph), 127.65 (C-naph), 127.60 (2CH-Ph), 125.9 (CH-naph), 125.8 (CH-naph), 125.0 (CH-naph), 123.17 (CH-naph), 121.6 (CH-naph), 119.84 (CH-naph); (fig. 89).

MS (EI, 200°C), \(m/e\) (%): 262 (M\(^+\), 28.35), 246 (26.86), 245 (100), 230 (15), 143 (59.7), 127 (23.88), 115 (70.14), 77 (35.82), 51 (10.44); (fig. 90).

Elemental analysis calculated for C\(_{17}\)H\(_{14}\)N\(_2\)O: C, 77.84; H, 5.3; N, 10.68 %. Found: C, 78.04; H, 5.09; N, 10.27 %.
Thermal Fragmentation of \(N\)-\(\alpha\)-Naphthylbenzamide Oxime XI

\(N\)-\(\alpha\)-Naphthylbenzamide oxime XI was heated at 220-250\(^\circ\)C under nitrogen atmosphere as discussed before.

The pyrolysate was separated into neutral, phenolic and basic components as mentioned previously.

The neutral products were separated by fractional distillation under reduced pressure followed by column chromatography to give the following fractions: Benzonitrile 17 and benzoic acid 41 were identified as mentioned before.

Fraction (a): Identified as \(\alpha\)-naphthylamine 214, collected bp 210-217\(^\circ\)C / 6 Torr; mp 47-50\(^\circ\)C.

Quantitative separation of the basic fractions was done by column chromatography into the following fractions:

Fraction (a): Identified as \(\alpha\)-naphthylamine 214 (in part) was eluted using pet. ether (60-80\(^\circ\)C) as eluent; mp 45-48\(^\circ\)C.

Fraction (b): \(N\)-(\(\alpha\)-Naphthyl)benzamide 216 was eluted using pet. ether (60-80\(^\circ\)C)-benzene (1:1 v/v) as eluent; mp 164-160\(^\circ\)C (lit. [140], mp 159-161\(^\circ\)C).

IR (KBr, cm\(^{-1}\)): 3237, 3047, 1649, 1593, 1526, 1501.

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) \(\delta\): 7.58-7.67 (m, 5H, Ar), 7.80 (d, 1H, \(J = 7.8\) Hz), 7.96-7.97 (m, 3H), 8.04 (d, 2H, \(J = 7.0\) Hz), 8.11 (d, 1H, \(J = 7.0\) Hz), 8.24 (1H, br, NH).

MS (EI, 200\(^\circ\)C), m/e (%): 247 (28), 144 (5), 115 (18), 105 (100), 77 (48), 51 (10); (fig. 91).

Fraction (c): Identified as 2-phenylnaph[1,2-d]oxazole 217 was eluted using 1% ether-pentane as eluent, mp 133-135\(^\circ\)C (lit. [141], mp 130-133\(^\circ\)C.

IR (KBr, cm\(^{-1}\)): 1551, 1485 (C=N), 1238 (C-O).
$^1$H-NMR (600 MHz, DMSO-$d_6$) δ: 7.55 (m, 2H), 7.70 (m, 3H), 8.10 (m, 2H), 8.32 (m, 4H); (fig. 92).

$^{13}$C-NMR (150 MHz, DMSO-$d_6$) δ: 106.5, 117.0, 124.8, 125.5, 126.1, 127.7, 127.9, 128.3, 129.3, 131.1, 131.3, 132.5, 141.4 149.0, 164.2; (fig. 93).

MS (EI, 200°C), m/e (%): 245 (100), 217 (5), 140 (3), 122 (6), 114 (45), 88 (7); (fig. 94).

Elemental analysis calculated for C$_{17}$H$_{11}$NO: C, 83.28; H, 4.52; N, 5.71.
Found: C, 83.28; H, 4.55; N, 5.74 %.

Fraction (d): 2-Phenylnaphth[1,2-d]imidazole 218 was eluted using 2% ether-pentane as eluent, mp 215-217°C (lit. [142], mp 216-218°C).

$^1$H-NMR (600 MHz, DMSO-$d_6$) δ: 7.55 (m, 2H), 7.76 (m, 3H), 8.17 (m, 2H), 8.34 (m, 4H); (fig. 95).

$^{13}$C-NMR (150 MHz, DMSO-$d_6$) δ: 153.5, 133.3, 133.2, 130.9, 129.6, 128.2, 128.0, 125.3, 124.4, 110.8; (fig. 96).

MS (EI, 200°C), m/e (%): 244 (100), 140, (20), 121 (33), 114 (18), 77 (5); (fig. 97).

Elemental analysis calculated for C$_{17}$H$_{11}$N$_2$: C, 83.57, H, 4.92; N, 11.47.
Found. C, 83.45; H, 5.04; N, 11.31 %.
5.2. Preparation of $N$-$\alpha$-Naphthylnicotinamide Oxime XII

This procedure involved two steps:

**Step 1: Preparation of $N$-$\alpha$-naphthylnicotinamidine 219**

To stirred anhydrous AlCl$_3$ (6.667 gm, 0.05 mole) was slowly added a mixture of 3-cyanopyridine 174 (5.205 gm, 0.05 mole), $\alpha$-naphthylamine 214 (7.159 gm, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with NaOH (5 N). The resulting mixture was extracted by chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (40-60$^\circ$C). The resulting solid was recrystallized from benzene, yield 69.8 %, mp 135-137$^\circ$C.

**Step 2: Preparation of $N$-$\alpha$-Naphthylnicotinamide Oxime XII**

$N$-$\alpha$-Naphthylnicotinamidine 219 (12.364 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The solid which separated furnished the pure amidoxime, as beige crystals on recrystallization from ethanol, mp 202-205$^\circ$C, yield 55.6 %. $R_f = 0.128$ (acetone: pet. ether (60-80$^\circ$C), 3:7 v/v).
IR (KBr, cm$^{-1}$): 3364.7 (OH, NH), 3054 (CH aromatic), 1611 (C=C aromatic), 1325 (C-N), 1127 (C-O).

$^{1}$H-NMR (600 MHz, DMSO-d$_{6}$) $\delta$: 10.87 (s, 1H, OH), 8.51 (s, 1H, NH), 8.43 (dd, 2H, $J = 10$, 2.4 Hz), 8.31 (d, 1H, $J = 8.4$ Hz), 7.9 (d, 1H, $J = 7.8$ Hz), 7.61 (d, 1H, $J = 1.8$ Hz), 7.55 (m, 3H), 7.20 (dd, 2H, $J = 5.4$, 2.4 Hz), 6.66 (d, 1H, 7.8 Hz); (fig. 99).

MS (EI, 200$^\circ$C), m/e (%): 263 (M$^+$, 14.63), 246 (70.73), 143 (19.51), 127 (21.95), 115 (100), 78 (37.8), 51 (58.53); (fig. 100).

Elemental analysis calculated for C$_{16}$H$_{13}$N$_{3}$O: C, 72.99; H, 4.98; N, 15.96%. Found: C, 73.16; H, 4.93; N, 16.07%.
5.3. Preparation of \(N\text{-}\alpha\text{-Naphthyl-2-Furamide Oxime XIII}\)

This procedure has been passed through two steps:

**Step 1: Preparation of \(N\text{-}\alpha\text{-Naphthyl-2-furamidine 220}\)**

To stirred anhydrous \(\text{AlCl}_3\) (6.667 gm, 0.05 mole) was slowly added a mixture of 2-cyanofuran 190 (4.37 ml, 0.05 mole), \(\alpha\text{-naphthylamine 214}\) (4.54 mL, 0.05 mole) in 1,1,2,2-tetrachloroethane (40 mL). The solution was heated at reflux for 30 min. It was then treated with \(\text{NaOH}\) (5 N). The resulting mixture was extracted by chloroform (100 mL). The organic layer was washed with water (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the residue was treated with pet. ether (60-80ºC). The resulting solid 220 was recrystallized from benzene, yield 69 %, mp 107-110ºC.

![Reaction Diagram](image)

**Step 2: Preparation of \(N\text{-}\alpha\text{-Naphthyl-2-furamide Oxime XIII}\)**

\(N\text{-}\alpha\text{-Naphthyl-2-furamidine 220}\) (11.81 gm, 0.05 mole) was added to a solution of hydroxylamine hydrochloride (5.2 g, 0.75 mole) in water (45 mL). The suspension was boiled for 10 min, made just alkaline with ammonia, and boiled for a further 10 min. The residue was treated with pet. ether (60-80ºC) and the solid separated furnished the pure of \(N\text{-}\alpha\text{-naphthyl-2-furamide oxime, as colourless needles on recrystallization from benzene mp 128-129ºC, R}_f = 0.279\) (acetone: petr. ether (60-80ºC), 3:7 v/v).
IR (KBr, cm\(^{-1}\)): 3419.18 (OH, NH), 3055.22 (CH aromatic), 1617 (C=C aromatic), 1388 (C-N), 1011.48 (C-O).

\(^1\)H-NMR (600 MHz, CDCl\(_3\)) δ: 8.01 (d, 1H, \(J = 8.4\) Hz), 7.84 (d, 1H, \(J = 8.4\) Hz), 7.58 (d, 1H, \(J = 8.4\) Hz), 7.53 (s, 1H, OH), 7.475 (dd, 2H, \(J = 7.2, 7.8\) Hz), 7.43 (dd, 2H, \(J = 7.2, 7.2\) Hz), 7.25 (d, 1H, \(J = 6\) Hz), 7.06 (d, 1H, \(J = 7.2\) Hz), 6.59 (s, 1H, NH); (fig. 101).

MS (EI, 200°C), \(m/e\) (%): 252 (M\(^+\), 48.4), 236 (5.9), 143 (62.7), 127 (100), 115 (83.6), 101 (10.4), 75 (19.4), 58 (57.5); (fig. 102).

Elemental analysis calculated for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_2\): C, 71.42; H, 4.79; N, 11.10 %. Found: C, 70.94; H, 4.87; N, 11.63 %.

Elemental analysis calculated for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_2\): C, 71.42; H, 4.79; N, 11.10 %. Found: C, 70.94; H, 4.87; N, 11.63 %.
RESULTS AND DISCUSSION
RESULTS AND DISCUSSION

Thermal Fragmentation of \( N-p \)-Chlorophenylbenzamide Oxime I

\( N-p \)-Chlorophenylbenzamide oxime I on thermolysis at 220-250°C under nitrogen atmosphere for 5 h produced 5-chloro-2-phenyl benzimidazole 159 and \( N \)-(4-chlorophenyl)benzamide 157 as the major products, in addition to benzonitrile 17, benzoic acid 41, \( p \)-chlorophenol 155, 3,6-dichloro-9H-carbazole 158, \( p \)-chlooroaniline 153, 2-amino-5-chlorophenol 156 as minor products as shown in Schemes (37-40).

The nature of the products obtained in all these experiments was assigned primarily by TLC analysis followed by quantitative estimations either by GC (c. f. figures 9, 10, 17, 26, 35, 41, 48, 59, 67, 75, 87 and 98), column chromatography using gradient elution technique or by fractional vacuum distillation and measurements of the physical constants including mps, bps and IR, \(^1\)HNMR, \(^{13}\)CNMR, MS and GC/MS of the pure products as compared with authentic samples as represented in details in the experimental section.

Although some of the products are present in small amounts due to the variable rate of decay of the free radical intermediates, their presence is of great importance for mechanistic interpretation.

A number of preliminary experiments were carried out to determine the proper temperature for thermolysis. The decomposition of I starts only 220°C till 250°C, it was found that 220°C is the lowest temperature at which the conversion of \( N-p \)-chlorophenylbenzamide oxime I was complete at the end of 5h thermolysis time.

The process may imply the preliminary homolysis of the N-O bond (route a) [143] to give \( N-p \)-chlorophenylbenzamidinyl and hydroxyl radical
pairs. The benzamidinyl radicals may undergo intramolecular cyclization to form 5-chloro-2-phenylbenzimidazole 159 m/e 228 [144,145], Scheme 37.

![Diagram of chemical reaction]

(Scheme 37)

Another competing pathway for the thermal fragmentation of N-p-chlorophenylbenzamide oxime I is the homolysis of the C-N bond (route b) leading to the formation of N-p-chlorophenylbenzminyl and hydroxylaminyl radical pairs. The benziminyln radical couple with a hydroxyl radical which is readily available in the reaction medium as mentioned above to produce N-(4-chlorophenyl)benzamide 157 m/e 231[146] (Scheme 38). The latter compound ultimately undergoes extended hydrolysis to give benzoic acid 41 m/e 122 and p-chloroanilino radical [147]. The latter radical may couple with hydroxyaminyl radicals followed by dehydrogenation and extrusion of nitrogen to produce p-chlorophenol 155 m/e 128, whereas the hydroxyaminyl radicals may abstract hydrogen from a suitable source to afford hydroxylamine which subsequently decomposes into ammonia and water [148] as shown in Scheme 38.
Moreover, the homolysis of the C-N bond (route b), via the tautomeric form of I as reported by Tiemann and Kruger [149], gives \( p \)-chboroanilino and benziminoxyl radical pairs. The former radical may abstract hydrogen from a suitable source to give \( p \)-chboroaniline 153, whereas the latter
radical undergoes fragmentation under the same conditions to form benzonitrile 17 and the hydroxyl radical [60], Scheme 39.

Furthermore, the 2-amino-5-chlorophenol 156 m/e 143 can reasonably be assumed through coupling of hydroxyl radical with \( p \)-chloroanilino radicals [150], Scheme 39.

A plausible mechanism for the formation of 3,6-dichloro-9H-carbazole 158 m/e 236 is through dimerization of the \( p \)-chloroanilino radicals followed by elimination of ammonia [151], as shown in Scheme 40.
GC chromatogram of these products are shown in fig. 9, p. 188. The formation of these products is in agreement with the suggested mechanism of the thermal fragmentation of \textit{N-p}\text{-}chlorophenylbenzamide oxime I as shown in Schemes (37-40).

The results are summarized in Table 1.

\textbf{Table 1.} Thermolysis products of \textit{N-p}\text{-}chlorophenylbenzamide oxime I in % yield.

<table>
<thead>
<tr>
<th>Products (^a)</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzonitrile</td>
<td>4.1</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>2.2</td>
</tr>
<tr>
<td>\textit{p}\text{-}Chlorophenol</td>
<td>6.2</td>
</tr>
<tr>
<td>\textit{p}\text{-}Chloroaniline</td>
<td>8.5</td>
</tr>
<tr>
<td>\textit{N}\text{-}(4-Chlorophenyl)benzamide</td>
<td>15.1</td>
</tr>
<tr>
<td>2-Amino-5-chlorophenol</td>
<td>6.2</td>
</tr>
<tr>
<td>3,6-Dichloro-9H-carbazole</td>
<td>7.0</td>
</tr>
<tr>
<td>5-Chloro-2-phenylbenzimidazole</td>
<td>45.2</td>
</tr>
<tr>
<td>Unchanged benzamide oxime (g)</td>
<td>(0.14)</td>
</tr>
</tbody>
</table>

\(^a\) NH\textsubscript{3} gas was detected by chemical means.

H\textsubscript{2}O as a trace amount was separated with ether and dried drops were identified by dipicrylamine test [115]
Thermal Fragmentation of $N$-$p$-Chlorophenylbenzamide Oxime I in the Presence of Naphthalene

Thermolysis of $N$-$p$-chlorophenylbenzamide oxime I at 220-250°C under nitrogen atmosphere in the presence of naphthalene as a radical scavenger gave α- and β-naphthols 76 and 77, respectively in addition to the previously mentioned products in case of neat thermolysis of $N$-$p$-chlorophenylbenzamide oxime I.

The formation of these products can be assumed to follow the series of reaction shown in Scheme 37 implies the preliminary homolysis of N-O bond (route a) forming $N$-$p$-chlorophenylbenzamidinyl and hydroxyl radical pairs. The former radical may behaves the same route as in the last experiment (neat thermolysis of compound I; Scheme 37). Whereas the hydroxy radicals attack the naphthalene nucleus in the α- and β-position through the formation of the benzyclohexadienyl free radical intermediate (i) which subsequently dehydrogenates to give α- and β-naphthols 76 and 77 [59]. (Estimated by GLC 16 % yield in the ratio 1:6, respectively), as shown in Scheme 41.
It is noteworthy that, in each case the $\beta$-isomer is predominating in spite of the observed reactivity of the $\alpha$-position in naphthalene as compared with its $\beta$-position towards radical substitution [152].
Thermal Fragmentation of \( \textit{N-}{p}\text{-Chlorophenylbenzamide Oxime I} \) in Tetralin

Thermolysis of \( \textit{N-}{p}\text{-chlorophenylbenzamide oxime I} \) under reflux at boiling anhydrous tetralin as hydrogen donor (distillation over lithium aluminum hydride under nitrogen) bp ca. 210°C for 8 h formed 1-hydroxytetralin 81, \( \alpha\)-tetralone 78 and 1,1'-bitetralyl 79 beside the same products as mentioned before in case of thermolysis of compound I, as shown in Schemes 37-40.

A possible pathway for the formation of 1-hydroxytetralin 81 m/e 148 (8.20 %), \( \alpha\)-tetralone 78 m/e 146 (10 %) and 1,1'-bitetralyl 79 (m/e 262 (15 %) may take place through a process of initial hydrogen abstraction [153] from the solvent nuclei (tetralin) to form 1-tetralyl radicals that couple with hydroxyl radicals which are readily available in the reaction medium, followed by oxidative dehydrogenation and the 1-tetralyl radicals may undergo dimerization [154]; respectively as shown in Scheme 42.
It is noticed that $\alpha$-and $\beta$-naphthols were absent from the pyrolysate as demonstrated by GC/MS. This is because that the hydroxyl radical prefers to couple with 1-tetralyl radical to form 1-hydroxytetralin, hence consumption of hydroxyl radical due to the presence of other competing pathway namely H-abstraction.

GC chromatogram of these products are shown in (fig. 10, p. 189). The products are in accord with the suggested mechanism of thermolysis of I in tetralin.
Thermal Fragmentation of \textit{N-p}-Nitrophenylbenzamide Oxime II

\textit{N-p}-Nitrophenylbenzamide oxime II was subjected to thermolysis by reflux at 220-250 °C under nitrogen stream. Benzonitrile 17, benzoic acid 41, 3,6-dinitro-9H-carbazole 164, 6-nitro-2-phenylbenzoxazole 165, p-nitrophenol 162 and 5-nitro-1,2-diphenylbenzimidazole 166, \textit{p}-nitroaniline 160 as the minor products together with \textit{N}-(4-nitrophenyl)benzamide 163 and 5-nitro-2-phenylbenzimidazole 167 as the major products as shown in Schemes (43-46) and Table 2.

The nature of the identified products in the thermolysis of \textit{N-p}-nitrophenylbenzamide oxime II points to a free radical mechanism involving the homolysis of the N-O bond (route a) [155] to give \textit{N-p}-nitrophenylbenzamidinyl and hydroxyl radical pairs. The benzamidinyl radical undergoes intramolecular cyclization to form 5-nitro-2-phenylbenzimidazole 167 m/e 239 [144,145] as shown in Scheme 43.

![Scheme 43](image)

Another competing pathway for thermal fragmentation of \textit{N-p}-nitrophenylbenzamide oxime II is the homolysis of the C-N bond (route b) to form \textit{p}-nitrophenylbenzimiminyl and hydroxyaminyl radical pairs. The former radicals may couple with hydroxyl radicals which are readily available from the route a, Scheme 44 to give \textit{N}-(4-nitrophenyl)benzamide...
163 m/e 242, which ultimately undergoes decomposition under the same conditions to form benzoic acid 41 m/e 122 and p-nitroanilino radicals [147]. The latter radicals may couple with the hydroxyaminyl radicals followed by dehydrogenation and extrusion of nitrogen to produce p-nitrophenol 162 m/e 139. Moreover, the hydroxyaminyl radicals may abstract hydrogen from a suitable source to afford hydroxylamine which subsequently decomposes into ammonia and water [148] as shown in Scheme 44.
A possible pathway for the formation of 5-nitro-1,2-diphenylbenzimidazole 166 m/e 315 can be assumed to take place through coupling of \( p \)-nitroanilino radicals with benzimimyl radicals to give anilinobenzyl-ideneamine, which ultimately undergoes intramolecular cyclization, Scheme 44.

Moreover, the homolysis of the C-N bond (route b), via the tautomeric form of II as reported by Tiemann and Kruger [149], to give \( p \)-nitroanilino and benziminoxyl radical pairs. The \( p \)-nitroanilino radical may abstract hydrogen to give \( p \)-nitroaniline 160, whereas the benziminoxyl radicals undergo fragmentation to form benzonitrile 17 and hydroxyl radicals [60], Scheme 45.

The observed absence of 2-amino-5-nitrophenol can be attributed to its consumption in the formation of 6-nitro-2-phenylbenzoxazole 165 m/e 240 which can be suggested to proceed through condensation of benzoic acid which is readily available in the reaction medium (Scheme 44) with 2-amino-5-nitrophenol followed by elimination of water [156], Scheme 45.
The formation of 3,6-dinitro-9H-carbazole 164 m/e 257 can be explained on the basis of dimerization of \( p \)-nitroanilino radicals followed by elimination of ammonia [150], Scheme 46.

GC chromatogram of these products are shown in fig. 17, p. 193. The products are in agreement with the suggested mechanism of the thermal fragmentation of \( N-p \)-nitrophenylbenzamide oxime II as shown in Schemes (43-46).

**Table 2.** Thermolysis products of \( N-p \)-nitrophenylbenzamide oxime II in % yield

<table>
<thead>
<tr>
<th>Products a</th>
<th>II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzonitrile</td>
<td>2.5</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>3.1</td>
</tr>
<tr>
<td>( p )-Nitrophenol</td>
<td>4.5</td>
</tr>
<tr>
<td>( p )-Nitroaniline</td>
<td>5.8</td>
</tr>
<tr>
<td>( N-(4 \text{-Nitrophenyl}) )benzamide</td>
<td>12.8</td>
</tr>
<tr>
<td>3,6-Dinitro-9H-carbazole</td>
<td>6.5</td>
</tr>
<tr>
<td>6-Nitro-2-phenylbenzoxazole</td>
<td>6.8</td>
</tr>
<tr>
<td>5-Nitro-1,2-diphenylbenzimidazole</td>
<td>9.2</td>
</tr>
<tr>
<td>5-Nitro-2-phenylbenzimidazole</td>
<td>46.1</td>
</tr>
<tr>
<td>Recovered benzamide oxime (g)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

*NH3 gas was detected by chemical means.

\( \text{H}_2 \text{O} \) as a trace amount was separated with dry ether.
Thermal Fragmentation of $N$-$p$-Methoxyphenylbenzamide Oxime III

$N$-$p$-Methoxyphenylbenzamide oxime III on the thermolysis by refluxing in an atmosphere of nitrogen at 220-250ºC leads to the formation of benzonitrile 17, $p$-anisidine 168, phenol 74a, benzoic acid 41, $N$-(4-methoxyphenyl) benzamide 170, 6-methoxy-2-phenylbenzoxazole 172, 3,6-dimethoxy-9H-carbazole 171 and 5-methoxy-2-phenylbenzimidazole 173 as the major product.

The formation of the identified products strongly points to a free radical mechanism starting by the preferential homolysis of the N-O bond Scheme 47 (route a) rather than the C-N bond (route b) [155] forming $N$-$p$-methoxyphenylbenzamidinyl and hydroxyl radical pairs. The benzamidinyl radicals undergo intramolecular cyclization to give 5-methoxy-2-phenylbenzimidazole 173 m/e 224 [105, 145], Scheme 47.

Another competing pathway for thermal fragmentation of $N$-$p$-methoxyphenylbenzamide oxime III is the homolysis of the C-N bond (route b) to from $N$-$p$-methoxyphenylbenziminyl and hydroxyl radicals which are readily available in the reaction medium to yield $N$-(4-methoxyphenyl)benzamide 170 m/e 227, which ultimately undergo
extended hydrolysis to give benzoic acid 41 m/e 122 and \( p \)-anisyl radicals [147].

It may be noted that the high yield of \( N \)-(4-methoxyphenyl) benzamide observed among pyrolysates of \( N \)-\( p \)-methoxyphenyl benzamide oxime III was attributed to the high reactivity of the anisyl as compared with benzoyl radicals; hence the predominant formation of benzoic acid 41 and \( p \)-anisidine 168 as shown in Scheme 48.

Also, the hydroxaminyl radical may abstract hydrogen from a suitable source to afford hydroxylamine which subsequently decomposes into ammonia and water [148] as shown in Scheme 48.
A possible pathway for the formation of phenol can be explained on the basis of bimolecular reaction between \( p \)-anisidine molecules to form \( N \)-methyl-\( p \)-aminophenol which undergoes further pyrolysis to give phenol 74a m/e 94 and methylamine which was identified as its hydrochloride derivative [150, 157]; Scheme 49.

\[
\begin{align*}
\text{NH}_2 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{NH}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{NH}_2 \\
\end{align*}
\]

\[
\text{NH-CH}_3 \\
\text{OH} \\
\text{OH} \\
\text{m/e} 94 \\
\text{CH}_3 \text{NH}_2 \\
\text{168} \\
\text{74a} \\
\]

(Scheme 49)

Furthermore, the homolysis of the C-N bond (route b) via the tautomeric form of III as reported by Tiemann and Kruger [149] to give \( p \)-anisyl and benziminoxyl radical pairs. The anisyl radical may abstract hydrogen to give \( p \)-anisidine 168, whereas the benziminoxyl radical undergoes fragmentation to form benzonitrile 17 and the hydroxyl radical [60]; Scheme 50.

A plausible mechanism for the formation of 6-methoxy-2-phenylbenzoxazole 172 m/e 225 is through condensation of benzoic acid, which is readily available in the reaction medium, with 2-amino-5-methoxyphenol followed by elimination of water [156], Scheme 50.
An alternative reasonable mechanism for the formation of 3,6-dimethoxy-9H-carbazole 171 is suggested through dimerization of \( p \)-anisyl radical followed by loss of ammonia [151] as shown in Scheme 51.

GC chromatogram of these products are shown in fig. 26, p. 198. The products are in agreement with the suggested mechanism of the thermal fragmentation of \( N\)-\( p \)-methoxyphenylbenzamide oxime III as shown in Schemes (47-51).
**Table 3.** Thermolysis products of \( N-p \)-methoxyphenylbenzamide oxime III in % yield

<table>
<thead>
<tr>
<th>Products</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzonitrile</td>
<td>3.1</td>
</tr>
<tr>
<td>( p )-Anisidine</td>
<td>5.1</td>
</tr>
<tr>
<td>Phenol</td>
<td>4.5</td>
</tr>
<tr>
<td>( N )-(4-Methoxyphenyl)benzamide</td>
<td>19.5</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>1.8</td>
</tr>
<tr>
<td>3,6-Dimethoxy-9H-carbazole</td>
<td>5.2</td>
</tr>
<tr>
<td>6-Methoxy-2-phenylbenzoxazole</td>
<td>5.4</td>
</tr>
<tr>
<td>5- Methoxy-2-phenylbenzimidazole</td>
<td>52.6</td>
</tr>
<tr>
<td>Recovered benzamide oxime (g)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

\( ^a \)NH\(_3\) gas was detected by chemical means.

\( H_2O \) as a trace amount was separated with ether.
Thermal Fragmentation of $N$-Phenylnicotinamide Oxime IV

Heating of $N$-phenylnicotinamide oxime IV under nitrogen atmosphere at 220-250°C gave rise to nicotnonitrile 177, aniline 71a, phenol 74a, nicotinic acid 176, 9H-carbazole 179 and 2-(pyridin-3-yl)benzoxazole 180 in addition to $N$-phenylnicotinamide 178 and 2-(pyridin-3-yl)benzimidazole 181 as the major products (15.1 and 65.5 %, respectively) as shown in Schemes 52-55.

Although some of the products are present in small amounts due to the variable rate of decay of the free radical intermediates, they are of great importance for mechanistic interpretation.

The process may imply the preliminary homolysis of the N-O bond (route a, Scheme 52) [155] to give $N$-phenylnicotinamidinyl and hydroxyl radical pairs. The nicotinamidinyl radical undergoes intramolecular cyclization to form 2-(pyridin-3-yl)benzimidazole 181 m/e 195 (60.5 %) [144, 145]; Scheme 52.

Also, another competing pathway for the thermal fragmentation of $N$-phenylnicotinamide oxime IV is the homolysis of the C-N bond (route b; Scheme 53) leading to the formation of $N$-phenylnicotininiminy1 and hydroxyaminyl radical pairs. The nicotininiminy1 radical may couple with hydroxyl radical which is readily available in the reaction medium (route a;
Scheme 52) to produce N-phenylnicotinamide 178 m/e 198, which ultimately undergoes extended hydrolysis and decomposition under the same conditions to give nicotinic acid 176 m/e 123 and anilino radical [147]. The latter radical may couple with the hydroxyaminyl radical (route b) followed by dehydrogenation and extrusion of nitrogen to yield phenol 74a m/e 94, whereas the hydroxyaminyl radical may abstract hydrogen from a suitable source to give hydroxylamine which decomposes into ammonia and water [148] as shown in Scheme 53.
On the other hand, the homolysis of the C-N bond (route b), via the tautomeric form of IV as reported by Tiemann and Kruger [149], gives anilino and nicotiniminoxyl radical pairs. The anilino radical may abstract hydrogen to give aniline 71a, whereas the nicotiniminoxyl radical undergoes fragmentation to form nicotinonitrile 177 and the hydroxyl radical [60], Scheme 54.

The observed absence of o-aminophenol can be attributed to its consumption in the formation of 2-(pyridn-3-yl)benzoxazole 180 (6.5%) m/e 196 which can be suggested to proceed through condensation of nicotinic acid which is readily available in the reaction medium with o-aminophenol followed by elimination of water [121]; Scheme 54.

A plausible mechanism for the formation of 9H-carbazole 179 m/e 167 is through dimerization of the anilino radicals followed by loss of ammonia [150] as shown in Scheme 55.
GC chromatogram of these products are represented in (fig. 35, p. 203). The products are in agreement with the suggested mechanism of thermal fragmentation of \(N\)-phenylnicotinamide oxime IV as shown in Schemes 52-55. The results are given in Table 4.

**Table 4.** Thermolysis products of \(N\)-phenylnicotinamide oxime IV in % yield.

<table>
<thead>
<tr>
<th>Products (^a)</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinonitrile</td>
<td>3.1</td>
</tr>
<tr>
<td>Phenol</td>
<td>3.2</td>
</tr>
<tr>
<td>Aniline</td>
<td>4.8</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>2.3</td>
</tr>
<tr>
<td>(N)-Phenylnicotinamide</td>
<td>13.1</td>
</tr>
<tr>
<td>9H-Carbazole</td>
<td>4.2</td>
</tr>
<tr>
<td>2-(Pyridin-3-yl)benzoazole</td>
<td>6.2</td>
</tr>
<tr>
<td>2-(Pyridin-3-yl)benzimidazole</td>
<td>60.5</td>
</tr>
<tr>
<td>Unchanged nicotinamide oxime (g)</td>
<td>(0.14)</td>
</tr>
</tbody>
</table>

\(^a\)NH\(_3\) gas was detected by chemical means. H\(_2\)O as a trace amount was separated with ether.
Thermal Fragmentation of N-Phenylnicotinamide Oxime IV in Naphthalene

Thermolysis of N-phenylnicotinamide oxime IV at 220-250°C under nitrogen atmosphere in presence of naphthalene as radical scavenger gave α- and β-naphthols 76 and 77, respectively in addition to the previously mentioned products in case of thermolysis of N-phenylnicotinamide oxime IV without solvents.

These results point strongly to a free radical mechanism starting by the homolysis of the N-O bond leading to the formation of N-p-nicotinamidinyl and hydroxyl free radicals. The nicotinamidinyl radicals may behave the same route as shown in Scheme 52 (neat thermolysis of IV); whereas the hydroxyl radical may substitute on aromatic nuclei (naphthalene) in the α- and β-position through the formation of benzocyclohexadienyl free radical intermediate (i) which subsequently dehydrogenates to give α- and β-naphthols 76 and 77 [59] (estimated by GLC 20 % yield in the ratio 1:5 respectively) as shown in Scheme 56.

(Scheme 56)
Thermal Fragmentation of N-Phenylnicotinamide Oxime IV in Tetralin

Heating of N-phenylnicotinamide oxime IV under reflux in boiling anhydrous tetralin as a hydrogen donor bp ca. 210ºC for 8 h afforded 1-hydroxytetralin 81, α-tetralone 78 and 1,1′-bitetralyl 79 in addition to the previously mentioned products as cited before in case of compound I; Scheme 42.

The formation of such products strongly suggested that thermolysis of IV proceeds through a process of initial hydrogen abstraction [153] from the solvent nuclei (tetralin) to give 1-tetralyl free radicals that couple with the hydroxyl radicals which are readily available in the reaction medium to from 1-hydroxytetralin 81 (8.2 %), followed by oxidative dehydrogenation to yield α-tetralone 78 (10 %). Moreover, the 1-tetralyl radicals may undergo dimerization [154] to produce 1,1′-bitetralyl 79 (15 %) as shown in Scheme 42.

It is noteworthy that α- and β-naphthols was absent from the thermolysate as demonstrated by GC/MS. This is because the hydroxyl radicals prefer coupling with 1-tetralyl radicals to yield 1-hydroxytetralin.
Thermal Fragmentation of *N*-p-Methylphenylnicotinamide Oxime V

*N*-p-Methylphenylnicotinamide oxime V undergoes thermolysis by refluxing in an atmosphere of nitrogen at 220-250°C to afford nicotinonitrile 177, *p*-toluidine 75b, *p*-cresol 74b, 2-amino-5-methylphenol 183, nicotinic acid 176, 3,6-dimethyl-9H-carbazole 185 in addition to *N*-(4-methylphenyl) nicotinamide 184 and 5-methyl-2-(pyridin-3-yl)benzimidazole 186 as the major products (16.2 and 62.1 %), respectively.

The formation of these products may be suggested to start with homolysis of the N-O bond forming *N*-p-methylphenylnicotinamidinyl and hydroxyl free radicals. The facility of bond rupture parallels a decrease in dissociation energy values, being of the order 104, 70 and 48 Kcal.mol\(^{-1}\) (at 25°C) for O-H, C-N and N-O bonds, respectively [155]. The nicotinamidinyl radical undergoes intramolecular cyclization to give 5-methyl-2-(pyridin-3-yl)benzimidazole 186 (m/e 209) 62.1 % [144, 145] as shown in Scheme 57.

On the other hand, Scheme 58 includes the C-N bond homolysis (route b), to give *N*-p-methylphenylnicotiniminyl and hydroxyaminyl free radicals. The nicotiminyl radical may couple with hydroxyl radicals (route a, Scheme 57) to form *N*-(4-methylphenyl)nicotinamide 184 m/e
212, which ultimately undergoes extended hydrolysis and fragmentation under the conditions used to give nicotinic acid 176 and p-methylanilino radicals [147]. The p-methylanilino radicals may couple with the hydroxyaminyl radicals which are readily available in the reaction medium followed by oxidative dehydrogenation and extrusion of nitrogen to produce p-cresol 74b m/e 108, whereas the hydroxyaminyl radicals may abstract hydrogen from a suitable source for hydroxylamine which subsequently decomposes into ammonia and water [148] as shown in Scheme 58.

(Scheme 58)
Furthermore, the homolysis of the C-N bond (route b), via the tautomeric from of V as reported by Tiemann and Kruger [149] to give \( p \)-methylanilino and nicotiniminoxyl radical pairs. The former radicals may abstract hydrogen to give \( p \)-toluidine 75b, whereas the nicotiniminoxyl radicals undergo decomposition to form nicotinonitrile 177 and the hydroxyl radical [60], Scheme 59.

The formation of 2-amino-5-methylphenol 183 can be assumed to proceed through attack of the hydroxyl free radicals with \( p \)-toluidine on the ortho-position [150], Scheme 59.

Possible route for the formation 3,6-dimethyl-9H-carbazole 185 m/e 195 through dimerization of \( p \)-methylanilino radical followed by cyclization and extrusion of ammonia [150], Scheme 60.
GC chromatogram of these products are shown (fig. 41, p. 207). The products are analogous to that obtained from thermolysis of \( N-p-\) methylnicotinamide oxime \( \text{V} \) as shown in Schemes (57-60). The results are summarized in Table 5.

**Table 5.** Thermolysis products of \( N-p \)-methylphenylnicotinamide oxime \( \text{V} \) in % yield

<table>
<thead>
<tr>
<th>Products (^a)</th>
<th>( \text{V} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinonitrile</td>
<td>2.5</td>
</tr>
<tr>
<td>( p )-Cresol</td>
<td>2.8</td>
</tr>
<tr>
<td>( p )-Toluidine</td>
<td>3.3</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>2.2</td>
</tr>
<tr>
<td>( N )-(4-Methylphenyl)nicotinamide</td>
<td>14.2</td>
</tr>
<tr>
<td>2-Amino-5-methylphenol</td>
<td>2.1</td>
</tr>
<tr>
<td>3,6-Dimethyl-9H-carbazole</td>
<td>3.6</td>
</tr>
<tr>
<td>5-Methyl-2-(pyridin-3-yl)benzimidazole</td>
<td>62.1</td>
</tr>
<tr>
<td>Unchanged nicotinamide oxime (g)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

\(^a\) NH\(_3\) gas was detected by chemical means.

\( \text{H}_2\text{O} \) as a trace amount was separated with ether.
Thermal Fragmentation of \(N-p\)-Chlorophenylnicotinamide Oxime VI

\(N-p\)-Chlorophenylnicotinamide oxime VI on thermolysis at 220-250\(^\circ\)C under nitrogen atmosphere for 5 h leads to the formation of \(p\)-chloroaniline 153, nicotinic acid 176, \(p\)-chlorophenol 155, 3,6-dichloro-9H-carbazole 158, 2-amino-5-chlorophenol 156, beside 5-chloro-2-(pyridin-3-yl)benzimidazole 189 and \(N\)-(4-chlorophenyl)nicotinamide 188 (60.5 and 15.2 \%, respectively) as the major products as shown in Schemes 61-64.

The formation of the identified products strongly points to a free radical mechanism starting by the preferential homolysis of the N-O bond (route a) rather than the C-N bond (route b) [143] forming \(N-p\)-chlorophenylnicotinamidinyll and hydroxyl radical pairs. The nicotinamidinyll radical undergoes intermolecular cyclization to give 5-chloro-2-(pyridin-3-yl)benzimidazole 189 m/e 229 (60.5\%) [144,145]; Scheme 61.

As shown in Scheme 62 which includes the homolysis of the C-N bond (route b) giving \(N-p\)-chlorophenylnicotiniminyll and hydroxyaminyl free radicals. The nicotiniminyll radicals may couple with hydroxyl radicals (route a) to form \(N\)-(4-chlorophenyl)nicotinamide 188 m/e 233, which ultimately undergoes extended hydrolysis and decomposition into nicotinic acid 176 and \(p\)-chloroanilino radical [147]. The latter radicals may couple with the hydroxyaminyl followed by dehydrogenation and extrusion of
nitrogen to produce \( p \)-chlorophenol 155 m/e 129 [158]. Also, the hydroxyaminyl radical may abstract hydrogen from a suitable source to form hydroxylamine which subsequently decomposes under the same conditions into ammonia and water [148] as shown in Scheme 62.

\[ \begin{align*}
\text{VI} & \quad \text{route b} \\
\text{ VI } & \quad \text{NH-OH} \\
\text{ m/e 233 } & \quad \text{NH-OH} + \text{H} \\
\text{Cl-C=O } & \quad \text{3NH}_2\text{-OH} \\
\text{m/e 233 } & \quad \text{NH}_3 + \text{N}_2 + 3\text{H}_2\text{O} \\
\text{Cl-C=O } & \quad \text{NH}_3 + \text{N}_2 + 3\text{H}_2\text{O} \\
\end{align*} \]
Another competing pathway for the thermal fragmentation of *N*-p-chlorophenylnicotinamide oxime VI is the homolysis of the C-N bond (route b) via the tautomeric form of VI as reported by Tiemann and Kruger [149] to give *p*-chloroanilino and nicotiniminoxyl radical pairs. The *p*-chloroanilino radicals may abstract hydrogen to yield *p*-chloroaniline 153, whereas the nicotiniminoxyl radicals undergo decomposition to form nicotinonitrile 177 and hydroxyl radical [60], Scheme 63.

![Scheme 63](image)

The formation 2-amino-5-chlorophenol 156 may be explained to take place through the interaction of the hydroxyl radicals with *p*-chloroaniline 153 on the ortho-position [150]; Scheme 63.

An alternative reasonable mechanism for the formation 3,6-dichloro-9H-carbazole 158 m/e 238 may be suggested to proceed through dimerization of *p*-chloroanilino radical followed by cyclization and loss of ammonia [151] as shown in Scheme 40.

GC chromatogram of these products are found is (fig. 48, p. 211). The products are in agreement with the suggested mechanism of thermal
fragmentation of $N$-$p$-chlorophenynicotinamide oxime VI as shown in Schemes (61-63).

The results are given in Table 6.

**Table 6.** Thermolysis products of $N$-$p$-chlorophenynicotinamide oxime VI in % yield

<table>
<thead>
<tr>
<th>Products</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotinonitrile</td>
<td>2.6</td>
</tr>
<tr>
<td>$p$-Chlorophenol</td>
<td>3.0</td>
</tr>
<tr>
<td>$p$-Chloroaniline</td>
<td>5.1</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>2.4</td>
</tr>
<tr>
<td>2-Amino-5-chlorophenol</td>
<td>2.5</td>
</tr>
<tr>
<td>$N$-(4-Chlorophenyl)nicotinamide</td>
<td>13.2</td>
</tr>
<tr>
<td>5-Chloro-2-(pyridin-3-yl)benzimidazole</td>
<td>60.0</td>
</tr>
<tr>
<td>Residue (g)</td>
<td>(0.02)</td>
</tr>
</tbody>
</table>

$^a$ NH$_3$ gas was detected by chemical means.

H$_2$O as a trace amount was separated with ether.
Thermal Fragmentation of N-Phenyl-2-Furamide Oxime VII

N-Phenyl-2-furamide oxime VII undergoes thermolysis at 220-250°C under nitrogen atmosphere for 5 h gave rise to 2-furoic acid 192, furil 193, 2-furonitrile 195, aniline 71a, 9H-carbazole 179, phenol 74a, 2-furamide 194, 2-(furan-2-yl)benzoxazole 196, N-phenyl-2-furamide 197 in addition to 2-(furan-2-yl)-1H-benzimidazole 198 (37.1 %) as the major product.

Formation of the various products can be assumed to follow the series of reactions shown in Schemes (64-67), which involves preliminary homolysis of the N-O bond (route a) [155] to form N-phenyl-2-furamidinyl and hydroxyl radical pairs. The furamidinyl radical undergoes intramolecular cyclization to give 2-(furan-2-yl)benzimidazole 198 m/e 184 [144, 145] as shown in Scheme 64.

Another competing pathway for thermal fragmentation of N-phenyl-2-furamide oxime VII is the homolysis of the C-N bond (route b) leading to the formation to N-phenyl-2-furiminyl and hydroxyaminyl free radicals. The furiminyl radicals may couple with hydroxyl radicals, which are readily available in the reaction medium, to yield N-phenyl-2-furamide 197
m/e 187 [159] as shown in Scheme 65. The latter compound undergoes extended hydrolysis with fragmentation under the conditions used forming 2-furoic acid 192 m/e 112 and anilino radical [147]. The anilino radicals may couple with the hydroxyaminyl radical followed by oxidative dehydrogenation and extrusion of nitrogen to give phenol 74a m/e 94 [158] (Scheme 65).

Moreover, the hydroxyaminyl radical (route b, Scheme 65) may abstract hydrogen from a suitable source to give hydroxylamine which ultimately decomposes into ammonia and water [147]; Scheme 65.
On the other hand, Scheme 66 involves the homolysis of the C-N bond (route b) for thermolysis of $N$-phenyl-2-furamide 197 under the same conditions to form 2-furoic acid 192 m/e 112, furil 193 m/e 190 and 2-furamide 194 m/e 111 through furoyl and anilino radical pairs. The furoyl radicals can be considered as the precursor of the aforementioned products [159] through coupling with hydroxyl radical, dimerization and interaction with ammonia, respectively as shown in Scheme 66.

Furthermore, the homolysis of the C-N bond (route b), via the tautomeric form of VII as reported by Tiemann and Kruger [149] to give anilino and furiminoxyl radical pairs. The anilino radicals may abstract hydrogen to give aniline, whereas the furiminoxyl radicals undergo fragmentation to form 2-furonitrile 195 and hydroxyl radicals [60], Scheme 67.

The observed absence of $o$-aminophenol can be attributed to its incorporation in the formation of 2-(furan-2-yl)benzoxazole 196 m/e 185 which can be suggested to proceed through condensation of 2-furoic acid,
which is present in the reaction medium, with o-aminophenol followed by elimination of water [160]; Scheme 67.

The formation of 9H-carbazole 179 m/e 167 can be explained through dimerization of anilino radicals followed by intramolecular cyclization with extrusion of ammonia [150] as shown in Scheme 55.

The formation of 2-furoic acid 192 and aniline 71a through two routes (Schemes 65, 66 and route b) may account for their high yields among the isolated products, see Table 7.

GC chromatogram of these mentioned products are found in (fig. 59, p. 217). These products are in accord with the suggest mechanism of thermal fragmentation of N-phenyl-2-furamide oxime VII as shown in Schemes 65-67.

The results are summarized in Table 7.
Table 7. Thermolysis product of *N*-phenyl-2-furamide oxime VII in % yield.

<table>
<thead>
<tr>
<th>Products a</th>
<th>VII</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Furonitrile</td>
<td>2.5</td>
</tr>
<tr>
<td>2-Furoic acid</td>
<td>10.2</td>
</tr>
<tr>
<td>2-Furamide</td>
<td>1.8</td>
</tr>
<tr>
<td>Aniline</td>
<td>12.1</td>
</tr>
<tr>
<td>Furil</td>
<td>2.2</td>
</tr>
<tr>
<td><em>N</em>-Phenyl-2-furamide</td>
<td>13.4</td>
</tr>
<tr>
<td>Phenol</td>
<td>3.1</td>
</tr>
<tr>
<td>2-(Furan-2-yl)benzoxazole</td>
<td>6.8</td>
</tr>
<tr>
<td>9H-Carbazole</td>
<td>6.3</td>
</tr>
<tr>
<td>2-(Furan-2-yl)benzimidazole</td>
<td>37.1</td>
</tr>
<tr>
<td>Recovered benzamide oxime (g)</td>
<td>(1.1)</td>
</tr>
</tbody>
</table>

aNH₃ gas was detected by chemical test.
H₂O as a trace amount was separated by ether.
Thermal Fragmentation of \textit{N}-Phenyl-2-Furamide Oxime VII in naphthalene as Radical Scavenger

Thermolysis of \textit{N}-phenyl-2-furamide oxime VII at 220-250°C under nitrogen stream in the presence of naphthalene as radical trap gave rise to \( \alpha \)- and \( \beta \)-naphthols 76 and 77, respectively (20 \%) in addition to the aforementioned products.

The formation of these products can be assumed to follow the series of reaction shown in Scheme 68 which implies \textit{N}-phenylfuramidinyl and hydroxyl free radicals. The normal fate of furamidinyl radicals was discussed as shown previously (Scheme 64, route a). Moreover, the hydroxyl radicals may attack naphthalene nuclei in the \( \alpha \)-and \( \beta \)-positions through the formation of the benzocyclohexadienyl free radical intermediates (i) which subsequently dehydrogenate to form \( \alpha \)- and \( \beta \)-naphthols 76 and 77 [59] (estimated by GLC 20 \% yield in the ratio 1:5, respectively) as in Scheme 68.

\[ \text{(Scheme 68)} \]
Thermal Fragmentation of \textit{N}-\textit{p}-Methylphenyl-2-Furamide Oxime VIII

Thermolysis of \textit{N}-\textit{p}-methylphenyl-2-furamide oxime \textbf{VIII} on heating at 220-250°C under nitrogen atmosphere gave rise to 2-furonitrile \textbf{195}, \textit{p}-cresol \textbf{74b}, \textit{p}-toluidine \textbf{75b}, 3,6-dimethyl-9H-carbazole \textbf{185}, 2-furoic acid \textbf{192} and \textit{N}-(4-methylphenyl)-2-furamide \textbf{200} in addition to 6-methyl-2-(furan-2-yl) benzoxazole \textbf{201} and 5-methyl-2-(furan-2-yl) benzimidazole \textbf{202} as the major products (18.2 and 47.5 \%) as shown in Schemes 69-71.

The nature of the products suggest the preliminary homolysis of the N-O bond [155] (Scheme 69, route a) giving \textit{N}-\textit{p}-methylphenyl-2-furamidinyl and hydroxyl radical pairs. The former radical undergoes intramolecular cyclization to form 5-methyl-2-(furan-2-yl) benzimidazole \textbf{202} m/e 198 (47.5 \%) [144, 145]; Scheme 69; whereas the fate of the hydroxyl radicals was discussed as mentioned before as in Scheme 70.

Another competing pathway for thermolysis of \textit{N}-\textit{p}-methylphenyl-2-furamide oxime \textbf{VIII} is the homolysis of the C-N bond (route b: Scheme 70) forming \textit{N}-\textit{p}-methylphenyl-2-furiminyl and hydroxyaminyl free radicals. The furiminyln radicals may couple with hydroxyl radicals to afford \textit{N}-(4-methylphenyl)-2-furamide \textbf{200} m/e 201 (18.1\%) which ultimately undergoes extended hydrolysis and decomposes to give 2-furoic acid \textbf{192} m/e 112 and \textit{p}-methylanilino radicals [147]. The latter ones may
couple with the hydroxyaminyl radicals in the reaction medium (route b) followed by dehydrogenation and elimination of nitrogen to yield \( p \)-cresol 74b m/e 108 [158]. Moreover, the hydroxyaminyl radicals may abstract hydrogen from a suitable source to produce hydroxylamine which subsequently decomposes into ammonia and water [148] as in Scheme 70.

(Scheme 70)
Furthermore, Scheme 71 also includes the homolysis of the C-N bond (route b), via the tautomeric form of VIII as reported by Tiemann and Kruger [149], affording p-methylanilino and 2-furiminoxyl radical pairs. The p-methylanilino radicals may abstract hydrogen to give p-toluidine 75b, whereas the 2-furiminy radicals undergo decomposition into 2-furonitrile 195 and hydroxyl radical [60]; Scheme 71.

The formation of p-toluidine 75b by both two Schemes (Schemes 70 and 71; route b) may explained its high yield among the isolated products.

A possible pathway for the formation of 6-methyl-2-(furan-2-yl)benzoxazole 201 m/e 199 through condensation of 2-furoic acid 192 in the reaction medium with 2-amino-5-methylphenol followed by elimination of water [131]; Scheme 71.
The observed absence of 2-amino-5-methylphenol 183 among the identified products can be attributed to its incorporation in the formation of 6-methyl-2-(furan-2-yl)benzoxazole 201.

A possible route for the formation of 3,6-dimethyl-9H-carbazole 185 m/e 195 can be suggested to take place through dimerization of \( p \)-methylanilino free radicals followed by intramolecular cyclization and elimination of ammonia [150] as shown in Scheme 60 as mentioned previously.

GC chromatogram of these products are found in (fig. 67, p. 222). These observed products are in agreement with the suggested mechanism of thermolysis of \( N-p \)-methylphenyl-2-furamide oxime VIII as shown in Schemes 69-71.

The results are given in Table 8.

**Table 8.** Thermolysis products of \( N-p \)-methylphenyl-2-furamide oxime VIII in % yield.

<table>
<thead>
<tr>
<th>Products (^a)</th>
<th>VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Furonitrile</td>
<td>5.3</td>
</tr>
<tr>
<td>2-Furoic acid</td>
<td>2.8</td>
</tr>
<tr>
<td>( p )-Toluidine</td>
<td>10.5</td>
</tr>
<tr>
<td>( P )-Cresol</td>
<td>4.2</td>
</tr>
<tr>
<td>3,6-Dimethyl-9H-carbazole</td>
<td>7.1</td>
</tr>
<tr>
<td>( N )-(4-Methylphenyl)-2-furamide</td>
<td>16.2</td>
</tr>
<tr>
<td>6-Methyl-2-(furan-2-yl)benzoxazole</td>
<td>6.9</td>
</tr>
<tr>
<td>Methyl-2-(furan-2-yl) benzimidazole</td>
<td>45.5</td>
</tr>
<tr>
<td>Recovered benzamide oxime (g)</td>
<td>(0.5)</td>
</tr>
</tbody>
</table>

\(^a\) NH\(_3\) as was detected by chemical means

H\(_2\)O as a trace amount was separated by ether.
Thermal Fragmentation of N-p-Chlorophenyl-2-Furamide Oxime IX

Heating of N-p-chlorophenyl-2-furamide oxime IX at 220-250°C for 5 h under nitrogen atmosphere gives rise to 2-furonitrile 195, p-chlorophenol 155, p-chloroaniline 153, 2-furoic acid 192, 3,6-dichloro-9H-carbazole 158 and 6-chloro-2-(furan-2-yl)benzoxazole 204 in addition to N-(4-chlorophenyl)-2-furamide 205 and 5-chloro-2-furan-2-yl)benzimidazole 206 as the major products (15.1 and 40.3 %), respectively as shown in Schemes 72-74.

The formation of these products appears to follow a series of reaction shown in Scheme 72. Preliminary homolysis of the N-O bond [143] (route a) forms N-p-chlorophenyl-2-furamidinyl and hydroxyl radical pairs. The furamidinyl radical undergoes intramolecular cyclization to give 5-chloro-2-(furan-2-yl)benzimidazole 206 m/e 218 (40.3 %) [144, 145], Scheme 72; whereas, the hydroxyl radicals incorporate in other processes as shown in other Schemes.

![Scheme 72](image)

As shown in Scheme 73 which includes the homolysis of the C-N bond (route b) to form 2-furiminyl and hydroxyaminyl free radical. The former radicals may couple with hydroxyl radical in the reaction medium (Scheme 72) to afford N-(4-chlorophenyl)-2-furamide 205 m/e 221 which
spontaneously undergoes hydroxylation and decomposes into 2-furoic acid 192 and p-chloroanilino radical [147]. The p-chloroanilino radical may couple with the hydroxyaminyl radical in the reaction medium followed by dehydrogenation and extrusion of nitrogen to produce p-chlorophenol 155 m/e 129 [158], whereas the hydroxyaminyl radical may abstracts hydrogen from a suitable source to give hydroxylamine which subsequently fragmentation into ammonia and water [148] as in Scheme 73.

(Scheme 73)
Furthermore, the homolysis of the C-N bond (route b) via the
tautomeric form of IX as reported by Tiemann and Kruger [149], forms p-
chloroanilino and 2-furiminoxyl radical pairs. The latter radical undergoes
decomposes into 2-furonitrile 195 and hydroxyl radical [60]; Scheme 74.

The observed absence of 2-amino-5-chlorophenol among the identified
products can be explained to its incorporation in the formation of 6-chloro-
2-(furan-2-yl)benzoxazole 204 m/e 219 which can be suggested to take
place through condensation of 2-furoic acid 192 in the reaction medium
with 2-amino-5-chlorophenol followed by elimination of water [161];
Scheme 74.

![Scheme 74](image)

The formation of 3,6-dichloro-9H-carbazole 158 m/e 235 can be suggested
on the basis of dimerization of p-chloroanilino radical followed by
intramolecular cyclization and elimination of ammonia [150] as depicted in
Scheme 40.
GC chromatogram of the isolated products are found in (fig. 75, p. 227). The identified products showed nearly in agreement with the suggested mechanism of thermolysis of N-p-chlorophenyl-2-furamide oxime IX as in Schemes 72-74.

The results are summarized in Table 9.

**Table 9.** Thermolysis products of N-p-chlorophenyl-2-furamide oxime IX in % yield.

<table>
<thead>
<tr>
<th>Products a</th>
<th>IX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Furoic acid</td>
<td>5.0</td>
</tr>
<tr>
<td>p-Chlorophenol</td>
<td>4.2</td>
</tr>
<tr>
<td>p-Chloroaniline</td>
<td>11.2</td>
</tr>
<tr>
<td>2-Furonitrile</td>
<td>3.2</td>
</tr>
<tr>
<td>3,6-Dichloro-9H-carbazole</td>
<td>6.2</td>
</tr>
<tr>
<td>N-(4-Chlorophenyl)-2-furamide</td>
<td>15.1</td>
</tr>
<tr>
<td>6-Chloro-2-(furan-2-yl)benzoxazole</td>
<td>6.7</td>
</tr>
<tr>
<td>5-Chloro-2-(furan-2-yl)benzimidazole</td>
<td>40.3</td>
</tr>
<tr>
<td>Unidentified products (g)</td>
<td>(2.2)</td>
</tr>
</tbody>
</table>

a NH₃ gas was evolved and detected by chemical means.

H₂O as a trace amount was separated with ether.
Thermal Fragmentation of N-2-Pyridylbenzamide Oxime X

Thermolysis of N-2-pyridylbenzamide oxime X on heating at 220-250°C under nitrogen atmosphere leads to the formation of 2-hydroxypyridine 209, banzonitrile 17, benzoic acid 41, 2-aminopyridine 207, 2-phenyloxazolo[4,5-b]pyridine 212, 9H-pyrrolo[2,3-b: 5,4-b']dipyridine 211 and 2,4,6-triphenyl-1,3,5-triazine 19 in addition to 2-phenylimidazo[4,5-b]pyridine 213 and N-(pyridin-2-yl)benzamide 210 as the major products (52.4 and 18.11 %), respectively as shown in Schemes 75-78.

The formation of the identified products can be rationalized by a series of reactions shown in Scheme 75, which imply the primary homolysis of the N-O bond (route a) [155] to form N-2-pyridyl benzamidinyl and hydroxyl radical pairs. The pyridylbenzamidinyl radicals undergo isomerization followed by intramolecular cyclization to give 2-phenylimidazo[4,5-b]pyridine 213 m/e 195 (52.4 %) [162] as shown in Scheme 75. Whereas the hydroxyl radicals may be involved in other processes as in Scheme 75.

Another competing pathway for the thermolysis of N-2-pyridyl benzamide oxime X is the homolysis of the C-N bond (route b) giving N-2-pyridylbenzimidinyl and hydroxyaminyl free radicals. The benzimidinyl radicals may couple with hydroxyl radicals (Scheme 76, route a), which are
readily available in the reaction medium, to form $N$-(pyridin-2-yl) benzamide 210 m/e 198, which ultimately undergoes extended hydrolysis and decomposes into benzoic acid 41 and 2-pyridaminyl radical [147].

Moreover, the 2-pyridaminyl radicals may couple with the hydroxyaminyl radical followed by dehydrogenation and extrusion of nitrogen to produce 2-hydroxypyridine 209 [158]. In addition, the hydroxyaminyl radicals may abstract hydrogen to form hydroxylamine which subsequently decomposes into ammonia and water [148] as shown in Scheme 76.

(Scheme 76)
Furthermore, the homolysis of the C-N bond (route b), via the tautomeric form of X as reported by Tiemann and Kruger [149] to afford 2-pyridaminy radical which may abstract hydrogen to give 2-amino pyridine, whereas the benziminoxyl radicals undergo fragmentation to yield benzonitrile 17 and the hydroxyl radical [60]; Scheme 77.

The observed absence of 2-amino-3-hydroxypyridine which may be suggested to be formed through attack of the hydroxyl radicals on 2-aminopyridine in the reaction medium among the isolated products may be due to its consumption in the formation of the 2-(phenyloxazolo[4,5-b]pyridine 212 m/e 196 which can be suggested to take place through condensation of benzoic acid with 2-amino-3-hydroxypyridine in the reaction medium followed by elimination of water [163]; Scheme 77.

A plausible mechanism for the formation of 2,4,6-triphenyl-1,3,5-triazine 19 m/e 309 is through cyclotrimerization of benzonitrile which is readily available in the reaction medium as reported previously [164]; Scheme 77.
The formation of 9H-pyrrolo[2,3-b:5,4-b’]dipyridine 211 m/e 169 may take place through dimerization of 2-pyridaminyl radicals followed by cyclization and elimination of ammonia [137] as shown in Scheme 78.

\[ \text{Scheme 78} \]

GC chromatogram of these products are shown in (fig. 87, p. 234). The observed products are in agreement with the suggested mechanism of thermolysis of \( N \)-2-pyridylbenzamide oxime \( X \) as shown in Schemes (75-78).

The results are summarized in Table 10.

**Table 10.** Thermolysis products of \( N \)-2-pyridylbenzamide oxime \( X \) in % yield

<table>
<thead>
<tr>
<th>Products (^a)</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzonitrile</td>
<td>2.67</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>2.08</td>
</tr>
<tr>
<td>2-Aminopyridine</td>
<td>2.60</td>
</tr>
<tr>
<td>2-Hydroxypyridine</td>
<td>3.65</td>
</tr>
<tr>
<td>( N )-(Pyridin-2-yl)benzamide</td>
<td>18.13</td>
</tr>
<tr>
<td>2-Phenoxazolo[4,5-b]pyridine</td>
<td>4.26</td>
</tr>
<tr>
<td>2,4,6-Triphenyl-1,3,5-triazine</td>
<td>2.83</td>
</tr>
<tr>
<td>2-Phenylimidazo[4,5-b]pyridine</td>
<td>52.4</td>
</tr>
<tr>
<td>9H-Pyrrolo[2,3-b: 5,4-b']dipyridine</td>
<td>3.5</td>
</tr>
<tr>
<td>Unchanged benzamide oxime (g)</td>
<td>5.2</td>
</tr>
</tbody>
</table>

\( ^a \)NH\(_3\) gas evolved and was detected by chemical test. H\(_2\)O as a trace amount was separated with ether.
Thermal Fragmentation of \( N-\alpha \)-Naphthylbenzamide Oxime XI

\( N-\alpha \)-Naphthylbenzamide oxime XI on heating at 220-250°C under nitrogen atmosphere for 5 h leads to the formation of benzoic acid 41, \( \alpha \)-naphthylamine 214, benzonitrile 17, \( N-(\alpha \)-naphthyl)benzamide 216, 2-phenynaphtho[1,2-d]oxazole 217 and 2-phenyl-1H-naphth[1,2-d]imidazole 218 as the major product (37.8%).

The formation of most of these products can be assumed to follow the series of reactions shown in Scheme 79, which imply the preliminary homolysis of the N-O bond (route a) [155] to form \( N-\alpha \)-naphthylbenzamidinyl and hydroxyl radical pairs. The former radicals undergo intramolecular cyclization followed by dehydrogenation to give 2-phenyl-1H-naphtho[1,2-d]imidazole 218 m/e 244 [142]; Scheme 79.

On the other hand, the hydroxyl radicals may be consumed in the other processes as usual.

Another competing pathway for the thermolysis of \( N-\alpha \)-naphthyl benzamide oxime XI is the homolysis of the of the C-N bond (route b) to afford \( N-\alpha \)-naphthylbenziminyln and hydroxaminyl free radicals. The benziminyln radicals may couple with hydroxyl radicals which are readily
available in the reaction medium to give $N$-($\alpha$-naphthyl)benzamide 216 m/e 247, which ultimately undergoes extended hydrolysis and decomposes into benzoic acid 41 and $\alpha$-naphthaminyl radicals [147]. The latter radicals may abstract hydrogen from a suitable source to yield $\alpha$-naphthylamine 214 as shown in Scheme 80.

Moreover, the hydroxyaminyl radical may abstract hydrogen to form hydroxylamine, which subsequently suffer fragmentation to ammonia and water [148].
As in Scheme 81, the homolysis of the C-N bond (route b), via the tautomeric form of XI as reported by Tiemann and Kruger [149] may lead to the formation α-naphthaminyl and benziminoxyl radical pairs. The α-naphthaminyl radicals may behave the same route as in Scheme 81 to produce α-naphthylamine 214.
The formation of α-naphthylamine 214 through two routes (Scheme 79, route a and Scheme 80, route b) may correlate for its high yields among the observed products; Table 11.

Furthermore, the benziminoxyl radicals undergo fragmentation to produce benzonitrile 17 and hydroxyl radical [60]; Scheme 81.

(Scheme 81)

The formation of 2-phenynaphtho[1,2-d]oxazole 217 m/e 245 can be suggested to take place through condensation of benzoic acid 41 with 1-amino-2-naphthol which is readily present in the reaction medium followed by elimination of water [165]; Scheme 81.

GC chromatogram of these products are shown in (fig. 98, p. 240). These products are in agreement with the suggested mechanism of thermal fragmentation of N-(α-naphthyl)benzamide oxime XI as shown in Schemes (79-81). The results are presented in Table 11.
**Table 11.** Thermolysis products of N-(α-naphthyl)benzamide oxime XI in % yield

<table>
<thead>
<tr>
<th>Products</th>
<th>XI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzonitrile</td>
<td>4.3</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>6.5</td>
</tr>
<tr>
<td>α-Naphthylamine</td>
<td>11.3</td>
</tr>
<tr>
<td>N-(α-Naphthyl)benzamide</td>
<td>16.8</td>
</tr>
<tr>
<td>2-Phenynaphtho[1,2-d]oxazole</td>
<td>8.3</td>
</tr>
<tr>
<td>2-Phenyl-1H-naphth[1,2,d]imidazole</td>
<td>37.8</td>
</tr>
<tr>
<td>Unchanged benzamide oxime (g)</td>
<td>6.6</td>
</tr>
</tbody>
</table>

*NH₃ gas evolved and detected by chemical means

H₂O as a trace amount was separated with ether.
General Procedure for Preparation of \(N\)-\(p\)-Substituted phenylbenzamides and \(N\)-\(p\)-Substituted phenyl-2-Furamides [166].

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{C} & \quad \text{R}
\end{align*}
\]

A mixture of a carboxylic acid (8 mmoles) and thionyl chloride (28 mmoles) was heated at reflux for 30 min. The resulting solution was evaporated under aspirator pressure to remove excess thionyl chloride. The residual liquid was cooled in an ice-water bath and a solution of \(p\)-substituted aniline (16 mmoles) and triethylamine (10 mmoles) in dichloromethane (15 mL) was added slowly. The solution was heated at reflux for 1 h. It was then treated with saturated sodium bicarbonate solution until the aqueous layer was slightly basic (pH ~8). The organic layer was washed with water (10 mL) and dried over anhydrous sodium sulfate. The solvent was removed and the resulting solid was recrystallized from ethanol. The yields and mps are listed in the following Table:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>% Yield</th>
<th>Mp°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>163; (R= p\text{-NO}_2)</td>
<td>57</td>
<td>198-199</td>
</tr>
<tr>
<td>157; (R= p\text{-Cl})</td>
<td>51</td>
<td>192-193</td>
</tr>
<tr>
<td>170; (R= p\text{-OCH}_3)</td>
<td>67</td>
<td>157-158</td>
</tr>
<tr>
<td>197; (R= H)</td>
<td>63</td>
<td>123-124</td>
</tr>
<tr>
<td>200; (R= \text{CH}_3)</td>
<td>39</td>
<td>109-110</td>
</tr>
<tr>
<td>205; (R= \text{Cl})</td>
<td>51</td>
<td>151-152</td>
</tr>
</tbody>
</table>
General Procedure for Preparation of 2-(Pyridin-3-yl)benzimidazoles

181, 189 [167]

A mixture of 3-pyridinecarboxaldehyde (5.0 mmol) and 1,2-phenylenediamine (5.0 mmol) in absolute ethanol (100 mL) was stirred at room temperature for 2 h followed by addition of iodobenzene diacetate (7.0 mmol). After 1 h stirring, the solvent was removed under reduced pressure, the residue diluted with ethyl acetate and then washed with aqueous NaHCO₃ solution. The organic layer was separated, washed with brine, dried over anhydrous MgSO₄, and then evaporated in vacuo. The residue was purified by column chromatography on silica gel (n-hexane:ethyl acetate) to give the title compounds:

2-(Pyridin-3-yl)-1H-benzimidazole 181; as yellow powder, yield 52 %, mp 247-248ºC.

5-Chloro-2-(pyridin-3-yl)-1H-benzimidazole 189; as yellow crystal, yield 78 %, mp 147-148ºC.
2-Phenyl oxazolo [4,5-b] pyridine 212 [168]

\[
\text{\includegraphics[width=0.5\textwidth]{212.png}}
\]

2-Amino-3-hydroxypyridine (1g) was refluxed with benzoic anhydride (6 g) for 10 min. The cooled mixture was dissolved in benzene (200 mL) and extracted with ice-cold hydrochloric acid (3 x 20 mL). The combined extracts were filtered and basified with aqueous sodium hydroxide. The precipitate was collected and crystallized from aqueous acetone, giving the 2-phenyl derivative 212 as needles, mp 127-128°C
3,6-Dichloro-9H-carbazole 158 [169]

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{N} \quad \text{H}
\end{array}
\]

To a three-neck, 250 ml round-bottomed flask equipped with a mechanical stirrer and a thermometer, carbazole (10 g, 0.06 mol) and \( \text{CH}_2\text{Cl}_2 \) (100 mL) were added. The resulting mixture was cooled to 0°C and then \( \text{SO}_2\text{Cl}_2 \) (9.6 mL, 0.12 mol) was added drop wise while the solution was being vigorously stirred (note: the temperature did not exceed 2°C). After the addition, the cooling bath was removed and the reaction mixture was stirred for another 4 h at room temperature. Then, the solid precipitate was filtered off, washed with \( \text{CH}_2\text{Cl}_2 \) and dried to give crude product 3,6-dichlorocarbazole which was suspended in 250 mL of hexane and boiled for 30 min. The suspension was filtered, giving pure product (8.35 g, 59%); mp 200–203°C.
3,6-Dinitro-9H-carbazole 164 [111]

A homogeneous mixture of Cu(NO$_3$)$_2$·H$_2$O (7.0 g, 30 mmol), acetic acid (20 mL), and acetic anhydride (30 mL) was prepared at room temperature. To this solution were added carbazole (4.15 g, 25 mmol) in small portions over 10 min. Temperature was maintained at 15–20°C during addition of carbazole. The temperature was allowed to rise to room temperature (27°C) over a period of 30 min and then to 90–100°C. Reaction was continued with stirring for a period of 30 min at this temperature. The mixture was diluted with additional 10 mL of acetic acid, and poured into 250 mL of distilled water with constant stirring. The precipitate was collected by filtration, and washed five times each with about 100 mL of distilled water. The wet residue was dissolved in a cold solution of 20 g of KOH, 250 mL of ethanol, and 250 mL of water. The red solution was stirred for 30 min, and filtered. The filtrate was then acidified with concentrated hydrochloric acid, and allowed to settle for 30 min. A fluffy yellow precipitate was collected by filtration, washed several times with cold water, and dried in vacuum at 100°C. Yield: 5.55 g, 85%; mp 296-300°C.
To stirred benzonitrile (550 mL, 5.36 mmol) at ca. 20°C was added portionwise powdered anhydrous AlCl₃ (706 mg, 5.36 mmol). The reaction mixture was then heated (ca. 100°C) until a homogenous melt was formed. To this was added aniline (489 mL, 5.36 mmol) and the mixture was heated for 4 h and then allowed to cool to ca. 20°C. The resultant solid mass was then crushed and slurred in 12.5% NaOH (40 mL). There salting mixture was extracted by (DCM), washed with water and dried by (Na₂SO₄). Removal of the volatiles followed by chromatography of the residue gave 2,4,6-triphenyl-1,3,5-triazine 19 (16.4 mg, 30%) as light yellow needles, mp 231-232°C (benzene); R_f = 0.36 (n-hexane / DCM, 9:1)
**N-(Pyridin-2-yl)benzamide 210 [170]**

![Chemical Structure](image)

A 0.2 M solution of 2-aminopyridine (1.1 equiv) was cooled to 0°C. *n*-Butyl lithium (2.2 equiv of 2.5 M in hexanes) was added, usually accompanied by a color change from clear to dark red or purple, and the reaction stirred for 1 h at room temperature. The solution was then cooled to -78 °C and benzoyl chloride (1 equiv) was added. After approximately 12 h at room temperature, the reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were washed with brine, then dried (MgSO₄), filtered and concentrated. The amide 210 was purified by flash column chromatography eluting with 30% acetone/n-hexane to give the amide as yellow crystals; R<br = 0.26 (30:70 acetone/n-hexane); mp 81-83°C.
A mixture of nicotinoyl chloride (1 mmole) and aniline (1 mmole) in 50 ml of tetrahydrofuran solution was stirred for 8 h at ambient temperature in the presence of a catalytic quantity of triethylamine (5 mL). The reaction mixture was neutralized with a saturated aqueous sodium hydrogen carbonate solution and the resulting aqueous mixture was extracted with ethyl acetate and then concentrated under reduced pressure. Then, it was subjected to chromatography on silica gel, using hexane–ethyl acetate gradients. Crystals were grown from an ethanolic solution; yield 66%; mp 123-124°C.
2,2'-Dipyridylamine (103 mg) in tetrahydrofuran (300 mL) was irradiated for 48 hr. After 6 hr, the absorbance at 264 nm had diminished by 75%, but the rate of cyclisation later decreased. Evaporation of solvent gave a brown gum (121 mg), which was applied in chloroform (2 mL) to a column of alumina (Grade IV; 30 g). Benzene (50 mL) eluted unidentified yellow oil (7 mg). Benzene-chloroform (1:1 v/v) (50 mL) eluted unchanged dipyridylamine (8 mg). Chloroform (50 mL) eluted the product (53 mg), m.p. 229°C (crystallization from benzene).
2-(2-Furanyl) benzoxazole 196 [171]

A mixture of 2-aminophenol (2 mmol), 2-furoic acid (2 mmol), and tin(II) chloride (2 mmol) in dioxane (10 mL) was placed in a 50 mL stainless steel pressure vessel. After the system was flushed with argon, the mixture was stirred at 180°C for 30 h. Removal of solvent under reduced pressure left a crude mixture which was separated by column chromatography (ethylacetate/n-hexane = 1/10 v/v) to give the benzoxazole 196 as colourless crystals, mp 84-86°C (n-hexane).
To a solution of 2-aminophenol (0.109 g, 1.0 mmol) in MeOH (5 mL) was added 3-pyridinecarboxaldehyde (0.136 g, 1.0 mmol). The resulting mixture was heated at 45°C for 12 h. After concentration under reduced pressure, the residue was dissolved in CH$_2$Cl$_2$ (10 mL) and DDQ (0.250 g, 1.1 mmol) was then added. After stirring at room temperature for 30 min, the resulting mixture was diluted with additional CH$_2$Cl$_2$ (10 mL) and washed sequentially with saturated Na$_2$CO$_3$ (10 mL×2) and brine (10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$. After evaporation, the crude was purified by flash column chromatography (10 % ethylacetate in hexane) to afford the desired product as colourless crystals, yield 74 %, mp 113-114°C.
\[ N-(4-\text{Chlorophenyl}) \text{ nicotinamide 188} [173] \]
\[ N-(4-\text{Methylphenyl}) \text{ nicotinamide 184} [123] \]

Both \textbf{I} and \textbf{II} were prepared from nicotinoyl chloride hydrochloride (1 mole) and 4-chloroaniline/ 4-methylaniline (1 mole) in the presence of triethylamine (25 mL). The resulting mixture was heated under reflux then stirred for 20 min at room temperature and was then filtered. Crystals were obtained by slow evaporation of the solvent of \textbf{188} (yield 67 %); mp 174-175\textdegree C and \textbf{184} gave yield 52 %, mp 113-114\textdegree C.
**N-(α-Naphthyl)benzamide 216 [140]**

![Structural formula of N-(α-Naphthyl)benzamide 216]

**Step I:** Triphenylphosphine (PPh₃) (1.6 g, 6.0 mmol) in CH₂Cl₂ (3 mL) was added to a mixture of benzoic acid (3 mmol) and cyanotrichloro methane (6 mmol) in CH₂Cl₂ (3 mL) at room temperature. The mixture was stirred at reflux for 1 h.

**Step II:** A mixture of α-naphthylamine (3 mmol) and 4-picoline (9 mmol) was added to the above mixture. The reaction mixture was stirred at room temperature for 20 min. When the reaction was completed, the organic layer was washed with 10% HCl and saturated aqueous NaHCO₃, and consequently dried over Na₂SO₄ and evaporated in vacuo. The mixture was separated with a silica gel column chromatography eluting with n-hexane/ethylacetate (4:1v/v), yield 62%; mp 164-166°C.
2-Phenylnaptho[1,2-d]oxazole 217 [174]

![Chemical Structure](image)

**Modification of the Moffet’s Method:**

A mixture of \( \alpha \)-aminophenol (1 mole) and \( \alpha \)-naphthol (1 mole) and methyl benzoyl formate (1 mole) in pyridine (15 mL) as solvent under nitrogen and the mixture were heated at 120°C for 1.5-2 h. After this time, the reaction mixture was poured onto ice water. The precipitate was collected by filtration, washed with water, and purified by column chromatography (chloroform) on silica gel. 2-Phenyl-3H-naphtho[2,1-b],4-oxazin-3-one was obtained. Recrystallization from carbon tetrachloride gave yellow needles, mp 174–175°C. The latter compound (40 mg, 0.146 mmol) and 10 % KOH solution (2 mL) were refluxed in MeOH for 30 min. Immediately, the solution became an intense brownish red. The mixture was left overnight and then neutralized with acetic acid (10 %). The precipitate was collected by filtration, washed with water, and purified by column chromatography (chloroform) on silica gel gave 2-phenyl naphtho[1,2-d]oxazole 217. Recrystallization from ligroin to give colourless needles, mp 122–123°C.
A mixture of 3-pyridinecarboxaldehyde (2 mmol), 5-methyl-1,2-phenylenediamine (2 mmol), potassium persulfate (2 mmol), and CuSO\textsubscript{4} (0.02 mmol) were taken in 5–10 mL of aqueous micelles of sodium dodecyl sulfate (SDS) (0.05g/mL). The reaction was stirred for 25–60 min at 60°C. After completion of the reaction monitored by TLC, the reaction mixture was diluted with brine and the precipitate was filtered off. The oily product extracted with ethyl acetate. The pure product was obtained by crystallization of the crude in ethanol gave 5-methyl-2-(pyridin-3-yl)-1H-benzimidazole \textbf{186}, mp 220–221°C.
General Procedure for Preparation of 2-Phenyl-1H-benzimidazoles and 2-Phenynaphth[1,2-d]imidazole [218] [90]

\[ \text{R} \]

\[ \text{Ph} \]

\[ \text{N} \]

\[ \text{H} \]

\[ \text{159, } R = \text{Cl}; \quad \text{167, } R = \text{NO}_2; \quad \text{173, } R = \text{OCH}_3 \quad \text{218} \]

*N*-Substituted phenylbenzamide oximes (R= Cl, NO$_2$ and OCH$_3$) or *N*-α-naphthylbenzamide oxime (0.025 mole), was dissolved in a mixture of dry benzene (20 mL) with dry pyridine (10 mL) or dry triethylamine (10 mL) was treated during 30 min. at below 10°C with benzenesulfonyl chloride (0.025 mole) in dry benzene (10 mL). After being kept at 0-5°C overnight, the suspension was filtered. Solvent was removed from filtrate under reduced pressure and the residue triturated with aqueous sodium carbonate and crystallized from ethanol giving the target compounds as follows:

- **5-Chloro-2-phenyl-1H-benzimidazole 159**, yield 90 %; mp 210-212°C
- **5-Nitro-2-phenyl-1H-benzimidazole 167**, yield 63 %; mp 207-208°C.
- **5-Methoxy-2-phenyl-1H-benzimidazole 173**, yield 69 %; mp 145-147°C.
- **2-Phenynaphth[1,2-d]imidazole 218**, yield 96 %; mp 217-218°C.
2-Phenyl-1H-imidazo[4,5-b]pyridine 213 [139]

![Chemical Structure](image)

A mixture of 2,3-diaminopyridine (10 mmole) and benzaldehyde (11 mmole) in water (50 ml) was heated at 100°C for 10-12 h. The progress of the reaction was followed by TLC (dichloromethane/ methanol; 9:1). The reaction mixture was cooled to room temperature and the product was collected by filtration, washed with water, and dried. The product was recrystallized from ethanol to give 2-phenyl-1H-imidazo[4,5-b]pyridine 213; yield 83 %, mp 288-290°C.
General experimental procedure of 2-(furan-2-yl)-1H-benzo[d]imidazoles [175]

A mixture of a substituted aldehyde (2.0 equiv), \(o\)-phenylenediamine (1.0 equiv) in acetonitrile:water (10 mL) and 1-heptanesulfonic acid sodium salt (0.15 equiv) were placed in a round bottom flask. The mixture was stirred at room temperature until completion. The reaction was monitored by TLC. The reaction mixture was poured into ice-water (50 mL). Extracted with ethylacetate (25 x 2 mL), which was then dried over sodium sulphate and concentrated under vacuum till dryness. The residue was subjected to column chromatography (60–120 mesh size silica gel, eluted with hexane–acetone) to obtain the pure benzimidazoles.

198; \(R=\text{H}\)  202; \(R=\text{CH}_3\)  204; \(R=\text{Cl}\)

198; 2-(Furan-2-yl)-1H-benzo[d]imidazole, mp 285-287°C.
202; 5-Methyl-2-(furan-2-yl)-1H-benzo[d]imidazole, mp 198-200°C
204; 5-Chloro-2-(furan-2-yl)-1H-benzo[d]imidazole, mp 202-204°C.
To a mixture of 4-methyl-2-bromoaniline (1.89 mmol, 1.0 equiv), CuI (18 mg, 0.095 mmol, 0.05 equiv), 1,10-phenanthroline (34 mg, 0.19 mmol, 0.10 equiv), and Cs$_2$CO$_3$ (1.24 g, 3.78 mmol, 2.0 equiv) was added DME ($N,N'$-dimethylethylendiamine) (20 mL) at room temperature, under a nitrogen atmosphere. To the reaction mixture was added 2-furoyl chloride (1.98 mmol, 1.05 equiv). The reaction mixture was refluxed for 24 h then allowed to cool to room temperature. The reaction mixture was then diluted with ethylacetate (50 mL) and washed with H$_2$O (2 × 50 mL) and brine (1 × 25 mL). The organic layer was dried over MgSO$_4$, and the solvent was removed in vacuo. The crude product was passed through a thin layer of silica gel using CH$_2$Cl$_2$ eluent as brown crystals, yield 90 %, mp 52-53°C.
A. Preparation of N-(2-hydroxy-4-methoxyphenyl)benzamidine.

Liquid ammonia (250 mL) was condensed into a 1-L, three-necked flask equipped with mechanical stirrer and dry ice condenser. A few small crystals of ferric nitrate were placed in the flask and potassium metal (0.12 mol) was added in portions over a period of 10 min. When initially added, the solution turned bright blue. On complete conversion of potassium to potassium amide the color turned grey. The o-chlorobenzanilide (0.0217 g), was then added in small portions as quickly as possible and the reaction was stirred for 1 h. At this time, the reaction mixture was quenched by the careful addition of NH₄Cl (0.13 mole), the ammonia was evaporated by heating on a steam bath, the solid residue was extracted with acetonitrile (200 mL), and the mixture was filtered. Rotary evaporation of the mother liquor yielded N-(2-hydroxy-4-methoxyphenyl)benzamidine. This compound was dissolved in a minimum amount of 6 N hydrochloric acid and placed in a refrigerator overnight, during which time crystals of their hydrochloride salt precipitated. The crystals were dissolved in 25 mL of methanol, ether was added dropwise until the mixture appeared cloudy, and the mixture was placed in the refrigerator overnight. The purified crystals of the benzamidine was collected by filtration and dried.
B. Conversion of \( N-(2\text{-hydroxy-4-methoxyphenyl})\text{benzamidine} \) to 6-methoxy-2-phenylbenzoxazole.

The \( N-(2\text{-hydroxy-4-methoxyphenyl})\text{benzamidine} \) (1 mole) was heated at 150\(^\circ\)C (0.01 torr) in a typical vacuum sublimation apparatus equipped with water-cooled finger condenser. The benzoxazole which formed under these conditions sublimed and was removed periodically from the sides of the condenser as white solid, mp 66–69\(^\circ\)C; TLC (30% ethylacetate/n-hexane) \( R_f = 0.55 \).
A. 2-Phenylbenzoxazole was prepared directly by heating a mixture of benzaldehyde (1.5 g) and \( o \)-aminophenol (1.1 g) in hot glacial acetic acid (35 mL) with lead tetraacetate (4.5 g). The crude solid, on crystallization from ethanol (charcoal), gave the benzoxazole as pale yellow needles, m.p 102-104\(^\circ\)C.

B. 6-Nitro-2-benzylbenzoxazole. 2-Phenylbenzoxazole (6 g) was added slowly (10 min) to nitric acid (45 mL; \( d \) 1.5) and the mixture set aside for 30 min at room temperature. The nitration mixture was poured into water (150 mL), and the pale yellow precipitate (7.4 g) removed by filtration. Crystallization from acetic acid gave yellow needles (6.1 g), m.p 178-180\(^\circ\)C.
REFERENCE COMPOUNDS
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![$^1$H-NMR spectrum of 2-(furan-2-yl)benz[d]oxazole 196](image)
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الملخص العربي

تم في هذا البحث تحضير بعض مركبات البنزاميدوأوكزمي الأروماتية والغير متجانسة الحلقية التي تحتوى على نواة البريدين والفيوران والتي لها نشاط بكثير وفطرى كبير جداً. كما تعتبر مركبات البنزاميدوأوكزمي الأروماتية والغير متجانسة الحلقية مواد أولية في تحضير العديد من المركبات الغير متجانسة الحلقية المختلفة مثل مشتقات البنزاميدازول الوثيداوزلين والثيداوززين والثيدافونازول والأوكزازاوزول هذا بالإضافة إلى أنها تستخدم هذه المركبات كمادة أولية لأدوية وفي مجال البوليميرات كما ورد في الدراسات العلمية.

كما تم في هذا البحث دراسة التأثير الحاربي والتعديل التجزئي لهذه المركبات بعد تحضيرها وتنقيةها بصورة جيدة من خلال التحاليل الدقيقة والطيفية المختلفة.

أولا: دراسة التأثير الحاربي والتعديل التجزئي لبعض مشتقات البنزاميدواوكزمي الأروماتية كما يلي:

وقع وجد عند تسخين ن- بارا- كلوروفينيل بنزاميدو أوكزمي I عند درجة حرارة 300-350 م في جو من النتروجين لمدة خمس ساعات انة تتحلل إلى حمض البنزويك و بارا- كلوروفينول و بنزونيتريل و بارا- كلرواتيلين و أمبو- كلروفينول و 2-3 داي كلروكابازول و كما أعطي ن- بارا- كلروفينيل بنزاميدو و بنزاميدوزو- فينيل بنزاميدازول كمركب ذات نسبة كبيرة تصل الى 45% لذلك يعتبر التأثير الحاربي للمركب I طريقة هامة ونحيدة لتحضير 5- كلرو- 2- فينيل بنزاميدوزول.

كذلك عند تسخين N- بارا- كلروفينيل بنزاميدو أوكزمي II في وجود النفثيلين كمصددة للشقوق الحرة الطيفية عند نفس الظروف السابقة أعطي الفا وبيتا - نافثول ذو حصة 20% بالاضافة للمركبات السابقة.

أيضا عند تسخين N- بارا- كلروفينيل بنزاميدو أوكزمي I في وجود النترالين كذيب ومعطي للهيدروجين عند نفس الظروف السابقة تم الحصول على ألفا نترالون و هيدروكسي نترالين و 2-1 داي تتريل بالأضافة للمركبات السابقة.

كذلك وجد عند تسخين N- بارا- نيتروفينيل بنزاميدو أوكزمي II عند درجة حرارة 250-300 م في جو من النتروجين لمدة خمس ساعات تم الحصول على حمض البنزويك و بارا- نيتروفينول و بنزونيترييل و بارا- نيتروآتيدين و نيترو- 2- فينيل بنزو أوكزازول كما
أعطى ن- بارانيتروفينيل بنزاميد و 5- نيترو-2- فينيل بنزاميدازول كمركباً ذات نسبة كبيرة تصل إلى 46% لذلك يعتبر التأثير الحراري للمركب II طريقة هامة ودقيقة لتحضير 5- نيترو-2- فينيل بنزاميدازول.

أيضاً عند تسخين N- بارا- ميثوكسي فينيل بنزاميدو أوكزيم III في درجة حرارة 200-250 م في الجو من النتروجين لمدة خمس ساعات انها تتحلل إلى حمض البنزويك و فينول و بنزونيترييل و بارا- نيترو-2- فينيل بنزاميدازول و 2- 6- ديا ميثوكسي كاربازول و كما أعطى ن- بارا- ميثوكسي فينيل بنزاميد و 5- ميثوكسي-2- فينيل بنزاميدازول كمركب ذو حصة كبيرة تصل إلى 53% لذلك يعتبر التأثير الحراري للمركب III طريقة هامة ودقيقة لتحضير 5- ميثوكسي-2- فينيل بنزاميدازول.

ثانياً: دراسة التأثير الحراري والتعدل التجزئي لبعض مشتقات البنزاميدوأوكزيم ذات الحلقات الغير متجانسة مثل أنواع البيدين والفيوران كما يلي:

فقد وجد عند تسخين N- فينيل نيتكوناميد أوكزيم IV (N- فينيل-3- بردين أميدوأوكزيم) عند درجة حرارة 250-260 م في الجو من النتروجين لمدة خمس ساعات أعطى أندراو نيترو- و حمض النيقونتيك و كاربازول و نيكوتينيل و 2- 3- بردين) بنزاميدازول كما أعطى N- فينيل نيتكوناميد و 2- (3- بردين) بنزاميدازول كمركب ذات نسبة كبيرة تصل إلى 50% لذلك يعتبر التأثير الحراري للمركب IV طريقة هامة ودقيقة لتحضير 2- 3- بردين) بنزاميدازول.

كذلك عند تسخين N- فينيل نيتكوناميد أوكزيم V في وجود النثالين كمضادة للشفق الحرارة الطويلة عند نفس الظروف السابقة أعطى الها وبيبنا - نافوث بنسبة 16% بالإضافة للمركبات السابقة.

كذلك عند تسخين N- بارا- 2 ميثيل فينيل نيتكوناميد أوكزيم V عند درجة حرارة 250-260 م في الجو من النتروجين لمدة خمس ساعات أعطى بارا- تولدين و بارا- كريزول و حمض النيكوتنيك و 3- 6- داي ميثيل كاربازول و نيكوتينيل و 2- أمين-5- ميثيل فينول كما أعطى N- 5- ميثيل فينيل نيتكوناميد و 5- ميثيل-2- (بردين) بنزاميدازول كمركب ذو حصة كبيرة تصل إلى 27% لذلك يعتبر التأثير الحراري للمركب V طريقة هامة ودقيقة لتحضير 5- ميثيل-2- (بردين) بنزاميدازول.
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كذلك عند تسخين ن- بارا-كلوروفينيل نيكوتوناميد أوكزيزم VI عند درجة حرارة ٥٠٠-٢٠٢ م في جو من النتروجين لمدة خمس ساعات تم الحصول على بارا-كلوروأفينيل و بارا-كلوروفينول و حمض النيكوتينيك و ٣- لاي كلوروكارباول و نيكوتوناميد و ٢- أمينو- ٥- كلوروفينول كما أعطى ن- ٤-(كلوروفينيل) نيكوتوناميد و ٥- كلورو- (٢- بريدين) بنزاميدازول كمركباً ذو حصة كبيرة تصل إلى ٦٠% لذلك يعتبر التأثير الحراري للمركب VI بطريقة هامة و جديدة لتحضير ٥- كلورو- (٢- فوران) بنزاميدازول.

كذلك فقد وجد عند تسخين ن- فينيل- ٢- فيوراميد أوكزيزم VII عند درجة حرارة ٢٠٠-٥٠٠ م في جو من النتروجين لمدة خمس ساعات أعطى ألين و فورنيتيل و- ٢- حمض الفورنيك و فيريل و فينول و كارباول و ٢- فيوراميد و ٢- (٢- فوران) بنزاميدازول كما أعطى ن- فينيل- ٢- فيوراميد و ٢- (٢- فوران) بنزاميدازول كمركباً ذو حصول درجة حرارة VII تصل إلى ٣٧% لذلك يعتبر التأثير الحراري للمركب VII بطريقة هامة و جديدة لتحضير ٢- (٢- فيوران) بنزاميدازول.

كذلك عند تسخين ن- فينيل- فيوراميد أوكزيزم VII في وجود الباليونين كمصيدة للشقوق الحرة الطليقة عند نفس الظروف السابقة أعطى الباليونين نافثول بنسبة ٢٠% بالإضافة للمركبات السابقة.

كذلك عند تسخين ن- بارا- ميثيل فينيل- ٢- فيوراميد أوكزيزم VIII عند درجة حرارة ٢٠٠-٥٠٠ م في جو من النتروجين لمدة خمس ساعات تم الحصول على بارا- يودين و بارا- كريزول و ٢- فورنيتيل و- ٢- حمض الفورنيك و ٣- و ٣- داعي ميثيل كارباول و ٢- ميثيل و ٢- (٢- فيوران) بنزاميدازول كما أعطى N- (٤- ميثيل فينيل)- ٢- فيوراميد و ٥- ميثيل و ٢- (٢- فيوران) بنزاميدازول كمركباً ذو حصول درجة حرارة VIII تصل إلى ٤٧.٥% لذلك يعتبر التأثير الحراري للمركب VIII بطريقة هامة و جديدة لتحضير ٥- ميثيل- ٢- (٢- فيوران) بنزاميدازول.

ثالثًا: تحضير ودراسة التأثير الحراري والتعرض التجريبي لبعض مشتقات البينزاميدوإكزيم ذات حلقة النفثالية. كما يلي:

 فقد وجد عند تسخين N- ألفا - N- فثاليل بنزايميدوأوكزيم (XI) عند درجة حرارة 25-0-200 م في جو من النتروجين لمدة خمس ساعات تم الحصول على حمض البنزويك و بنزونتينيل و ألفا - N- فثاليل أمين و N- ألفا - N- فثاليل بنزاميود وأميدين البينزاميدوأوكزيم [b][1,2-b] بالإضافة إلى 2 فثاليل نفتا [b][1,2-b] amiédazol كمركب ذو حسيلة كبيرة تصل إلى 28% للكثير من تأثير الحاراري للمركب وخدمة طريقة هامة ونجمية لتحضير II فثاليل نفتا [b][1,2-b] amiédazol.

 كما تم تحضير N- ألفا - N- فثاليل نيكتوناميد أوكزيم (XI) من خلال تسخين كلوريد الألومينيوم الأمامي و 3- سيانوريدين مع ألفا - N- فثاليل أمين في وجود رباعي كلوروأيثان كمذيب لعطب. ألفا - N- فثاليل نيكتوناميدين الذي بدوره يتفاعل مع هيدروكسيل أمين هيدروكولريد في وجود الماء يعطي المركب XII. فقد وجد عندما تم تسخينة عند نفس الظروف المعطاة من قبل لم يتم الحصول على النتائج المتوقعة كما سبق في المركبات التي تم فحص التأثير الحراري لها.

 كذلك كما تم تحضير N- ألفا - N- فثاليل 2- فيورانياميدوأوكزيم (XIII) من خلال تسخين كلوريد الألومينيوم الأمامي و 2- سيانوفيوران مع ألفا - N- فثاليل أمين في وجود رباعي كلوروأيثان كمذيب لعطب. ألفا - N- فثاليل 2- فيورانياميدين الذي بدوره يتفاعل مع هيدروكسيل أمين هيدروكولريد في وجود الماء يعطي المركب XIII. فقد تم تسخينة عند نفس الظروف المعطاة من قبل لم يتم الحصول على النتائج المتوقعة كما سبق.

 من خلال النتائج السابقة التي تم الحصول عليها من التأثير الحراري لمشتقات مركبات البينزاميدوإكزيم الأورومانية والغير متجانسة الحلقة التي تحتوي على ألوية البريدرين والفيوران يتبين أن...
النتائج تكونت عن طريق ميكانيكية الشقوق الطلقيّة والتي تتضمن الكسر المتجانس للروابط N-O و C-N معطية شققات طلقيّة قامت بإحداث التفاعلات المعتادة مثل أنزاع الهيدروجين، الأزدواج، التقنت، التعديل التجزئي، التجمع الثاني، التشكّل، تكون حلقات.

وقد تمّ فصل النواتج السابقة بالقططير التجزئي عند ضغط مخلل وباستخدام كروماتوجرافيا الععمود عن طريق مذيبات متدرجة القطبية كما تم التعرف على هذه النواتج بتحضير عينات نقيّة من هذه النواتج وعمل مشتقات لها كما أمكن ذلك وعمل تحليل دقيق للعناصر لهذه النواتج كما تم دراسة طيف الأتمتاص لهذه المركبات للاشعة تحت الحمراء IR وكروماتوجرافيا الأغشية الرقيقة TLC ونقطة البروتون الرنين المغناطيسي H-NMR ونقطة الكربون الرنين المغناطيسي 13C-NMR ونقطة الكثافة الغازية MS ونقطة الكثافة المغزلي GC/MS. وكذا باستخدام كروماتوجرافيا الغاز مع طيف الكثافة
الإهداء

إلى تلك الأرواح الطيبة التي حفنتي برعايتها وبركة وجودها، حضورا وغيابا، منذ أن أُصبرت عيني نور الحياة روح والدتي الحبيب غفر الله له - وروح والدتي الحبيبة رحمها الله. أهدي هذا الجهد وهذا النتاج، وهذه الرسالة، التي ما كانت لتكون لولا ذلك الدعم والتوجيه والحنو والمؤازرة، والحشش الذي حظيت به على يديهما الكرمينين كان بودي أن يشاطرا في الفرحة بهذه اللحظة - لكن إرادة الله هي السابقة ولا مره لفضائله سيحانه، وحسبى أنهما معي في قلبي وفي وجدائي لم يبرحا وكأنهما ظلي ومرأتي أني توجهت لقيهما رب ارحمهما واغفر لهما كما ربيائي صغيرا.

ولا أنسى في هذا المقام أن أتقدم بالشكر والشكر لأخوتي وأبنائي الذين كان لوجودهم من حولي الأثر الكبير في تحقيق هذه الخطوة المباركة من خطوات حياتي العلمية والعملية، كما لا أنسى وفقات ودعوات كل الأحباب من زملائي وزميلات وأساتذة أفضيل، لم يخلوا علي بالرأي والنصيحة وحسن التوجيه.

والشكر موصول أيضا لجامعتي الفتيقة والعريقة على احتسابها لي، وعلى حجم ذلك العطاء المتدفق الذي تلقيته كطالبي عبر عقود ماضية، وخلال سنوات مورقة، كانت بمثابة الرياض والجنان التي لا تعطي سوى الظل والورد والأمل وكل ما يمنح هذه الحياة معانها.

والحمد لله رب العالمين.

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قسم الكيمياء

الطرق التحضيرية والتأثير الحراري لبعض مشتقات
البنزاميدوأوكزيم الأروماتية والغير متجانسة الحلقة
المختلفة

رسالة مقدمة من
ليلى أحمد إبراهيم طيب

كجزء من المتطلبات للحصول على درجة دكتوراه الفلسفة في
العلوم "الكيمياء"
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