CHAPTER II

SYNTHESIS OF HETEROCYCLIC HYDROXAMIC ACIDS
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SUMMARY

The syntheses and properties of the p- and m-substituted furo and theno hydroxamic acids are described.

The preparations are made by reacting N-aryl-hydroxylamines with corresponding acid chlorides at low temperature in diethyl ether medium containing aqueous suspension of sodium hydrogen carbonate. These acids are characterised by elemental analysis, mp, UV, and ir spectra.

The thermal and chemical stabilities are also studied.
INTRODUCTION

The hydroxamic acids (I), having the bidentate functional grouping (II), are the N-acyl derivatives of hydroxylamine and may be considered as N-hydroxy derivatives of acid amides (1-4).

\[
\begin{align*}
\text{R} - \text{N} - \text{OH} & \quad \text{R'} - \text{C} = \text{O} \\
& \quad \text{R} - \text{N} - \text{OH} \\
& \quad \text{R'} - \text{C} = \text{O}
\end{align*}
\]

(I) \quad (II)

Where R is phenyl, tolyl or p and m-chlorophenyl and R' is heterocyclic ring.

METHOD OF SYNTHESIS

A tremendous progress in the chemistry of the synthesis and analytical applications of the hydroxamic acids has been made since last five decades. The general method of preparation of acyl and aryl hydroxamic acids is summarised by Yale (1) in a well documented review article. The other reviews of information on synthesis are those by Sandler and Karo, Henecka and Kurtz, Metzger, Mathis, Smith, Coutts and Katritzky (5-11).

The synthesis of N-aryl hydroxamic acid is generally based on Schotten-Bauman reaction (12). N-phenylbenzo-hydroxamic acid (PBHA), the parent compound was first
synthesised by Bamberger (13) by reacting the N-phenyl-hydroxylamine, dissolved in hot water, with benzoyl chloride. Shome (14) modified the reaction condition and carried out the acylation reaction at room temperature. Ryan and his co-workers (15,16) dispensed with the aqueous medium and used diethyl ether, rendered basic with pyridine as the reaction medium. Tandon and Bhattacharyya (17) carried out the benzoylation at low temperature (0°C-5°C) in diethyl ether medium. Hydrochloric acid emitted during the reaction was neutralized by pyridine. Baumgarten (18) recommended a 5% aqueous solution of sodium hydroxide in place of liquor ammonia for extraction of hydroxamic acid. Tandon and Bhattacharyya's method (17) was radically modified by Priyadarshini and Tandon (19) and later by Agrawal and Tandon (20-22). In this modified procedure equimolar proportions of both N-arylhydroxylamine and acid chloride were taken and reacted at about 0°C in diethyl ether. Solutions were made alkaline with aqueous suspension of sodium hydrogen carbonate. It was observed that under these conditions the product obtained contained negligible amount of di-derivative and was readily purified by two or three crystallizations from suitable solvent.
THE PRESENT PROCEDURE

In the present investigation the hydroxylamines were prepared by reduction of nitrobenzenes using mild reducing agent like zinc dust and ammonium chloride in a protic solvent viz. ethyl alcohol or water. The reaction temperature was maintained around 60°C.

The following reaction conditions were maintained for the preparation of hydroxamic acids.

N-aryl hydroxylamine and acid chloride were used in just equimolar proportions. Diethyl ether or a mixture of diethyl ether and petroleum ether (80:20) is used as solvent. Finally, powdered sodium hydrogen carbonate suspended in small amount of water is used instead of pyridine for neutralizing the liberated hydrochloric acid during the reaction. Reaction is carried out at low temperature (0°C), while the reaction time is prolonged to 75-90 min. The use of just stoichiometric proportions of N-arylhydroxylamine and acid chloride gives a pure product with better yields.
EXPERIMENTAL

CHEMICALS

All the chemicals used were of G.R. and AnalaR grade of E. Merck and B.D.H., respectively, unless otherwise specified. The Koch-Light products of C.P. grade carboxylic acids were used.

Ethyl alcohol

The spectroscopic grade ethyl alcohol was prepared by twice distilling 95% ethyl alcohol over silver nitrate and potassium hydroxide (23).

APPARATUS

The ultraviolet spectra were scanned on Shimadzu recording spectrophotometer (UV-240) and measurements at constant wavelength were performed on a C.Z.Jena, VSU-2 P spectrophotometer with 10 mm matched quartz cells.

The infrared spectra were recorded on Perkin Elmer Model 221 spectrophotometer.

ACID CHLORIDES

The acid chlorides were prepared by the action of thionyl chloride on the corresponding carboxylic acids and refluxing them on a waterbath for 4-6 hrs. The excess of thionyl chloride was removed under reduced pressure.
HYDROXYLAMINES

(1) N-p-chlorophenylhydroxylamine

This was prepared by the reduction of N-p-chloronitrobenzene from alcoholic media with zinc dust as described by Agrawal (24).

A mixture of 30 g of p-chloronitrobenzene, 60 ml of ethyl alcohol, 40 ml of water and 6 g of ammonium chloride was stirred mechanically and treated with 30 g of zinc dust in small lots of 1.0-1.5 g during the course of 25-30 min. The reaction temperature was maintained between 60 and 65°C throughout, and stirring was continued for another 15 min while hot, the zinc oxide was filtered out and washed with 6x5 ml of hot ethyl alcohol. On addition of about 400 g of crashed ice to the filtrate, a light yellow product was obtained which on crystallization from benzene and petroleum ether gave white flakes in 75% yield, mp 90°C (reported 90°C) (25).

(2) N-m-chlorophenylhydroxylamine

A mixture of 12.5 g of N-m-chloronitrobenzene, 25 ml ethyl alcohol, 40 ml water and 2 g ammonium chloride was stirred mechanically and treated with 15 g of zinc dust in small lots of 1.0-1.5 g during 25-30 min. The reaction temperature was maintained between 55 and 65°C throughout,
and stirring was continued for another 15 min. The zinc oxide was filtered and washed with 3 x 10 ml of hot ethanol. On cooling the filtrate by adding about 400 g of crushed ice, white flakes appeared. Crystallization of the same from a mixture of benzene and petroleum ether gave white cubes in 70% yield, mp 90°C (20).

(3) N-phenyl-hydroxylamine

In a 500 ml beaker with thermometer and mechanical stirrer placed 12.5 g NH₄Cl, 150 ml H₂O and 20.0 ml redistilled nitrobenzene, stirred vigorously and added 30.0 g of zinc dust (90%) during 25 min. The reaction temperature was maintained between 60-65°C. After the addition was over the stirring continued for another 15 min, filtered the warm mixture, removed ZnO and washed with 100 ml hot water. The filtrate was saturated with sodium chloride and cooled in ice bath for about one hour for crystallization, filtered the pale yellow crystals with suction pump and then recrystallised it in a mixture of Benzene-petroleum ether.

(4) N-p-tolylhydroxylamine

A mixture of 30 g of p-nitrotoluene, 50 ml of EtOH, 40 ml of water and 4 g of ammonium chloride was stirred mechanically and treated with 30 g zinc dust in small lots of 1.0-1.5 g during 30 min. The temperature was maintained at 60-65°C.
throughout, stirring was continued for another 15 min. to complete the reduction. The hot zinc oxide was filtered and washed with a 50% hot EtOH. The amine was crystallised by even attaining the room temperature which on addition of ice gave quantitative amount of crystals.

**General procedure for the synthesis of hydroxamic acids**

Freshly prepared and recrystallized hydroxyl amine (0.1 M) is dissolved in 75 ml of diethyl ether and cooled externally to 0±5°C. To this added an aqueous suspension of sodium bicarbonate (0.2-0.3 M) and stirred it by magnetic stirrer, to this a solution of the acid chloride in 50 ml diethyl ether is added dropwise during 30-45 min. The precipitated product is filtered at the pump and the ether layer separated and the solvent is removed under vaccum. Any solid product thus obtained was combined with the bulk and triturated with saturated sodium bicarbonate solution to remove the acidic impurities, the solid product is filtered off, washed with water and dried. Further it was purified by crystallisation with benzene-petroleum ether.

A typical preparation of an N-aryl hydroxamic acid is given below.
PREPARATION OF N-p-TOLYL-2-FUROHYDROXAMIC ACID

In a 500-ml conical flask fitted with a dropping funnel taken 5 g freshly prepared and crystallized N-p-tolyl hydroxylamine dissolved in 75 ml of cold diethyl ether. An aqueous suspension of 5 g sodium bicarbonate in 30 ml of water is added and stirred with a magnetic stirrer. After the mixture was externally cooled to 0±5°C, 5.5 g of 2-furoylchloride dissolved in 50 ml of diethyl ether was added to the reaction mixture dropwise through the dropping funnel over a period of 30 min and the stirring was continued for another 15 min. Almost the entire amount of hydroxamic acid formed was precipitated as a granular solid. The light yellow ethereal layer on separation and distillation under vaccum gave a yellowish solid which was combined with the bulk of the product. It was thoroughly tritutrated in a glass mortar with a saturated solution of sodium bicarbonate to remove the acidic impurities, filtered, washed with water and dried, m.p. 138°C. The product was crystallised from a mixture of benzene and petroleum ether, dried over P₂O₅ under vaccum (yield 60%).
RESULTS AND DISCUSSION

PREPARATION

The method adopted here for the preparation of hydroxamic acid is very simple and of general applicability. It gives better yield. It may be mentioned that the stoichiometric proportion of hydroxylamine and the acid chloride was the most satisfactory. The excess of acid chloride results in increasing amount of di-derivative. Similarly an excess of hydroxyl amine leads to a product which is impure, probably due to the decomposition of the hydroxylamine (17-22), or due to the well known acid catalysed rearrangement of N-aryl hydroxylamine and its decomposition to the complex product (15).

PROPERTIES

The physical properties of the synthesised hydroxamic acids are given in Table 1. Other salient features are briefly discussed below.

Colour and Crystallinity

All the hydroxamic acids are white crystalline solids.

Solubility

All the hydroxamic acids are soluble in dioxan, chloroform, carbon tetrachloride, benzene, alcohol but
**TABLE 1**

Preparation and properties of N-aryl hydroxamic acids

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Hydroxamic acids</th>
<th>Molecular formula</th>
<th>Molecular weight (g/mol)</th>
<th>mp °C</th>
<th>Colour</th>
<th>Elemental Analysis (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C     H     N     Cl     S     O</td>
</tr>
<tr>
<td>I.</td>
<td>N-ph-2-furo-</td>
<td>C₁₁H₉NO₃</td>
<td>203.197</td>
<td>131</td>
<td>(130) White</td>
<td>66.00 4.60 7.50 - - 21.90</td>
</tr>
<tr>
<td>II.</td>
<td>N-p-tolyl-2-furo-</td>
<td>C₁₂H₁₁NO₃</td>
<td>217.224</td>
<td>138</td>
<td>(142) &quot;</td>
<td>66.64 5.50 6.61 - - 21.25</td>
</tr>
<tr>
<td>III.</td>
<td>N-p-c-ph-2-furo-</td>
<td>C₁₁H₈NO₃Cl</td>
<td>237.642</td>
<td>166</td>
<td>(164) &quot;</td>
<td>55.80 3.75 6.20 15.00 - 19.25</td>
</tr>
<tr>
<td>IV.</td>
<td>N-m-c-ph-2-furo-</td>
<td>C₁₁H₈NO₃Cl</td>
<td>237.642</td>
<td>165</td>
<td>(165) &quot;</td>
<td>55.82 3.74 6.19 14.96 - 19.29</td>
</tr>
<tr>
<td>V.</td>
<td>N-ph-2-theno-</td>
<td>C₁₁H₉NO₂S</td>
<td>219.262</td>
<td>97</td>
<td>&quot;</td>
<td>60.41 4.25 6.50 - 14.85 13.99</td>
</tr>
<tr>
<td>VI.</td>
<td>N-p-tolyl-2-theno-</td>
<td>C₁₂H₁₁NO₂S</td>
<td>233.29</td>
<td>122.5</td>
<td>(125.5) &quot;</td>
<td>61.65 4.91 6.40 - 13.55 13.39</td>
</tr>
<tr>
<td>VII.</td>
<td>N-p-c-ph-2-theno-</td>
<td>C₁₁H₈NO₂Cls</td>
<td>253.707</td>
<td>141</td>
<td>(143) &quot;</td>
<td>52.20 3.32 5.70 14.35 12.80 11.63</td>
</tr>
<tr>
<td>VIII.</td>
<td>N-m-c-ph-2-theno-</td>
<td>C₁₁H₈NO₂Cls</td>
<td>253.707</td>
<td>120</td>
<td>(120) &quot;</td>
<td>52.22 3.29 5.70 14.32 12.80 11.67</td>
</tr>
</tbody>
</table>

Reported values are given in the parentheses.
those derivatives of N-p-chlorophenylhydroxylamines are comparatively less soluble in benzene, chloroform, and insoluble in water.

Stability

The hydroxamic acids are stable to heat, light and air. The author stored these acids in stoppered amber bottles for two years.

Ultraviolet spectra

The characteristics of the ultraviolet spectra of the synthesised hydroxamic acids in 95% ethanol are given in Table 2. All the hydroxamic acids studied here possess the carbonyl and benzene chromophore in the molecule. They have two distinct bands, assigned as the primary and secondary bands of the benzene (26,27). The spectra of benzene gives distinct absorption bands arise from $\pi-\pi^*$ transitions. These bands are designated as bands I and II (26-28).

The absorption characteristics of benzene, furan and thiophene are given below (27).

<table>
<thead>
<tr>
<th></th>
<th>Band I</th>
<th>Band II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>180</td>
<td>200</td>
</tr>
<tr>
<td>Furan</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>Thiophene</td>
<td>204-260</td>
<td>235</td>
</tr>
</tbody>
</table>
TABLE 2

UV spectral characterization of Hydroxamic acids in 95% Ethanol

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Hydroxamic acids</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\epsilon$ ($\times 10^4$)</th>
<th>II/I</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.</td>
<td>N-phen-2-furo-</td>
<td>280 (216)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>II.</td>
<td>N-p-tolyl-2-furo-</td>
<td>282 (216)</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>III.</td>
<td>N-p-c-ph-2-furo-</td>
<td>286 (217)</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>IV.</td>
<td>N-m-c-ph-2-furo-</td>
<td>283 (216)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>V.</td>
<td>N-phen-2-theno-</td>
<td>286 (216)</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>VI.</td>
<td>N-p-tolyl-2-theno-</td>
<td>286 (216)</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>VII.</td>
<td>N-p-c-ph-2-theno-</td>
<td>293 (215)</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>VIII.</td>
<td>N-m-c-ph-2-theno-</td>
<td>292 (216)</td>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>
The absorption band due to the carbonyl group originating from the weak n-π* transition seems to be eclipsed in the strong secondary band of the benzene.

The ultraviolet spectra of hydroxamic acids can be correlated with that of the substituted amides and anilides because of their similarity in structure, the benzene band II is observed at 243 nm in the absorption spectra of acetanilide but in benzanilide the band is shifted to 267 nm. The same maxima is observed in hydroxamic acids also. The band II of hydroxamic acids derived from aliphatic carboxylic acids is at about 250 nm, whereas in N-phenylbenzohydroxamic acid it is seen at 268 nm. The substitution in benzene ring displaces the bands I and II.

In case of present hydroxamic acids (compounds I-VIII) the band I and band II are observed at around 216±1 nm and 285±8 nm, respectively. Hence it is seen that band II has bathochromic shift relative to the benzene or heterocyclic ring (29). On the basis of exhaustive studies of Doub and Vandenbelt (30), it is possible to correlate the spectra of substituted benzene. The bands are discriminated by their position, magnitude of intensity and the ratio of the wave length of the bands \( \lambda_{II}/\lambda_I \) in the present investigation, the hydroxamic acids, where both the bands are resolved, the ratio of the two bands, \( \lambda_{II}/\lambda_I \) is found to be \( \sim 1.3-1.4 \) which is in agreement with reported earlier (31).
INFRA RED SPECTRA

The frequencies of absorption bands of the synthesised N-aryl-hydroxamic acids examined here are given in Table 3. Those bands which are associated with the hydroxamic acid functional group.

\[
\begin{align*}
- \text{N} &- \text{OH} \\
\downarrow & \\
- \text{C} &- \text{O}
\end{align*}
\]

are due to (O-H) and (C=O) stretching vibrations and these can be assigned unambiguously. The (N-O), (C-N) and (C-Cl) stretching vibrations are assigned with less confirmity because of the overlapping with several other modes of vibrations and also the nonavailability of systematic data on the assignment of the bands in infrared spectra of these hydroxamic acids.

(O-H) stretching vibrations

In the heterocyclic hydroxamic acids examined here the band due to (O-H) stretching vibrations has been assigned in the region 3200 cm\(^{-1}\) and 3100 cm\(^{-1}\) (Table 3). It is known that the absorption bands due to the (O-H) stretching vibrations, when free, appear at around 3600 cm\(^{-1}\), hydrogen bonding shifts these bands to lower frequencies (32-35). Most of the changes in the (O-H) stretching vibrations are mainly due to the ability of acidic hydrogen of the hydroxyl group to form "hydrogen bonds" with electron rich atoms. In
hydroxamic acids, the acidic (O-H) group is placed in a very close proximity of the polar carbonyl group, $\equiv C^+\equiv O^-$. This substitution highly favours the formation of strong intramolecular hydrogen bonding of the type given below.

\[
\begin{array}{c}
\text{- N - O} \\
\text{H} \\
\text{- C = O} \\
\end{array}
\]

The formation of strong hydrogen bond causes a large shift in the absorption band to lower frequencies of the order of $500 \text{ cm}^{-1}$, and may be ascribed to the resonance stabilization.

A consequence of this resonance stabilization should be to lower the force constant of the carbon-oxygen bond and to increase the contribution of single bond form, thereby causing a fall in the frequency of the $(C=O)$ stretching vibrations. The assignment of bands, made here is supported by the work of Hadzi (37), Baumgarten (18) and others (36-40). The hydrogen bonding is of intramolecular type and is confirmed by solution studies made by other workers (37-42). Exner (43) has reported the $3296 \text{ cm}^{-1}$ band (in crystalline state) in benzohydroxamic acid as intramolecularly hydrogen bonded in accordance with the detailed study by Hadzi and Prevorsek (36).
(C=O) stretching vibrations

In the hydroxamic acids examined here the (C=O) stretching vibration bands are assigned in the region 1620-1590 cm\(^{-1}\). The assignment is made with reference to the spectra of amide, anilides and unsubstituted hydroxamic acids. It is well known that the amide I band is primarily due to C=O (44-45).

In unsubstituted amides, RCONH\(_2\), this band is located between 1690 and 1650 cm\(^{-1}\), while in substituted amides, RCONHR, it is observed between 1680 and 1650 cm\(^{-1}\) (45). In unsubstituted hydroxamic acids like benzohydroxamic acid at 1667 cm\(^{-1}\) by Farha (38), and 1661 cm\(^{-1}\) by Usova (46). Oriville-Thomas assigned this band at 1647 cm\(^{-1}\) in formohydroxamic acid (47).

Mathis (8) assigned this band in benzo-, propiono-, cinnamo- and p-methoxy benzohydroxamic acids at 1640±30 cm\(^{-1}\). The position of (C=O) stretching band is much influenced by molecular structure and generally shifted to lower frequencies (48,49).

Thus the hydrogen bonding lowers (C=O) by 10-45 cm\(^{-1}\) (48,49). Conjugation of the carbonyl group with C=C lowers the absorption band by about 30 cm\(^{-1}\) for first conjugation. When an aromatic ring is directly attached to the carbon atom of the carbonyl group, the frequency shift of the
The carbonyl group is generally less than that occurring with a full double bond in conjugation. The substituents in the aromatic ring and the ring strain also lower the carbonyl absorption frequency \((\text{C}=\text{O})\). Thus, the range of \((\text{C}=\text{O})\) absorption 1640-1600 cm\(^{-1}\) observed here for N-aryl hydroxamic acids is in fair agreement with the above referred empirical rules.

\((\text{N-O})\) stretching vibrations

In N-arylhydroxylamines this band appears around 915 cm\(^{-1}\) \((50,51)\). In aromatic hydroxamic acids such as PBHA it appears at 900 cm\(^{-1}\) \((8,52)\). In several oximes this band appears at around 950 cm\(^{-1}\) \((37,47,53)\). Therefore, it appears reasonable to look for this band in the region 950-900 cm\(^{-1}\). A reference sharp band at 920\(\pm\)20 cm\(^{-1}\) may be attributed to \((\text{N-O})\) stretching mode. The band is rather conspicuous in all the spectra examined here. This assignment is supported by the work of Pilipenko \((40)\) who assigned this band in the spectra of PBHA and N-phenyl-2-furohydroxamic acid at 915 and 912 cm\(^{-1}\), respectively.

Earlier Hadzi \((36)\) assigned this band at 890 cm\(^{-1}\) in PBHA. It may be noted that this portion of infrared spectrum contains several aromatic and other bands and hence caution must be exercised in assigning \((\text{N-O})\) band.
The assignment of the bands due to the vibrations of the (C-N) groups calls for more careful attention in the present study. The weak to medium absorption bands at 1330±20 cm\(^{-1}\) have been assigned to these vibrations. The spectra of N-aryl hydroxamic acids can be compared with the spectra of tertiary aromatic amines for (C-N) stretching vibrations. The (C-N) band in aromatic tertiary amines too, appears in the same region, e.g. at 1360-1310 cm\(^{-1}\)(33,35,53).

(C-Cl) stretching vibrations

The (C-Cl) stretching vibrations for the compound containing chlorine atom attached directly to benzene ring had been assigned between 750 and 700 cm\(^{-1}\) (32,33,35). The band observed in the spectrum of N-aryl hydroxamic acid reported here, corresponds to the N-phenyl chlorine atom.
THERMAL AND CHEMICAL STABILITY

The thermal stability tests show that these hydroxamic acids are very stable compounds. These acids are stable to \( \text{HCl (8 M)} \) and \( \text{HClO}_4 \) \( (8 \text{ M}) \) at 50°C. The degradation rate is of 1st order while with \( \text{HNO}_3 \) \( (0.8 \text{ M}) \), they decompose and the rate is of 2nd order. The thermal stability was tested as follows:

A 0.5 ml of 0.1 M chloroform solution of hydroxamic acid was transferred into fifteen 25-ml volumetric flasks, after evaporation of chloroform under vacuum, the flasks were heated in a thermostated oven. At regular intervals the remaining hydroxamic acid was determined colorimetrically.

The chemical stability was determined as follows:

0.1 M solution of hydroxamic acid in 8 M \( \text{HClO}_4 \), 8 M \( \text{HCl} \) or 0.8 M \( \text{HNO}_3 \) were kept in a thermostatic bath at 50±0.1°C and hydroxamic acid was determined colorimetrically at regular intervals.
REFERENCES


