CHAPTER II

PREPARATION AND PROPERTIES OF HYDROXAMIC ACIDS

ABSTRACT

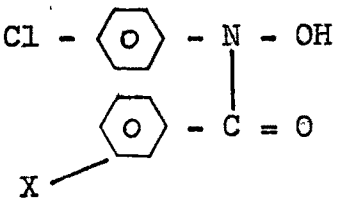
The preparation and properties of eight N-p-chlorophenyl-m-substituted benzohydroxamic acids, out of them two are the new compounds, have been described. The acids were prepared by reacting hydroxylamine with acid chloride in diethyl ether medium rendered alkaline by aqueous suspension of sodium bicarbonate at lower temperature (0°C or below).

These acids were characterized by m.p., elemental analysis, ultraviolet and infrared spectra.

The alkaline hydrolysis constants are reported.

PREPARATION AND PROPERTIES OF HYDROXAMIC ACIDS

In the present investigation, the preparation and properties of eight hydroxamic acids represented by the general formula (I), have been described.



(I)

(X = H, OCH_3, CH_3, F, Cl, Br, I, NO_2)

The m.p., ultraviolet and infrared spectra were determined for the characterization of the acids.

The rate constant (K) for the alkaline hydrolysis of the hydroxamic acids are also studied.

A REVIEW OF THE METHOD OF PREPARATION

There has been a progressive modification in the chemistry of preparation of hydroxamic acids. It was Yale (1) who summarised the general methods of preparation of various types of hydroxamic acids in a well documented review article in 1943. Later on, other useful reviews on this subject were documented by Sandler and Karo, Henecko

and Kurtz, Metzger, Mathis, Smith, Coutts and Katritky (2-8).

The general method of preparation is based on Schotten-Bauman reaction (9). N-phenylbenzohydroxamic acid (PBHA), the parent compound was first prepared by Bamberger (10) by reacting N-phenylhydroxylamine dissolved in hot water with benzoyl chloride. Shome (11) modified the reaction condition and carried out the acylation reaction at room temperature. Ryan and his co-workers (12,13) dispensed with the aqueous medium and used diethyl ether, rendered basic with pyridine as the reaction medium. Tandon and Bhattacharya (14) carried out the benzoylation at low temperature (0°C or lower) in diethyl ether medium. Hydrochloric acid liberated during the reaction was neutralised by pyridine. Baumgarten (15) recommended a 5% aqueous solution of sodium hydroxide in place of liquor ammonia for extraction of hydroxamic acid. Tandon and Bhattacharya's method (14) was radically modified by Priyadarshini and Tandon (16) and Agrawal and Tandon (17-19). In the modified procedure, both the N-arylhydroxylamine and acid chloride were taken in just equimolar propertions and were reacted at 0°C or below in diethyl ether medium. Solutions were made alkaline with aqueous suspension of sodium bicarbonate. It was found that under these conditions

the product obtained contained negligible amount of diderivative and was readily purified by two to three crystallisation from suitable solvent.

EXPERIMENTAL

CHEMICALS

All the chemicals used were of G.R. and AnalaR grades of E. Merck and B.D.H., respectively unless otherwise specified.

SOLVENTS

Distilled water

Pure distilled water, redistilled over alkaline potassium permanganate and freed from carbon dioxide was used. It was tested for absence of carbonate by Kolthoff's method (20).

Ethyl alcohol

The spectroscopic grade ethyl alcohol was prepared by twice distilling 95% ethyl alcohol over silver nitrate and potassium hydroxide (21).

Chloroform

The ethyl alcohol free chloroform was used. Ethyl alcohol was removed by washing the commercial chloroform five or six times with about half of its volume of water and distilling it after drying over fused calcium chloride.

Sodium hydroxide solution

A 0.01 M solution was prepared and standardised with potassium acid phthalate (22).

Ferric chloride solution

A 2% solution was prepared as described elsewhere (23).

APPARATUS

N.P.L. certified grade 'A' graduated apparatus (Gallenkamp Technico) was used for measurements.

The ultra violet spectra was scanned on Shimadzu UV-VIS 240 recording spectrophotometer and measurements at constant wavelength were performed on a Carl Zeiss, Jena, VSU 2-P spectrophotometer with 10 mm matched silica cells.

The infra red spectra were scanned on Unicam SP-200 spectrophotometer in nujol or as KBr pellets.

ACID CHLORIDE

m-substituted benzoyl chloride

These were prepared by refluxing 5 g of the corresponding m-substituted carboxylic acid with requisite quantity of thionyl chloride for five to eight hours. The excess thionyl chloride was distilled off. The acid chloride was purified by vacuum distillation.

HYDROXYLAMINE

N-p-Chlorophenylhydroxylamine

This was prepared by 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, 50 ml of water and 6 g of ammonium chloride was taken in a conical flask and stirred mechanically and treated with 30 g of zinc dust added in small lots of 1-1.5 g during a span of 30 min. The reaction temperature was maintained at 60-65°C and continued stirring for further 15 min. The zinc oxide was filtered while hot and washed with 6 x 5 ml of hot ethyl alcohol-water mixture (1:1). Finally washed with hot water. On addition of 400 g of ice to the filtrate, a pale yellow product was obtained, which on crystallisation from benzene-petroleum ether mixture gave white flakes in 80% yield, m.p. 90°C (reported m.p. 90°C) (25).

GENERAL PROCEDURE FOR PREPARATION OF HYDROXAMIC ACID

N-p-chlorophenyl-m-substituted benzohydroxamic acid

Freshly prepared and crystallised N-p-chlorophenyl hydroxylamine was dissolved in minimum quantity of diethyl

ether and rendered alkaline by aqueous suspension of sodium bicarbonate. The mixture was stirred mechanically and cooled to a temperature of 0±5°C by placing the flask in a freezing mixture. To this an equimolar solution of the acid chloride dissolved in minimum quantity of diethyl ether was added dropwise over a span of 30-45 min. The precipitated product was filtered and the ether layer was separated and removed under vacuum. Any solid product thus obtained was combined with the bulk and titurated with saturated sodium bicarbonate solution to remove any acidic impurities. The solid product was washed with water and dried. It was purified by crystallization from appropriate benzene-petroleum ether mixture.

RESULTS AND DISCUSSION

PREPARATION

The method adopted here for the preparation of hydroxamic acids, wherein stoichiometric proportions of N-p-chlorophenylhydroxylamine and acid chloride were taken, gave best yield of acid. Any excess of acid chloride results in formation of diderivatives. Similarly, an excessof hydroxylamine leads to impure products probably due to the decomposition of the hydroxylamine (15) or due to well known acid catalyzed rearrangement of N-aryl-hydroxylamine and its decomposition to the complex product (26). The preparation and properties of the synthesised hydroxamic acids are given in Table 1.

PROPERTIES

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

All the synthesised hydroxamic acids are white in colour except N-p-chlorophenyl-m-iodo- and m-nitro-hydroxamic acids which are light yellow in colour.

Solubility

All these acids are insoluble in water. They are

TABLE 1

PREPARATION AND PROPERTIES OF HYDROXAMIC ACIDS

Compd. No.	Hydroxamic acid	Molecular formula	Molecular weight	m.p. (°C)	Yield (%)	Colour	Elemental Analysis (%)		
							C	H	N
I.	N-p-Chlorophenylbenzo-	$C_{13}H_{10}NO_2Cl$	247.7	158 (158)[a]	70.0	White	63.1 (63.0)	4.2 (4.1)	5.7 (5.6)
II.	N-p-Chlorophenyl-m-methylbenzo-	$C_{14}H_{12}NO_2Cl$	261.7	101 (103)[a]	60.6	White	64.0 (64.2)	4.5 (4.6)	5.6 (5.3)
III.	N-p-Chlorophenyl-m-methoxybenzo-	$C_{14}H_{12}NO_3Cl$	277.7	102 (104)[a]	50.0	White	61.3 (61.4)	4.4 (4.4)	5.4 (5.1)
IV.	N-p-Chlorophenyl-m-fluorobenzo-	$C_{13}H_9NO_2ClF$	265.6	115	60.1	White	58.9 (58.7)	3.3 (3.4)	5.2 (5.2)
V.	N-p-Chlorophenyl-m-chlorobenzo-	$C_{13}H_9NO_2Cl_2$	282.1	108 (108)[a]	65.2	White	55.3 (55.3)	3.2 (3.2)	4.6 (4.9)
VI.	N-p-Chlorophenyl-m-bromobenzo-	$C_{13}H_9NO_2ClBr$	326.5	122 (126)[a]	50.0	White	47.9 (47.8)	2.4 (2.7)	4.1 (4.2)
VII.	N-p-Chlorophenyl-m-iodobenzo-	$C_{13}H_9NO_2ClI$	373.5	120	88.8	Light yellow	41.7 (41.7)	2.6 (2.4)	3.8 (3.7)
VIII.	N-p-Chlorophenyl-m-nitrobenzo-	$C_{13}H_9N_2O_4Cl$	292.6	119 (124)[a]	80.0	Light yellow	53.5 (53.3)	3.1 (3.1)	9.2 (9.5)

a - Reported m.p., Agrawal, D.R. and Tandon, S.G., J. Chem. Eng. Data, 17, 2 (1972).
Theoretical values are given in parenthesis.

sparingly soluble in carbon tetrachloride but readily soluble in ethyl alcohol, dioxan, chloroform and ethyl acetate.

All the acids are stable to heat, light and air. The author stored the acids in stoppered amber coloured 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 benzene and carbonyl chromophore in their molecule. Most of the hydroxamic acids have two distinct bands, around 225 nm and 270 nm. These two bands are assigned as the primary and secondary bands of the benzene (27,28). The spectra of benzene shows three distinct absorption bands arising from $\pi-\pi^*$ transitions. These bands are designated as bands I, II and III (27,29).

	Band I	Band II	Band III
	nm	nm	nm
Benzene	183 (50,000)	204 (~8,000)	230 (300)

These bands are also designated as the primary and

secondary bands. The absorption band due to the carbonyl group originating from the weak $n-\pi^*$ transition is presumed to be eclipsed in the strong secondary band of the benzene, as evident from the spectra (Table 2, Fig. 1).

It is inferred from the spectral data that the changes in the substitution in the molecule, usually produce changes in the position and intensity of absorption bands, but no new bands appear. The correlation of the spectral data of the hydroxamic acids and the characterization of the absorption bands are possible from the position, magnitude and intensity of the bands.

The ultraviolet spectra of the hydroxamic acids can be very well correlated with that of the substituted amides or anilides due to their structural similarity. The secondary band of benzene is observed at 243 nm in the absorption spectra of acetanilide but in benzanilide the band has been shifted to 267 nm. The same pattern is observed in the hydroxamic acids also. The secondary band of the hydroxamic acids derived from aliphatic carboxylic acids is around 250 nm, but for N-phenylbenzohydroxamic acid (PBHA), the band is observed at 268 nm. Substitution of the benzene ring displaces the primary and secondary bands.

In the present investigation, the synthesised hydroxamic acids have strong absorption band around 270$\pm$10 nm which

TABLE 2

ULTRAVIOLET AND INFRARED ABSORPTION CHARACTERISTICS OF THE HYDROXAMIC ACIDS

Compd. No.	Hydroxamic acid	UV Spectra (95% Ethanol)		IR Frequency (cm^{-1})		
		λ_{max} (nm)	$\epsilon \times 10^{-3}$	νO-H	νC=O	νN-O
I.	N-p-Chlorophenylbenzo-	274	11.5	3185	1613	920
II.	N-p-Chlorophenyl-m-methylbenzo-	276	12.3	3115	1603	910
III.	N-p-Chlorophenyl-m-methoxybenzo-	278	10.4	3106	1625	860
IV.	N-p-Chlorophenyl-m-fluorobenzo-	276	15.0	3150	1630	965
V.	N-p-Chlorophenyl-m-chlorobenzo-	276	10.9	3106	1625	920
VI.	N-p-Chlorophenyl-m-bromobenzo-	276	10.3	3112	1620	920
VII.	N-p-Chlorophenyl-m-iodobenzo-	275	17.6	3120	1625	915
VIII.	N-p-Chlorophenyl-m-nitrobenzo-	266	15.2	3118	1620	900

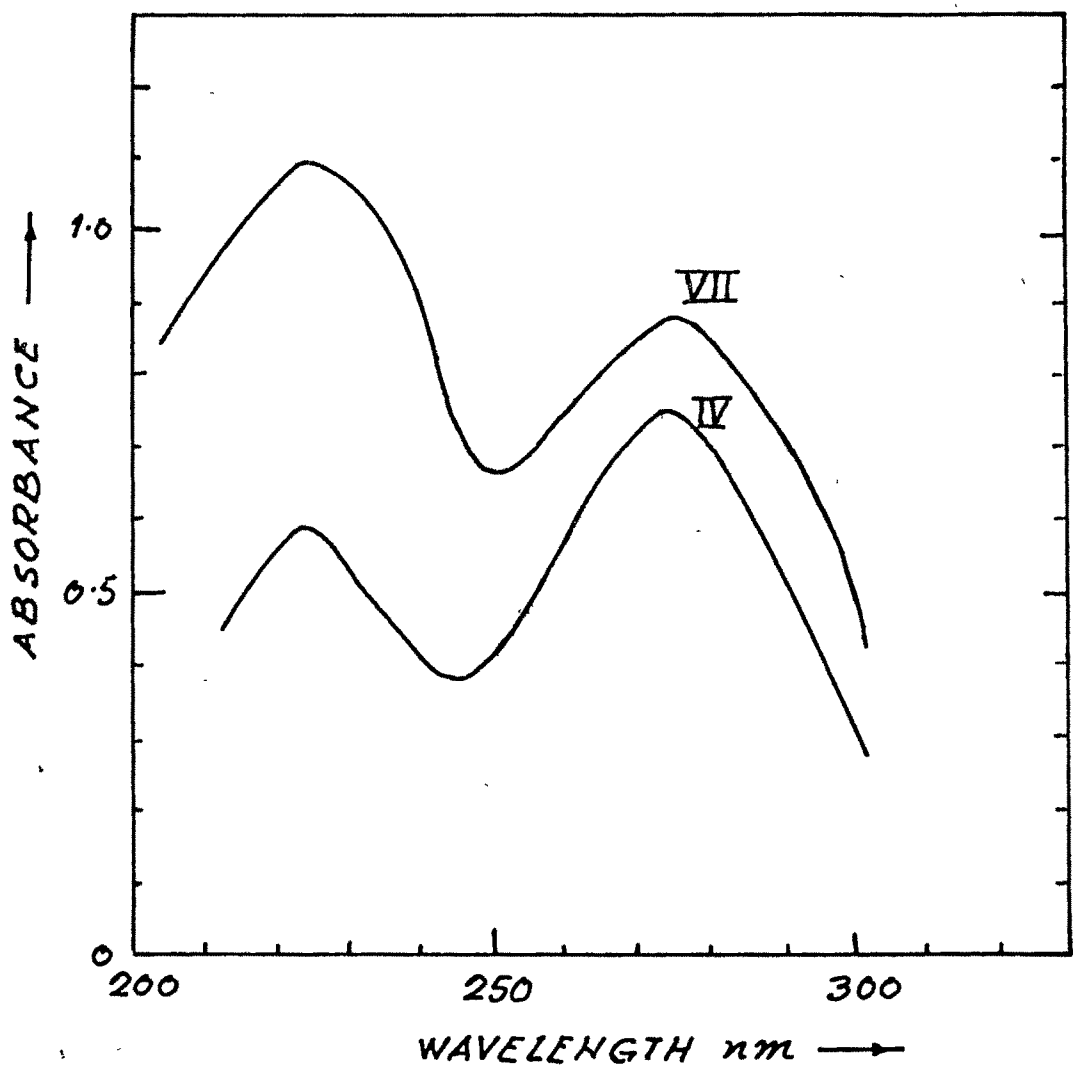


Fig. 1. Ultraviolet spectra of :

VII. N-p-chlorophenyl-m-iodobenzohydroxamic acid (5×10^{-5} M)

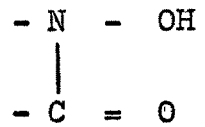
IV. N-p-chlorophenyl-m-fluorobenzohydroxamic acid (5×10^{-5} M)

in 95% ethanol.

is assigned as the second band (secondary bands) of the benzene ring. The bathochromic shift observed in the present case with respect to N-phenylbenzohydroxamic acid (PBHA) (λmax = 268 nm) can be due to the presence of substituted group in the aromatic nuclei of the hydroxamic acid.

INFRARED SPECTRA

The frequencies of the absorption bands of the hydroxamic acids under investigation are shown in Table 2. Only those bands which are associated with the hydroxamic acid functional group (II), and which are prominently displayed have been assigned for the characterization.

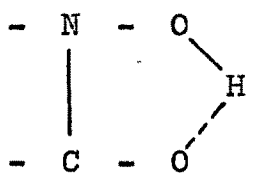


(II)

The principle bands associated with the grouping (II) are ν(O-H) and ν(C=O) and these can be assigned. The ν(N-O), ν(C-N) and ν(C-Cl) stretching vibrations are assigned with less confirmity because of the overlapping with several other modes of vibration and also the non-availability of systematic data on the assignment of the bands in infrared spectra of these hydroxamic acids.

(O-H) Stretching Vibrations

In the N-arylhydroxamic acids examined here, the absorption band due to the (O-H) stretching vibration has been assigned in the region 3185-3106 cm^{-1} (Table 2). The shifting of band to the lower frequency compared to the free (O-H) stretching vibration (around 3600 cm^{-1}) is due to the presence of strong intramolecular hydrogen bonding (30-34). Since in hydroxamic acids the acidic hydrogen of the (O-H) group is in close proximity of the polar carbonyl oxygen (C=O), the possibility of hydrogen bonding is high. Most of the shift in the (O-H) stretching vibration can be due to the change in the ability of the hydroxyl hydrogen to form hydrogen bond (III).



(III)

The presence of chlorine atom in the N-phenyl ring makes the hydroxyl group more acidic and changes the (O-H) stretching frequency. It can also be observed that a linear relationship exists between the (O-H) stretching frequency and the pK_a of the investigated acids. With increase in

ionization constant, vibration frequency increases. This is because, as the acidity of the molecule increases, the hydrogen bond strengthens and consequently the vibrational energy decreases.

So it can be concluded that the (O-H) stretching frequency is affected mainly by the substitution in the aromatic rings and the strength of the intramolecular hydrogen bonding where both are complimentary to each other.

(C=O) Stretching Vibrations

In the N-arylhydroxamic acids examined here, the (C=O) stretching vibration bands are assigned in the region between 1630 to 1603 cm^{-1}. The assignment is made with reference to the spectra of amides, anilides and unsubstituted hydroxamic acids. In unsubstituted amides the band appears between 1690 - 1650 cm^{-1} and in anilides at 1700 cm^{-1} (35,36). In unsubstituted hydroxamic acids the band is assigned between 1670 - 1600 cm^{-1} (5, 37-39). The molecular structure of the compound shifts the (C=O) stretching vibrations considerably. Thus hydrogen bonding lowers the (C=O) frequency by 10-45 cm^{-1}. The substituents in the aromatic ring and the ring strain also lower the carbonyl absorption frequency.

(N-O) Stretching Vibrations

In the N-arylhydroxamic acids examined here, the (N-O) stretching vibration bands are assigned in the region between 965-860 cm^{-1}. A reference sharp band at 920±20 cm^{-1} may be attributed to (N-O) stretching mode. The band is rather conspicuous in all the spectra examined here. It may be noted that this portion of the infrared spectrum contains several aromatic and other bands and hence caution must be exercised in assigning (N-O) bands.

KINETICS OF THE ALKALI HYDROLYSIS OF THE HYDROXAMIC ACIDS

PROCEDURE

In to a thermostated (35±0.1°C) 50 ml B-19 cylindrical flask, 10 ml each solution of 0.01M hydroxamic acid and 0.10 M sodium hydroxide were added. 1 ml aliquot of this reaction mixture was withdrawn at regular intervals of 30 min, starting from the time of mixing considered as the zero time, and then complexed with 2 ml $FeCl_3$ solution (2%). The complex was then diluted to 25 ml with distilled water. Absorbance (A_t) was measured at the wavelength corresponding to the λ max for the respective hydroxamic acid-Fe(III) complex (Table 3). The absorbance at infinite time (A_∞) was measured keeping the reaction mixture for 56 hr.

The rate constants were calculated by the formula :

$$K = \frac{2.303}{t} \log \left(\frac{A_o - A_\infty}{A_t - A_\infty} \right) \quad - \quad (i)$$

where K = Rate constant, t = time, A_o = Absorbance at time 'o', A_t = Absorbance at time 't', A_∞ = Absorbance at time '∞'.

The rate constants of the synthesised eight hydroxamic acids are given in Table 3. It has been found that the alkali hydrolysis of these acids are of pseudo first order, as

TABLE 3

CHARACTERISTICS OF THE ALKALINE HYDROLYSIS OF THE HYDROXAMIC ACIDS

Hydroxamic acid = 0.01 M

NaOH = 0.1 M

$FeCl_3$ = 2 ml (2% w/v)

Temperature = 35±0.1°C

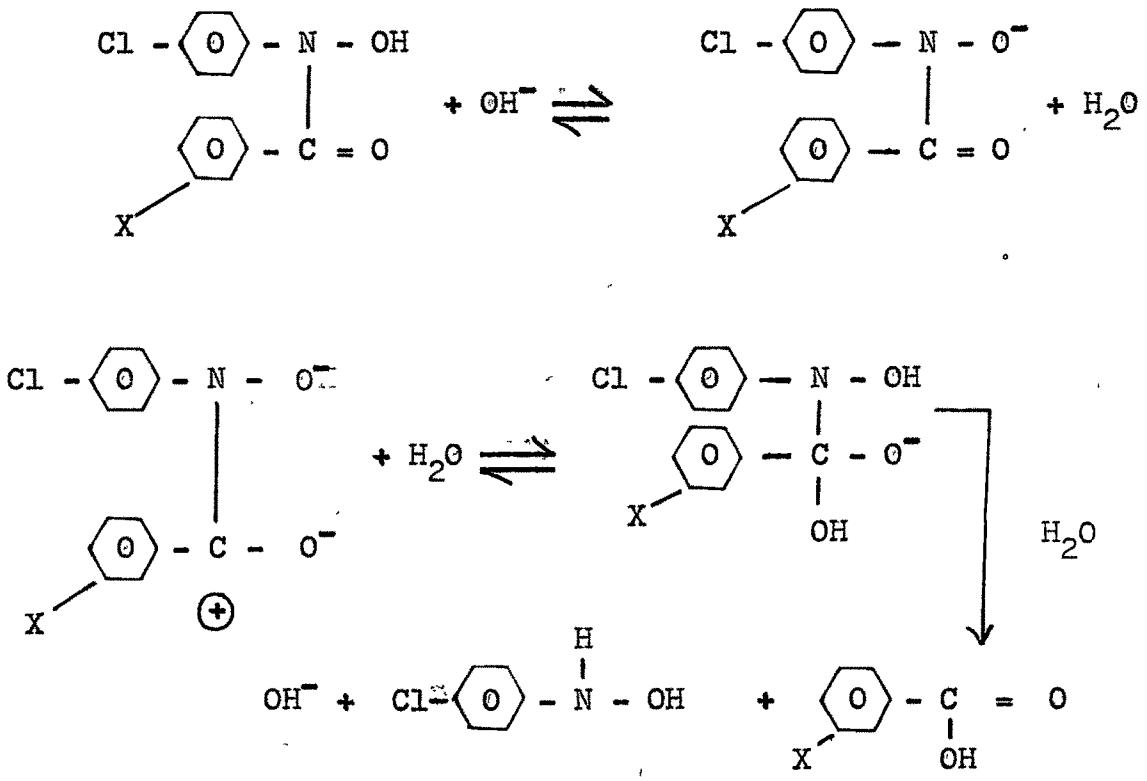
Order of reaction = Ist order

Colour = Violet

Compd. No.	Hydroxamic acid	λmax (nm)	Rate constant ($K/min \times 10^{-3}$)
I.	N-p-Chlorophenylbenzo-	520	1.68
II.	N-p-Chlorophenyl-m-methylbenzo-	520	1.60
III.	N-p-Chlorophenyl-m-methoxybenzo-	510	1.71
IV.	N-p-Chlorophenyl-m-fluorobenzo-	515	1.74
V.	N-p-Chlorophenyl-m-chlorobenzo-	510	2.71
VI.	N-p-Chlorophenyl-m-bromobenzo-	515	3.69
VII.	N-p-Chlorophenyl-m-iodobenzo-	515	2.02
VIII.	N-p-Chlorophenyl-m-nitrobenzo-	515	5.53

almost constant values were obtained for K (rate constant) by putting the values of the different parameters in equation (i). The plot of $\log\left(\frac{A_o - A_\infty}{A_t - A_\infty}\right)$ vs time (t) (Fig. 2) showed a linearity in case of all the acids which further confirmed that the hydrolysis reaction was of first order.

The possible mechanism for the hydrolysis reaction is given as :



(X = H, OCH_3, CH_3, F, Cl, Br, I, NO_2)

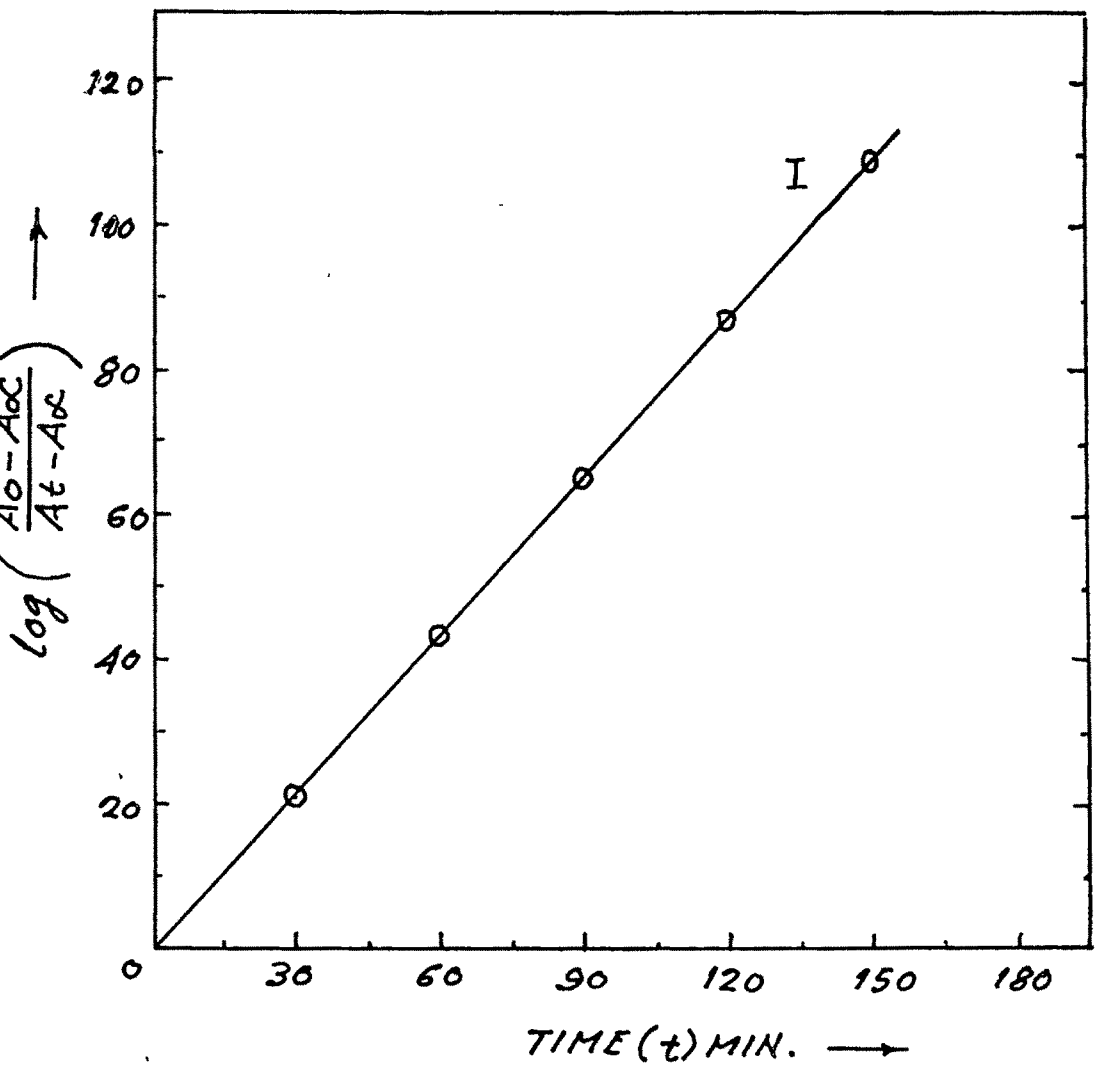


Fig. 2. Plot of $\log\left(\frac{A_0-A_\infty}{At-A_\infty}\right)$ vs Time (t)

I N-p-chlorophenylbenzohydroxamic acid.

It is evident from the Table 3 that the substituents have a marked effect on the rate of the alkaline hydrolysis of N-p-chlorophenyl-m-substituted benzohydroxamic acids. The rate constants follow the order of acidity of the substituted benzoic acids. The nitro substituted, N-p-chlorophenyl-m-nitrobenzohydroxamic acid, has the highest rate constant (5.53×10^{-3}/min) while the N-p-chlorophenyl-m-methylbenzohydroxamic acid has the lowest rate constant (1.60×10^{-3}/min). The following order is observed.

Rate constant of the hydroxamic acids	NO_2 >	Br >	Cl >	I >	F >	OCH_3 >	H >	CH_3
pK_a of Benzoic acids	CH_3 >	H >	OCH_3 >	F >	I >	Cl >	Br >	NO_2
	4.27	4.18	4.09	3.87	3.85	3.83	3.81	3.49

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