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Original scientific paper

Novel Mannich bases bearing pyrazolone moiety Synthesis, characterization and electrochemical studies

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Abstract

The present investigation describes a series of new {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1--ylmethyl-1,2-dihydro–indol-3-ylidene)-hydrazides synthesized by the Mannich reaction of {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]--phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide with aqueous formaldehyde and a solution of piperidine in dimethylformamide. These novel Mannich bases were characterized by elemental analysis, IR, ^{1}H NMR and mass spectral data. Electrochemical behavior of these compounds were studied by two techniques namely polarography and cyclic voltammetry. The results from both the techniques were compared and the reduction mechanism in acidic as well as basic medium was proposed.

Keywords

Mannich bases, Synthesis, Polarography, Cyclic voltammetry, Comparison, Reduction mechanism.

Introduction

Pyrazolones [1-5] and related heterocycles are widely used in medicinal chemistry as they possess wide range of biological and pharmacological properties. Further, Mannich bases exhibit pronounced biological activities. The key feature of Mannich reaction is that the amino carbonyl products are valuable synthons for synthesis [6-8] and can be readily converted to derivatives that possess useful applications in paint industry, polymer industry and particularly in medicine and the pharmaceutical industry [9-14]. Due to this reason, Mannich bases have engrossed a great deal of

attention of pharmaceutical chemists. In view of the above mentioned facts, we propose to synthesize certain novel Mannich bases containing a pyrazolone moiety.

The pharmacological properties of many compounds have been quantitatively related to their reduction process [15-18]. Structure-activity relationship studies [19,20] demonstrated that the reduction potential correlates with the antimicrobial activity of certain compounds.

Extensive work on electrochemical behavior of medicinally important compounds has been already reported from these laboratories [21,22]. In this article, the cyclic voltammetric behavior of Mannich bases on a hanging mercury drop electrode and modified carbon paste electrode is reported. A comparison of polarographic behavior of the compounds with their cyclic voltammetric behavior is also presented**.**

Experimental

All the chemicals and reagents used in the studies were analytical reagent grade obtained from Merck. Britton-Robinson buffer solutions were prepared from the appropriate volumes of acetic acid (0.04 M), phosphoric acid (0.04 M), boric acid (0.04 M) and sodium hydroxide (0.2M). pH meter, Model LI – 10 manufactured by ELICO Private Limited, Hyderabad, India was used for pH measurements.

A CL-25 Pen Recording Polarograph manufactured by ELICO Private Limited, Hyderabad, India was used to record current-voltage curves. The capillary having the characteristics 1.80 $mg^{2/3}$ $s^{-1/2}$ at h = 80 cm was employed in the studies.

The cyclic voltammeter used consists of an X-Y recorder (Model RE 0074), a PAR 175 Potentiostat and an PAR 175 Universal Programmer. A single compartment cell Model 303 SMDE with silver wire as reference electrode and platinum wire as counter electrode was used for cyclic voltammetric studies. A stationary mercury drop electrode (SMDE 303) with a drop area 0.0096 cm^2 was used as the working electrode.

General polarographic procedures (Scheme 1)

8.0 mL of the buffer solution of desired pH, 2.0 mL of Mannich base solution (1.0×10^{-2} M) in dimethylformamide, 6.0 mL of dimethylformamide (DMF) and 4.0 mL of distilled water were mixed thoroughly in the polarographic cell. The polarograms were recorded after the expulsion of dissolved oxygen with nitrogen gas. Geltain was used as the maximum suppressor in all the investigations except in the experiments where the effect of surfactants was studied.

Synthesis of Mannich bases

{4-[3-Methyl-5-oxo-4-(4$^{|}$-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid hydrazide I were synthesized and characterized by the procedures reported in the literature [23].

Synthesis of {4-[3-Methyl-5-oxo-4--(4$^{|}$-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]--phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)- hydrazide IV.

The required isatins were prepared by the procedure described by Marvel and Heirs [24].

Synthesis of isonitrosoacetanilide (II)

22 g of chloral hydrate and 300 mL of water was taken into a one litre round bottom flask. 3.25 g of sodium sulphate, 12 g of aniline (in 75 mL of water), 12 mL of concentrated hydrochloric acid and 27g of hydroxyl amine hydrochloride (in 25 mL of water) were added and heated over a

wire gauge for about 45 minutes. The reaction mixture was cooled, the solid separated was filtered and dried.

a. Synthesis of Isatin 46 (R = H). (III)

A miture of 8 mL of concentrated H_2SO_4, 18 g of dry isonitrosoacetanilide taken in a round bottem flask was heated to 80 ^oC for about 10 minutes. The reaction mixture was cooled to room temperature and poured onto crushed ice. The precipitated isatin was filtered, washed several times with cold water and dried.

c. Synthesis of {4-[3-Methyl-5-oxo-4-(4^l-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid(2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide IV.

A mixture of I (R = H) and III in 1 : 1 molar ratio when heated in DMF-water bath for 45 minutes, resulted in a compound with melting point 214 ^oC. Based on spectral data, the compound was assigned structure as {4-[3-Methyl-5-oxo-4-(phenyl - hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro – indol-3-ylidene)- hydrazide IVa (R = H).

Other members of the series were prepared by similar procedures and their characterization data are given in the Table 1.

Table 1. *Characterization of {4-[3-Methyl-5-oxo-4-(4^l-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide.*

Compound	R	M.P. ^oC	Yield, %	Molecular formula	Mass fraction found, % (Calc., %)					
					C	H	N	O	Cl	Br
IVa	H	214	70	$C_{26}H_{25}N_7O_4$	62.52 (62.48)	5.01 (4.89)	19.63 (19.50)	12.82 (12.70)		
IVb	CH_3	241	70	$C_{27}H_{27}N_7O_4$	63.15 (63.02)	5.26 (5.15)	19.10 (18.95)	12.47 (12.32)		
IVc	OCH_3	234	70	$C_{27}H_{27}N_7O_4$	61.24 (61.12)	5.10 (4.95)	18.52 (18.38)	15.12 (15.00)		
IVd	OC_2H_5	224	75	$C_{28}H_{29}N_7O_5$	61.87 (61.75)	5.34 (5.25)	18.04 (17.88)	14.73 (14.62)		
IVe	Cl	225	75	$C_{26}H_{24}ClN_7O_4$	58.48 (58.35)	4.49 (4.32)	18.38 (18.22)	11.99 (11.75)	6.65 (6.52)	
IVf	Br	243	80	$C_{26}H_{24}BrN_7O_4$	53.98 (53.82)	4.15 (3.98)	16.95 (16.80)	11.07 (10.95)		13.82 (13.65)

IR Spectral details

The IR (KBr) spectrum (Figure 1) of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro–indol-3-ylidene)- hydrazide (hydrazone) IVa showed characteristic strong absorption bands at 3205 (NH), 3170 (Indole NH), 1602 (C = N), 1656 (pyrazoline C = O), 1700 (Indole C = O) and 1618 (CONH). The spectral data and the respective assignments of IV are given in the Table 2.

^{1}H NMR Spectral details

The ^{1}H NMR (200 MHz) spectrum (Figure 2) of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5--dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro–indol-3-ylidene)-hydrazide (hydrazone) IVa in DMSO – d_6 showed the signals at δ1.1 (s, 3H, CH_3), δ10.93 (s, 1H, Ar – NH), δ5.78 (s, 2H, N-CH_2 – CO), δ12.75 (s, 1H, Indole NH) and δ7.1 – 7.3 (m, 9H, Ar – H) (Table 3).

Table 2: *IR (KBr) Spectral data of {4-[3-Methyl-5-oxo-4-(4[I]-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide.*

Compound	ν_{max} / cm^{-1}					
	>NH	Indole NH	>C=N-	Pyrazoloine C=O	Indole>C=O	>CO-NH-
IVa	3205	3170	1602	1656	1700	1618
IVb	3180	3140	1600	1654	1700	1622
IVc	3100	3150	1505	1654	1701	1625
IVd	3195	3155	1604	1654	1701	1624
IVe	3175	3140	1605	1654	1701	1624
IVf	3190	3150	1604	1654	1701	1624

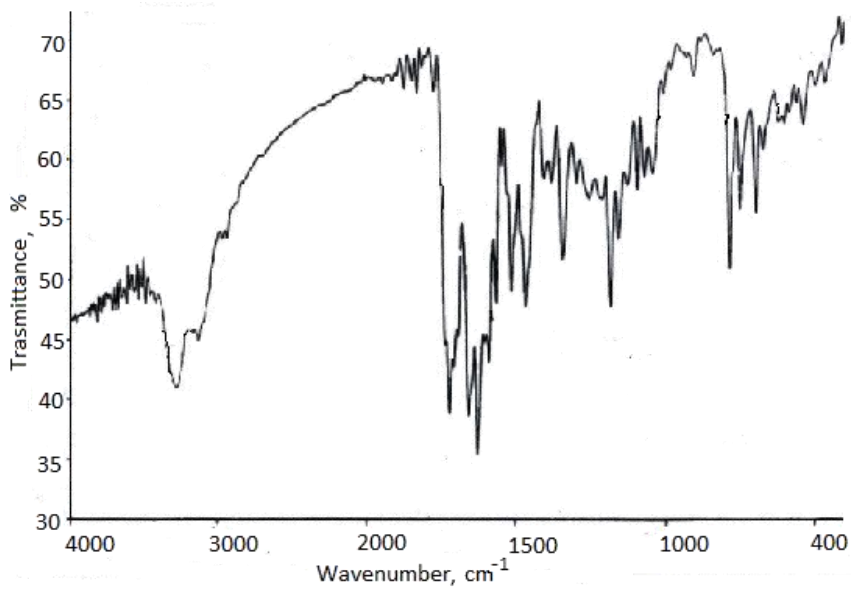


Figure 1. *IR Spectrum of {4-[3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]--phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide*

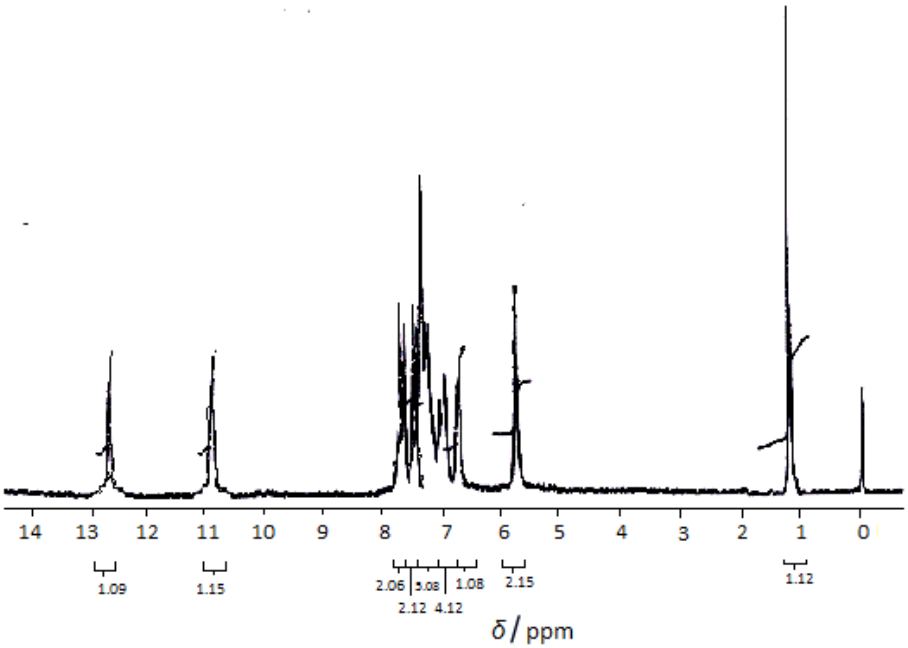
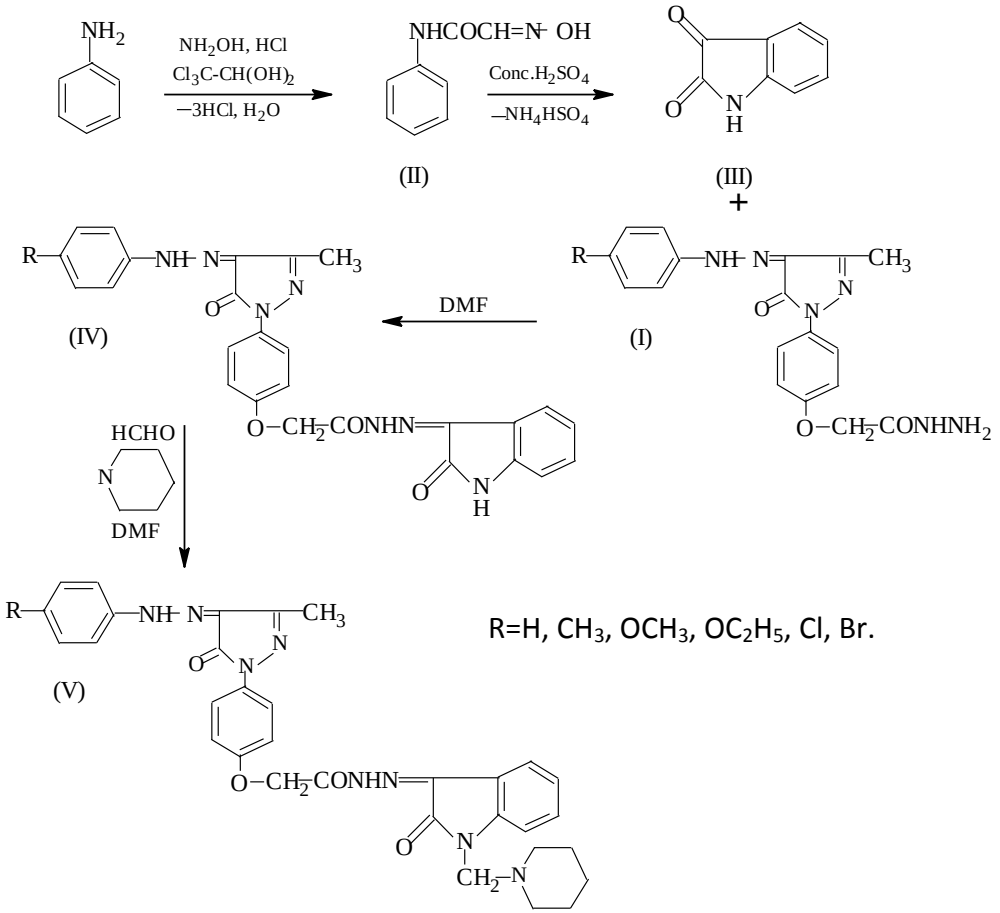


Figure 2. *[1]H NMR spectrum of {4-[3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1--yl]--phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide*

Table 3. *^{1}H NMR Spectral data of {4-[3-Methyl-5-oxo-4-(4^l-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide.*

Compound	δ / ppm
IVa	1.1 (s, 3H, CH_3), 5.78 (s, 2H, N-CH_2-CO), 6.8 (s, 1H, Ar–NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1–7.3 (m, 5H, Ar-H), 7.4 (d, 2H, C_6H_4), 7.7 (d, 2H, C_6H_4)' 10.93 (s, 1H, CONH), 12.75 (s, 1H, Indole NH)
IVb	0.95 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 5.82 (s, 2H, N-CH_2-CO), 6.8 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar–H), 7.4 (d, 2H, C_6H_4), 7.7 (d, 2H, C_6H_4), 10.95 (s, 1H, CONH), 12.75 (s, 1H, Indole NH)
IVc	1.12 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 5.8 (s, 2H, N-CH_2CO), 6.8 (s, 1H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 10.95 (s, 1H, CONH), 12.75 (s, 1H, Indole NH)
IVd	0.95 (s, 3H, CH_3), 1.15 (t, 3H, CH_3), 3.16 (q, 2H, O-CH_2), 5.76 (s, 2H, N-CH_2CO), 6.8 (s, 1H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 10.91 (s, H, CO-NH), 12.72 (s, 1H, Indole NH)
IVe	1.05 (s, 3H, CH_3), 5.8 (s, 2H, N-CH_2CO), 6.8 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H,C_6H_4) and 7.7 (d, 2H, C_6H_4), 10.93 (s, H, CO-NH), 12.7 (s, 1H, Indole NH)
IVf	1.02 (s, 3H, CH_3), 5.78 (s, 2H, N-CH_2CO), 6.8 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 10.93 (s, H, CO-NH), 12.75 (s, H, Indole NH)



Scheme 1. *Synthesis of {4-[3-Methyl-5-oxo-4-(4^l-{4-[3-Methyl-5-oxo-4-(4^l-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1- piperidine-1-ylmethyl-1,2 –dihydro – indol-5-ylidene)- hydrazide (V)*

d. Synthesis of {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)- -hydrazide (V).

A mixture of hydrazone IVa (R = H), aqueous formaldehyde and a solution of piperidine in DMF were stirred for about six hours at room temperature to give {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-di -hydro–indol-3-ylidene)- hydrazide V a (R = H).

Similar treatment of hydrazones IV b-f with piperidine in presence of formaldehyde in DMF at room temperature yielded respective {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5- -dihydro-pyrazol-1-yl]-phenoxy}-acetic acid-(2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-yli-dene)- hydrazide V b-f (R = CH_3, OC_2H_5, -Cl, -Br).

The structures of the compounds V a- f were established on the basis of elemental analysis and spectral data (Table 4) and spectral data (Table 5 and Table 6).

IR Spectral details

The IR (KBr) spectrum (Figure 3) of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyra-zol-1--yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)- hydra-zide V a exhibited characteristic bands at around 3195 (NH), 1610 (C = N), 1676 (pyrazoline C = O), 1720 (Indole C = O), 1654 (C – NH) and 2933 cm^{-1} (CH_2) (Table 5).

The spectral data and the respective assignments of V are detailed below.

Table 4. *Characterization data of {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene) - hydrazide V*

Compd	R	M.P.	Yield, %	Molecular formula	Mass fraction Found, % (Calc., %)					
					C	H	N	O	Cl	Br
Va	H	158	70	$C_{32}H_{32}N_8O_4$	64.86 (64.72)	5.40 (5.28)	19.91 (19.86)	10.81 (10.75)		
Vb	CH_3	164	70	$C_{33}H_{34}N_8O_4$	65.34 (65.21)	5.61 (5.45)	18.48 (18.34)	10.56 (10.38)		
Vc	OCH_3	167	70	$C_{33}H_{34}N_8O_5$	63.66 (63.56)	5.46 (5.32)	18.00 (17.85)	12.86 (12.64)		
Vd	OC_2H_5	159	75	$C_{34}H_{36}N_8O_5$	64.15 (64.01)	5.66 (5.45)	17.61 (17.50)	12.56 (12.42)		
Ve	Cl	161	75	$C_{32}H_{31}ClN_8O_4$	61.29 (61.15)	4.94 (4.78)	17.87 (17.73)	10.21 (10.8)	5.66 (5.45)	
Vf	Br	160	80	$C_{32}H_{31}BrN_8O$	57.23 (57.08)	4.62 (4.42)	16.69 (16.54)	9.53 (9.38)		11.90 (11.70)

Table 5. *IR (KBr) spectral data of {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)- hydrazide V.*

Compound	ν_{max} / cm^{-1}					
	>NH	>C=N-	Pyrazoloine C=O	Indole C=O	>CO-NH-	$>CH_2$-
Va	3195	1610	1676	1720	1654	2933
Vb	3170	1616	1674	1715	1658	2920
Vc	3120	1610	1680	1712	1654	2625
Vd	3175	1614	1674	1711	1656	2915
Ve	3155	1616	1674	1714	1658	2920
Vf	3170	1614	1674	1716	1626	2625

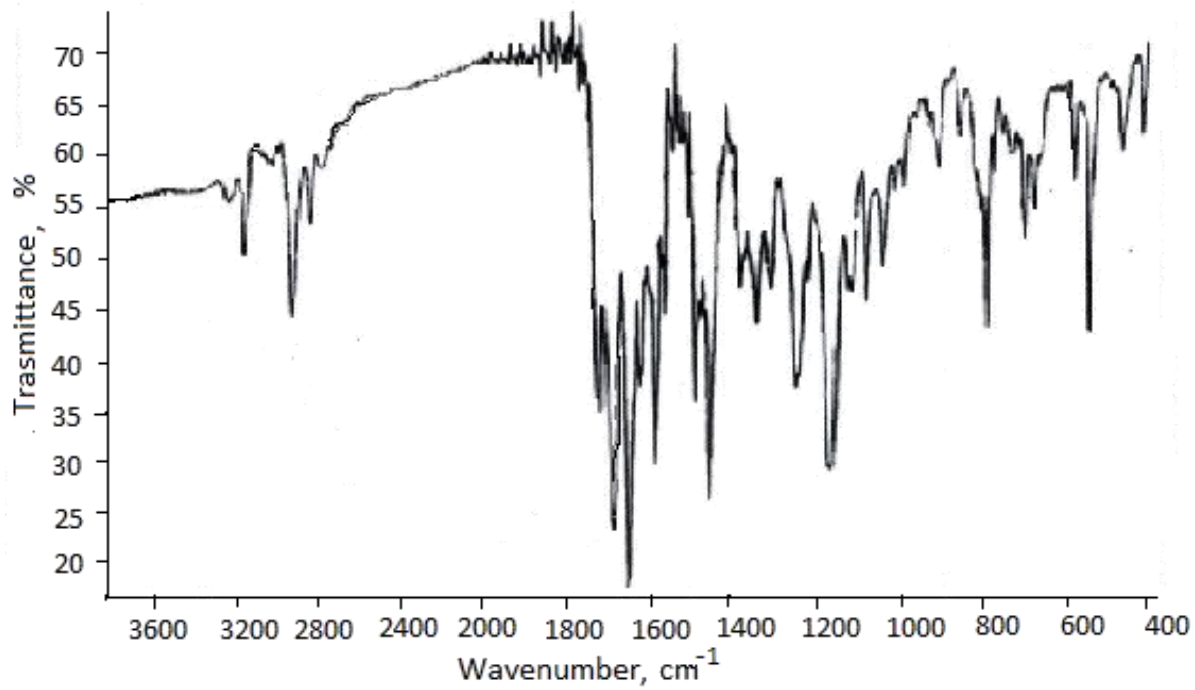


Figure 3. *IR Spectrum of {4-[3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro pyrazol-1-yl]-phenoxy} –acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide*

^{1}H NMR Spectral details

The ^{1}H NMR (200 MHz) spectrum (Figure 4) of 3-[methyl-5-oxo-4-(4$^|$-*substituted* phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-yl-methyl-1,2-dihydro–indol-3-ylidene)- hydrazide V was recorded in DMSO-d_6 and the data is given below. The appearance of a signal at δ 4.5 due to N–CH_2-N, confirmed the formation of Mannich bases (Table 6).

Table 6. *^{1}H NMR Spectral data of {4-[3-Methyl-5-oxo-4-(4$^|$-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)- hydrazide*

Compound	*δ* / ppm
Va	1.14 (s, 3H, CH_3), 1.45 (m, 6H, $(CH_2)_3$), 2.56 (t, 4H, CH_2-N-CH_2), 4.45 (s, 2H, N-CH_2-N), 5.9 (s, 2H, N-CH_2CO), 6.8 (s, 1H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 5H, Ar -H), 7.4 (d, 2H, C_6H_4), 7.7 (d, 2H, C_6H_4), 9.5 (s, H, -CONH).
Vb	0.97 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 5.90 (s, 2H, N-CH_2-CO), 6.81 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar–H), 7.4 (d, 2H, C_6H_4), 7.7 (d, 2H, C_6H_4), 9.6 (s, 1H, CONH), 1.45 (m, 6H, $(CH_2)_3$), 2.54 (t, 4H, CH_2-N-CH_2), 4.48 (s, 2H, N-CH_2-N).
Vc	1.15 (s, 3H, CH_3), 3.12(s, 3H, OCH_3), 5.91 (s, 2H, N-CH_2CO), 6.8 (s, 1H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 2.51 (t, 4H, CH_2-N-CH_2), 1.41 (m, 6H, $(CH_2)_3$), 4.41(s, 2H, N-CH_2-N), 9.51 (s, 1H, CONH).
Vd	0.98 (s, 3H, CH_3), 1.11 (t, 3H, CH_3), 3.11 (q, 2H, O-CH_2), 2.58 (t, 4H, CH_2-N-CH_2), 4.42 (s, 2H, N-CH_2-N), 5.81 (s, 2H, N-CH_2CO), 6.82(s, 1H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 1.45 (m, 6H, $(CH_2)_3$), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 9.41 (s, H, CO-NH).
Ve	1.07 (s, 3H, CH_3), 2.57(t, 4H, CH_2-N-CH_2), 4.47 (s, 2H, N-CH_2-N), 5.92 (s, 2H, N-CH_2CO), 6.8 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H,C_6H_4) and 7.7 (d, 2H, C_6H_4), 1.47 (m, 6H, $(CH_2)_3$), 9.38 (s, H, CO-NH).
Vf	1.06 (s, 3H, CH_3), 1.43 (m, 6H, $(CH_2)_3$), 5.91 (s, 2H, N-CH_2CO), 6.79 (s, H, Ar-NH), 6.9-7.0 (m, 4H, C_6H_4), 7.1-7.3 (m, 4H, Ar-H), 7.4 (d, 2H, C_6H_4) and 7.7 (d, 2H, C_6H_4), 9.51 (s, H, CO-NH), 2.52 (t, 4H, CH_2-N-CH_2), 4.49 (s, 2H, N-CH_2-N).

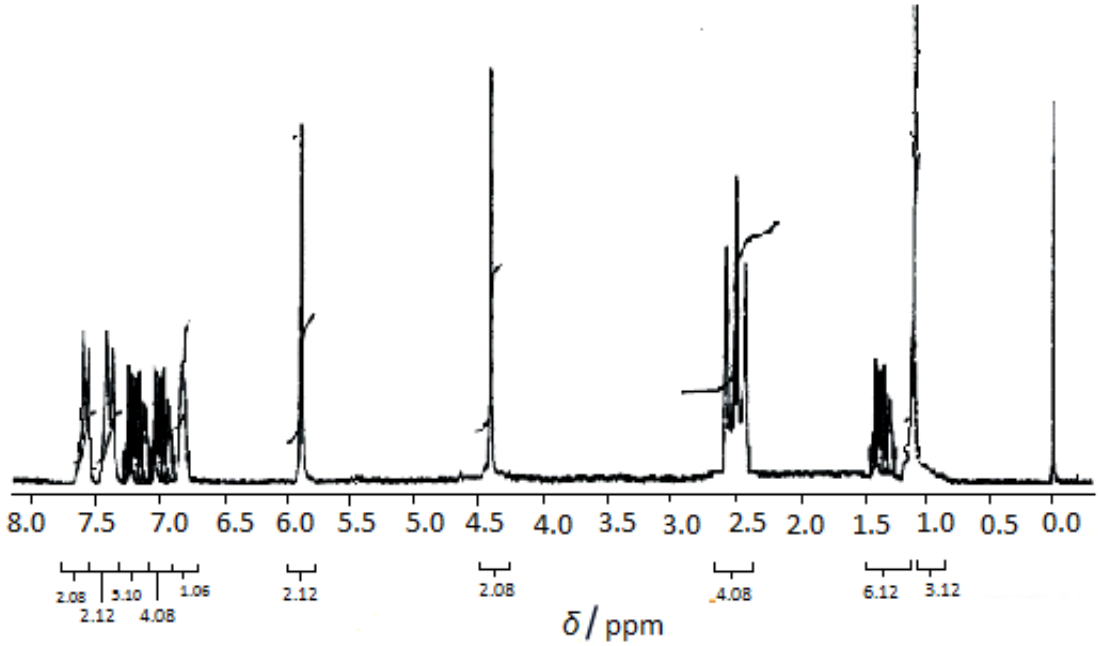
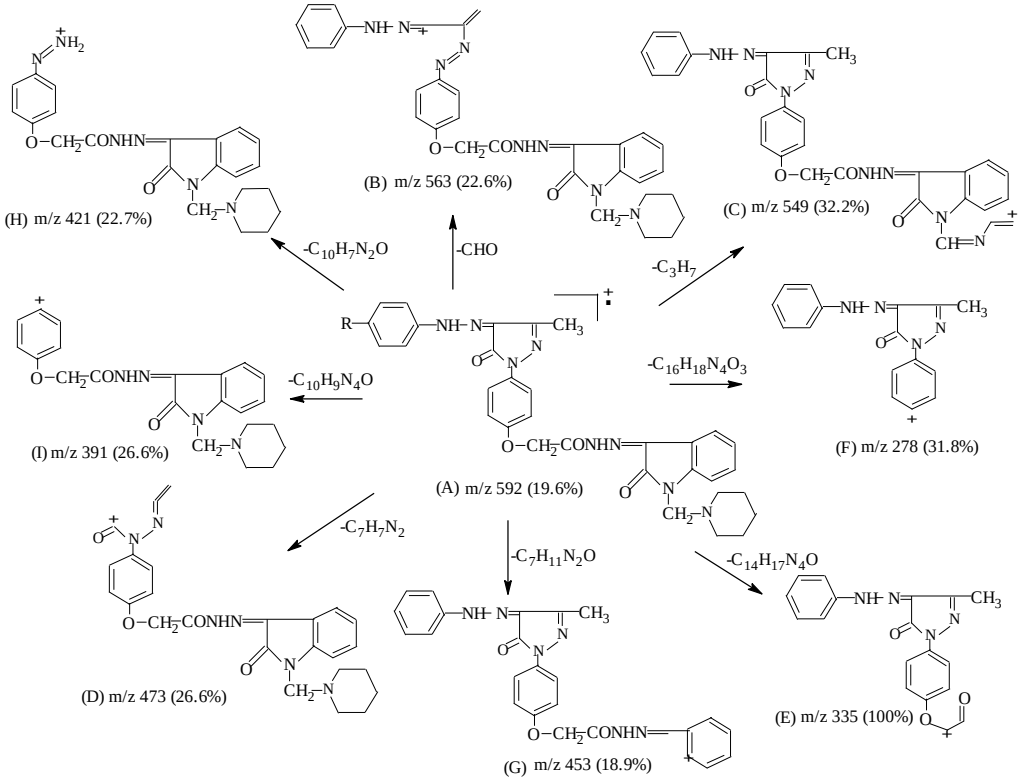


Figure 4. *^{1}HNMR spectrum of {4-[3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro pyrazol-1-yl]-phenoxy} – acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide*

Mass spectral details

The mass spectrum of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-yl methyl-1,2-dihydro-indol-3-ylidene)-hydrazide Va (R = H, X = CH_2) exhibited the molecular (M^+) ion peak at m/z 592.

The fragmentation pattern noticed in the mass spectrum of {4-[3-Methyl-5-oxo-4-(4$^|$-phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-yl methyl-1,2-dihydro-indol-3-ylidene)-hydrazide Va (R = H, X = CH_2) is presented in Scheme 2.



Scheme 2. *Fragmentation details of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1--yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide*

The molecular ion A was observed at m/z 592 (19.6 %). Disintegration of molecular ion A yielded the cation B at m/z 563 (22.6 %). Elimination of C_3H_7 molecule from molecular ion A resulted in the formation of cation C at m/z 549 (32.2 %). Loss of $C_7H_7N_2$ radical from A resulted in the formation of cation D at m/z 473 (26.6 %). Expulsion of $C_{14}H_{17}N_4O$ radical from molecular ion yielded cation E at m/z 335 (100 %). The other important fragments noticed were 278 (31.8 %, F), 453 (18.9 %, G), 421 (22.7 %, H) and 391 (26.6 %, I).

Results and Discussion

Polarographic behaviour of Mannich bases

General polarographic behaviour

{4-[3-methyl-5-oxo-4-(4^{I}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)-hydrazides Va-f (Table 7) gave two cathodic waves in the pH range 1.1-7.1 and three cathodic waves in the pH range 8.1-10.1. The Polarograms of Va is shown in the Figure 5. An inspection of structure of above compounds showed that the sites susceptible for reduction at the dropping mercury electrode were exocylic >C=N, exocyclic >C=O and cyclic >C=N.

Table 7. Details of Mannich bases synthesized

Compound	Substituent (-R)
Va	H
Vb	4^{I}-CH_3
Vc	4^{I}-OCH_3
Vd	4^{I}-OC_2H_5
Ve	4^{I}-Cl
Vf	4^{I}- Br

Among these groups exocyclic azomethine group was more susceptible for reduction than other groups. However [3-methyl-4,5-dioxo-4,5-dihydro-pyrazol-1-yl]-acetic acid hydrazide does not give reduction wave under experimental conditions. This was probably due to stabilization [25] of the pyrazoline-5-one by ketoenol tautomerism. These observations unambiguously suggest that the waves observed in the present studies were due to reduction of two exocyclic azomethine groups.

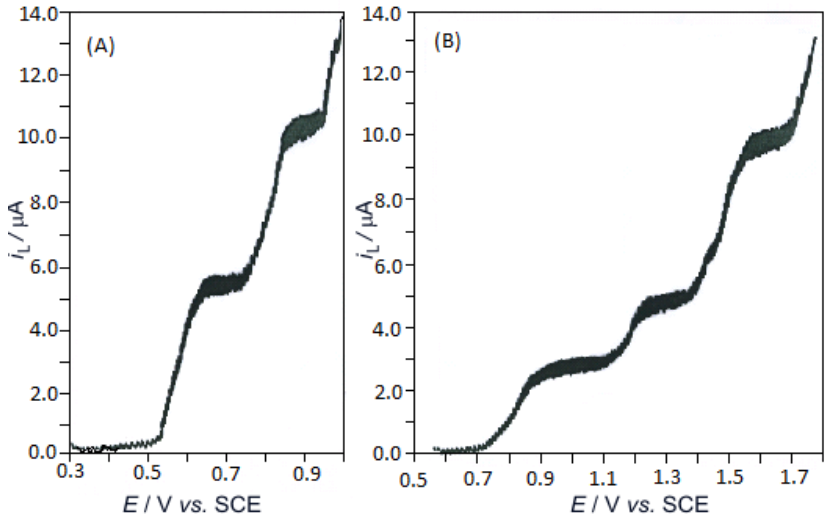


***Figure 5**. Polarograms of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1--yl]--phenoxy}-acetic acid (2-oxo-1--piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide ; c = 1 mM; Medium : Aqueous dimethylformamide (40 % v/v). A represents the polarogram at pH 4.1 and B that at indicate 8.1 respectively.*

Half wave potential-pH relation

Half wave potentials of first and second waves shifted to more negative potentials with increase in pH of the medium in the range 1.1-7.1 (Table 1 in Supplementary material). The typical $E_{1/2}$ – pH graphs are shown in Figure 6. The half wave potentials of the waves were not altered in alkaline medium. The value of $\Delta E_{½}/\Delta$pH for both waves lie in the range of 0.089-0.094. The $E_{1/2}$-pH plots observed in the pH range 1.1-10.1 suggest that both the protonated form (acidic) and the deprotonated form (basic) of the depolariser were electroactive.

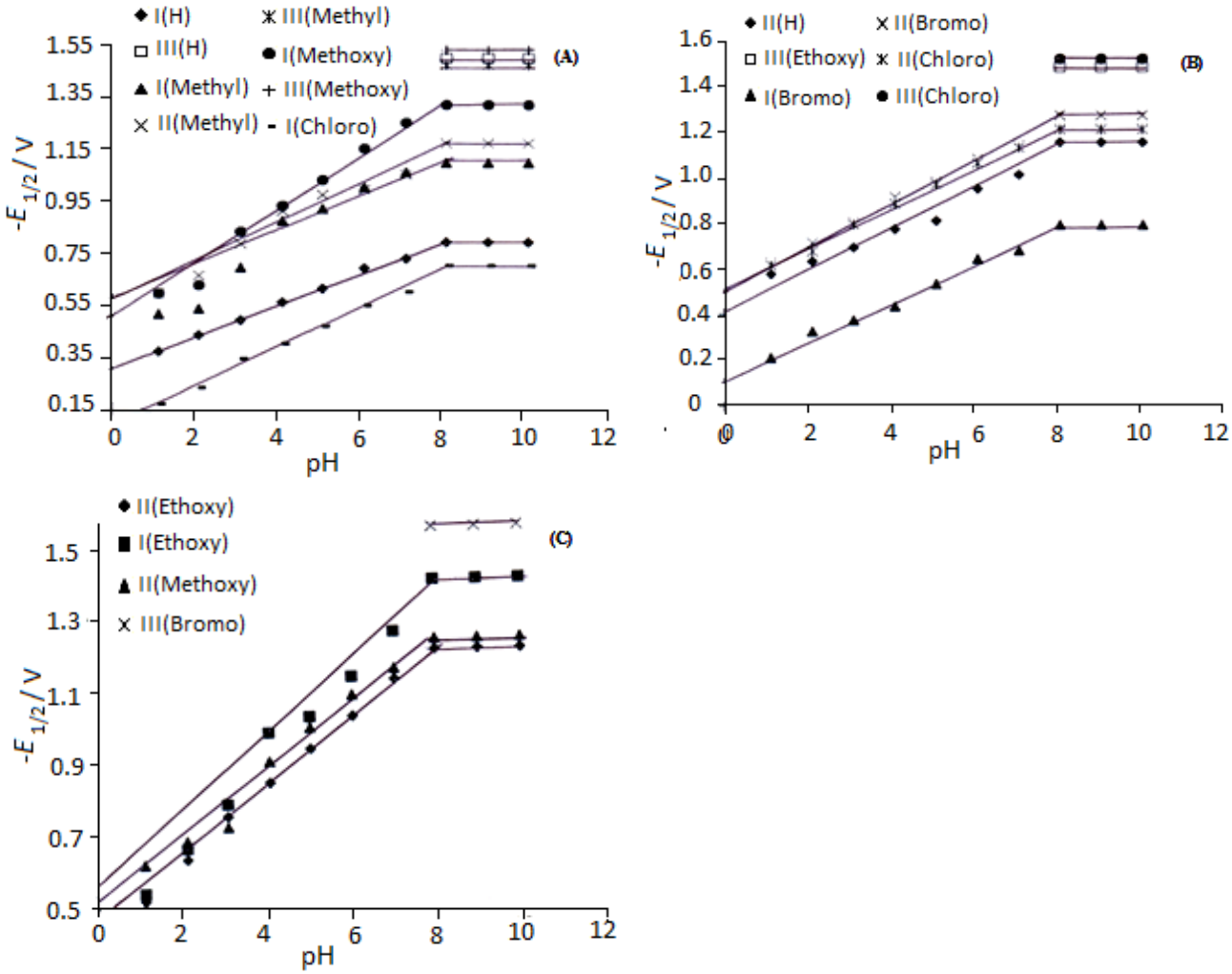


Figure 6. *Plot of pH vs $-E_{1/2}$ for Mannich bases. c= 1 mM; Medium = Dimethylformamide (40 % v/v). I, II and III indicate first, second and third wave respectively of corresponding compound at indicated pH as shown in the figures (A), (B), (C), (D) and (E).*

Effect of the height of mercury column head on the limiting current

The limiting currents (i_L) recorded at different heights of the mercury column vary linearly with the square root of mercury column height ($h^{1/2}$). The constant values of $i_L/h^{1/2}$ confirm the diffusion controlled nature of first and second waves. $i_L - h^{1/2}$ plots are shown in Figure 7.

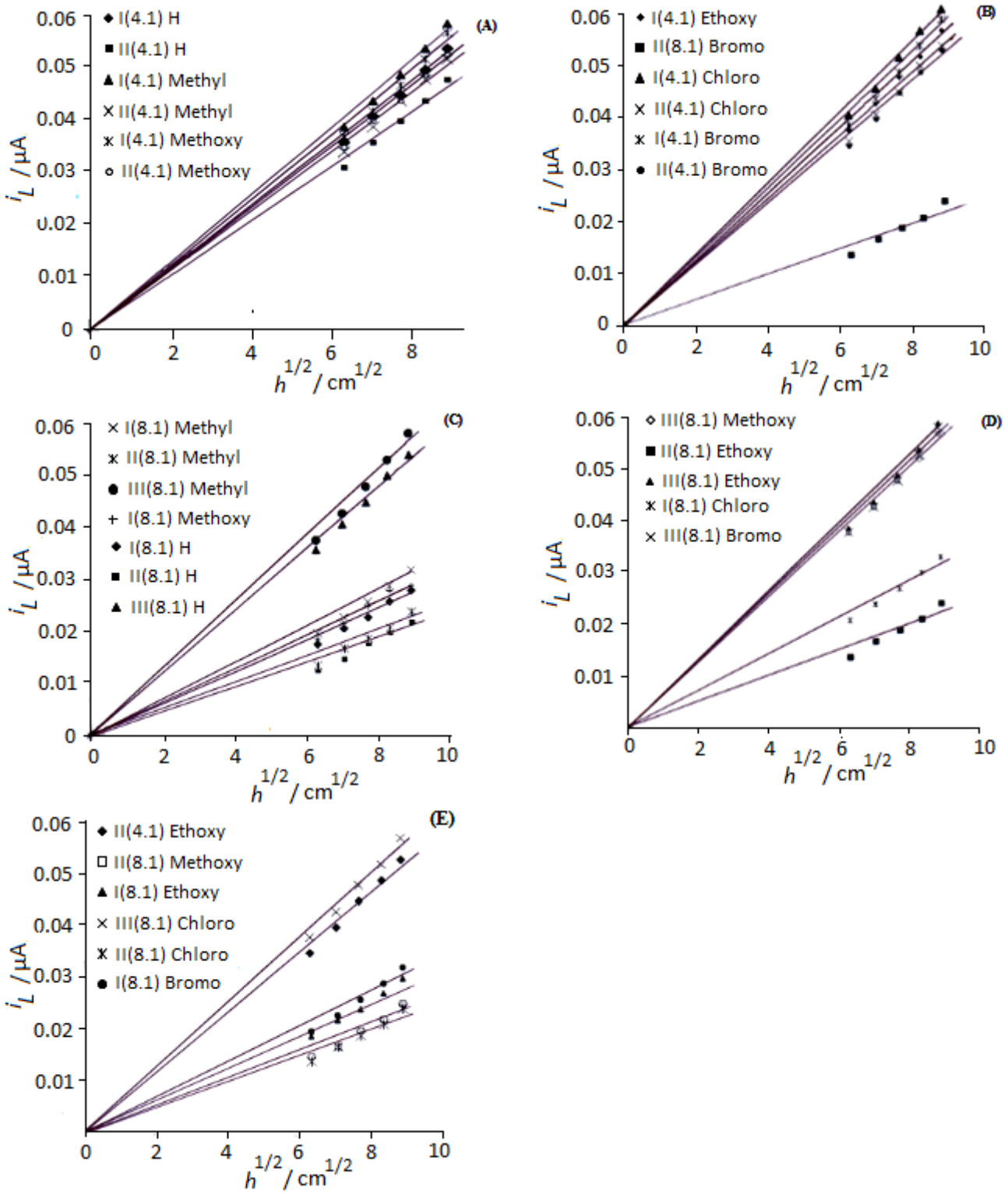


Figure 7. *Effect of mercury column height (h) on limiting current (i_L). c= 1 mM Medium = Dimethylformamide (40 % v/v). I, II and III indicate first, second and third wave resp.*

Effect of concentration on the diffusion current

The influence of concentration on the limiting current in the range 0.5-3.5 mM was recorded in solutions of pH 4.1. The limiting current-concentration plots are presented in Figure 8. The plots were linear and passing through the origin. This observation further confirms the diffusion controlled nature of two waves. (First wave and second wave).

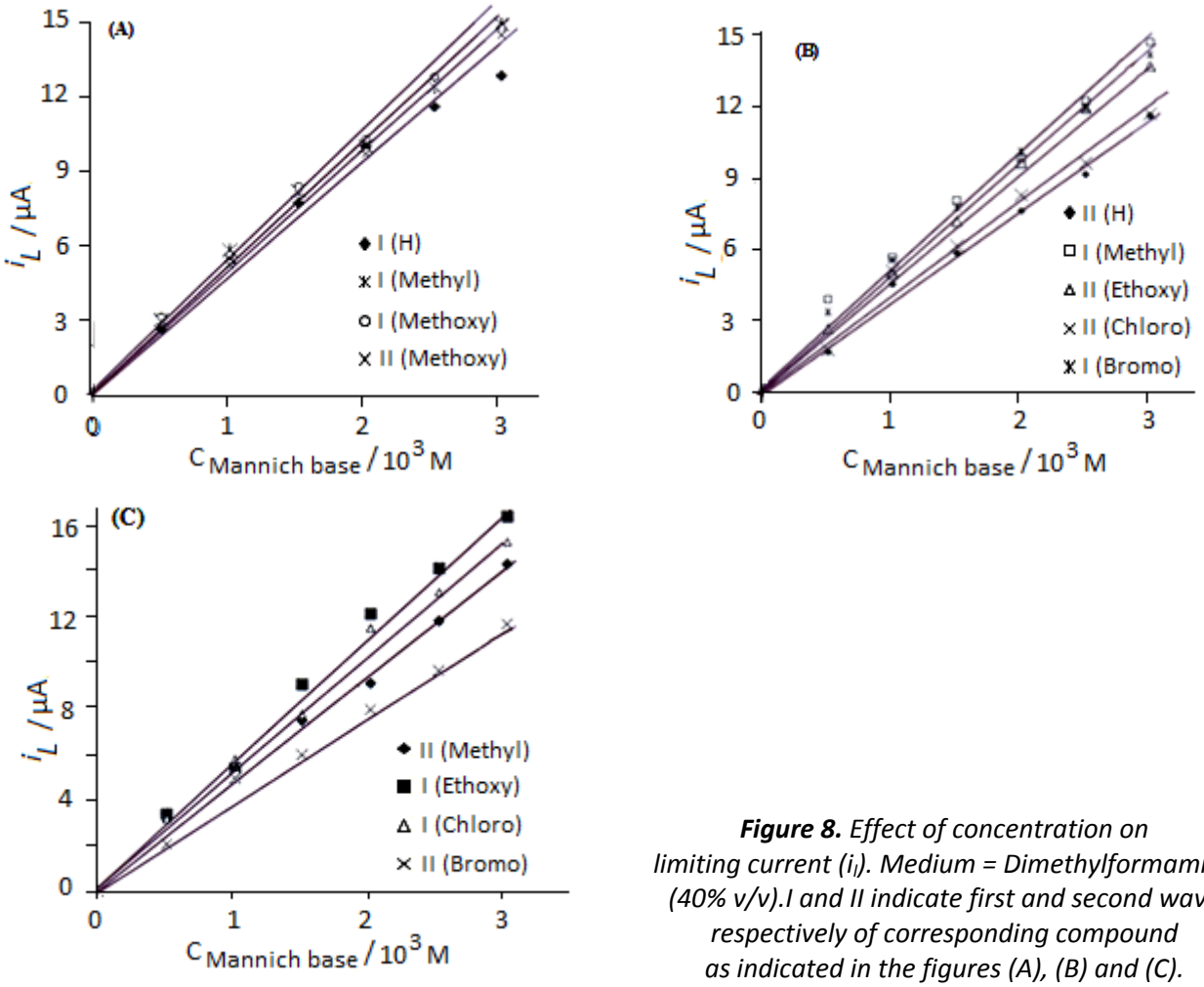


Figure 8. *Effect of concentration on limiting current (i_l). Medium = Dimethylformamide (40% v/v).I and II indicate first and second wave respectively of corresponding compound as indicated in the figures (A), (B) and (C).*

Nature of the electrode process

The linear E_{dme} versus log (i/i_d-i) plots at typical pH 4.1 are shown in Figure 9. The slopes were linear in the range 0.066-0.10 V and were not in agreement with the theoretical values 0.030 V and 0.015 V expected for two electron and four electron reversible reduction process respectively. This indicates the irreversible nature of reduction process. The irreversible nature of the polarographic waves was further confirmed by employing Tome's criteria [26]. The α_{na} values are presented in Table 1 in Supplementary material. The irreversible nature of the two waves was attributed to the bulky group present at the end of >C=N-NH-linkage [27].

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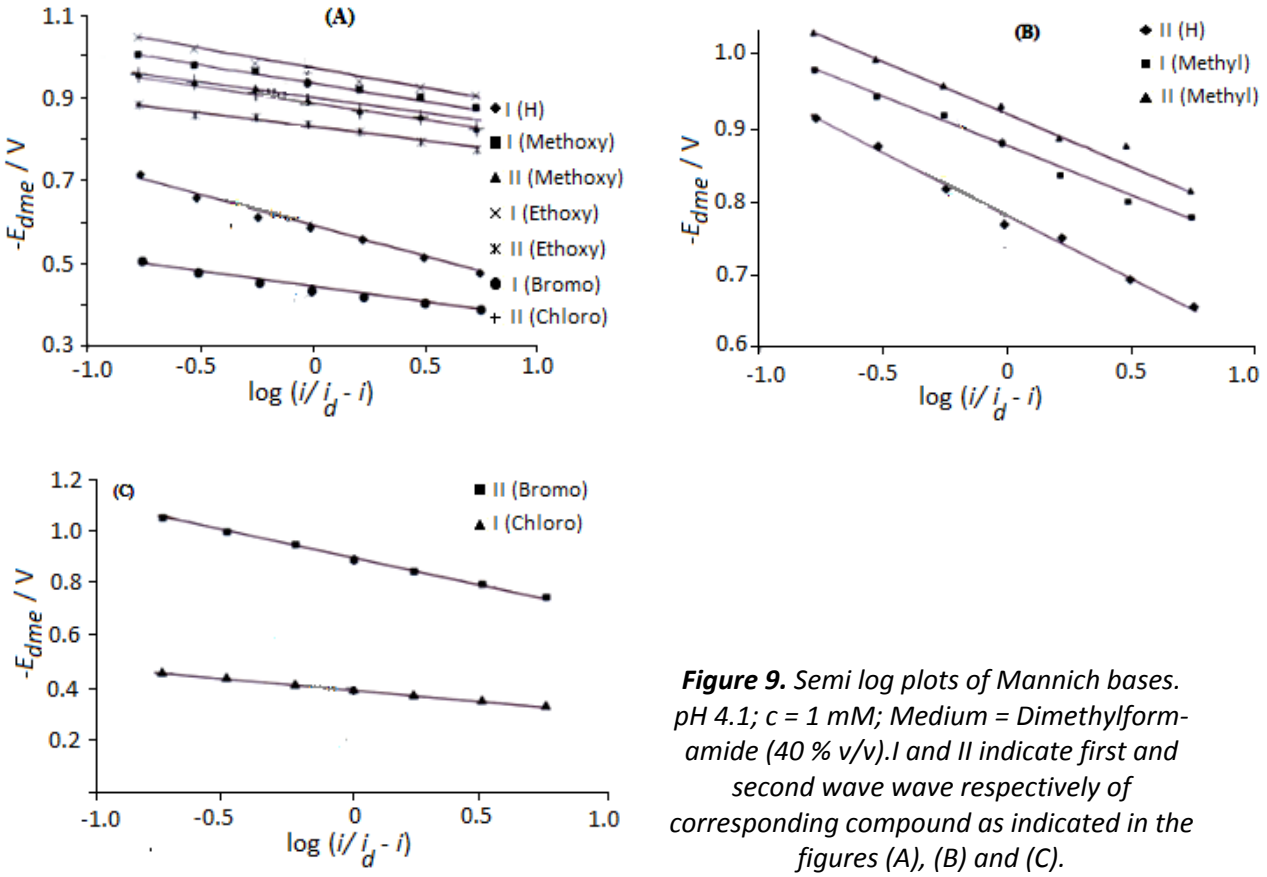


Figure 9. *Semi log plots of Mannich bases. pH 4.1; c = 1 mM; Medium = Dimethylformamide (40 % v/v).I and II indicate first and second wave wave respectively of corresponding compound as indicated in the figures (A), (B) and (C).*

Kinetic parameters of the electrode reaction

The kinetic parameters k^{o}_{fh} and ΔG^* of the electrode reaction at typical pH values evaluated for first and second waves are presented in Table 1 in Supplementary material. The magnitude of k^{o}_{fh} decreases and ΔG^* increases with the increase in pH of the medium. This indicates irreversible nature of the electrode process [28].

Controlled potential electrolysis

The electrochemical reduction of {4-[3-methyl-5-oxo-4-(4^{I}-substituted phenyl hydrazono)-4,5--dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3--ylidene)-hydrazide (V) has been studied by the method of controlled potential electrolysis at pH 4.1.

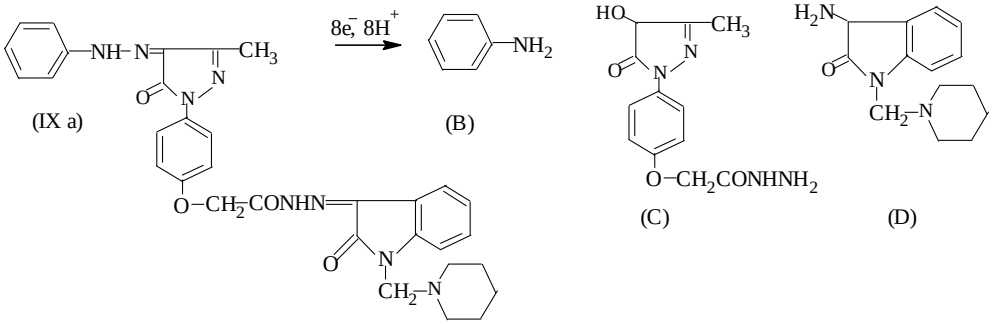
Controlled potential electrolysis was carried out in a Lingane H-type cell. A large pool of mercury at the bottom of the large compartment was used as cathode and a similar pool of mercury at the bottom of smaller compartment served as anode. The cathode compartment contains 10 mL of V (0.01 M), 30 mL of DMF, 20 mL of KCl (1.0 M) and 40 mL of the buffer solution of required pH (4.1). A potential of -1.2 V was applied and maintained at constant potential by the manual control of output from the battery. The electrolysis was followed by recording the decrease in current with time. The number of electrons per molecule was calculated from i-t curves and was found to be 8 [29]. 1 mL of solution was withdrawn from the electrolysis cell to confirm the presence of aniline by standard spot test [30]. Part of the experimental solution was partially evaporated on water bath to half of its volume, allowed to cool to room temperature and was extracted with ether. The ether layer was evaporated under reduced pressure. The yellow crystalline solid obtained was identified to be 2-(5-thioxo- 4,5- dihydro-[1,3,4]-oxadiazole-2--ylmethyl)-2,4-dihydro-pyrazol-3-one 'A' by elemental analysis, TLC, IR, and ^{1}H NMR spectral data.

Remaining experimental solution was made slightly alkaline and extracted with ethylacetate. The ethylacetate extract was subjected to column chromatography and three compounds were

separated by using benzene-methanol 4:1 (v/v) solvent as an eluent. The compounds B, C and D were found to be aniline, (4-Amino-3-methyl-5-oxo-4,5-dihydro-pyrazol-1-yl)-acetic acid hydrazide and 3-Amino-1--piperidin-1-ylmethyl-1,3-dihydro-indol-2-one respectively.

***Table 8**. Characterization data of 2-(5-thioxo-4,5-dihydro-[1,3,4]-oxadiazole-2-ylmethyl)-2,4-di-hydro-pyrazol-3-one*

Mass fraction of element found, % (Calc., %)	C 36.34 (36.36), N 28.31 (28.27), O 16.18 (16.14), S 16.11 (16.18)
IR (KBr) Spectral data (ν_{max} / cm^{-1})	3126 (oxadiazole NH); 3180 (NH); 1603 (C = N); 1670 (C = O); 1134 (C = S)
^{1}H NMR Spectral data (δ /ppm)	2.3(s, H, CH_3); 5.45 (s, 2H, N – CH_2), 14.7 (s, H, thiol-thione tautomeric proton NH), 3.9 & 4.1 (NH_2)
Mass spectral data: m/e (Relative abundance, %)	172(77); 171(100); 156(10); 143(33.3); 140(40); 127(47.7); 112(57.7); 100(8.8); 84(13.3); 59(53.3); 57(34.4); 51(28.8); 29(38.8); 27(12.2)



The compounds were characterized by IR and ^{1}H NMR data. The compound B was further confirmed as aniline by azodye test.

***Table 9.** Elemental analysis and spectral data of B , C and D.*

Comp.	Mass fraction of element found, % (Calc., %)	IR Spectral data (ν_{max} / cm^{-1})	^{1}H NMR Spectral data (δ/ ppm)
B	C 77. 31 (77.33), N 15. 13 (15.09)	3180 (NH), 760 (ArH).	4.0 (s, 2H, ArNH), 6.46 – 7.01 (m, 5H, ArH)
C	C 38. 90 (38.96), N 37.68 (37.78), O 17.45 (17.34)	1676 (C=O), 1654 (CONH), 2933 (CH_2).	0.9 (s, 3H, CH_3), 4.09 (s, 2H, N – CH_2), 3.9 & 4.2 (s, 2H, NH_2), 6.0 (s, 2H, $CONH_2$).
D	C 68.59 (68.51), N 17.21 (17.17), O 6.45 (6.54)	3180 (NH), 1666 (C = O).	4.52 (s, 2H, NCH_2N), 2.0 (s, 2H, NH_2), 2.70 (t, 4H, NCH_2), 6.44 (m, 4H, ArH).

Reduction mechanism in acidic medium

Based on the experimental results (Table 10), it was proposed that two azomethine groups in the compounds Va-f were reduced separately involving four electrons. The reduction steps appear as two waves in solutions of pH 1.1-7.1.

It was clear that compounds Va-f were reduced at the dropping mercury electrode through a mechanism which involves the azomethine, imine intermediate and amine via usual sequence.

Hydrazone → Imine → Amine

V was protonated at azomethine group to yield protonated form II. The weak >C=N-NH undergo cleavage at >C=N-NH single bond [31,32] with the uptake of four electrons and two protons to form the unstable imine intermediates IV and V which subsequently undergo two electron reduction to form VI and VII.

It was reported [33,34] that the above mentioned steps of the reduction (formation of VI & VII) occur at the same potential. The mechanism (Scheme 3) proposed was also supported by the results obtained in cyclic voltammetry.

Reduction mechanism in basic medium

In alkaline medium (pH>pK_a), V exists in the azomethine anionic form (I). The latter in alkaline solutions, was susceptible to chemical cleavage partially into the corresponding carbonyl compounds III, IV and V as shown in the Scheme 4. The first and second waves noticed in alkaline solutions were attributed to the two 4 electron reduction processes of azomethine anionic form to the species containing amino group. The third wave was attributed to the two 2 electron reduction process of heterocyclic carbonyl compounds (IV and V) obtained during the chemical cleavage of dianion I. The heterocyclic carbonyl compounds were reduced to carbinols by two electron reduction process. The decrease in the height of the first and second waves with increase in alkali concentration was attributed to the partial chemical cleavage of dianion.

Effect of substituents on polarographic behaviour

It is known that the polarographic reduction of compound depends on the nature of the compound, the position of the substituent and the reaction medium. Heyrovsky [35,36] correlated the polarographic behaviour of a representative number of compounds with their structure. He opined that the the reducibility of given compound is influenced by conjugated double bonds, triple bonds and aromatic rings present in the substrate.

$E_{1/2}$-σ plots for the compounds under investigation are presented in Figure 10. The values of specific reaction constant (ρ) [38] are presented in Table 11.

Table 10. *Millicoulometric [37] data of {4-[3-methyl-5-oxo-4(4^{l}-substituted phenyl hydrazono)-4,5-di -hidro-pyrazole-1-yl)-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihdro-indol-3-ylidene)- -hydrazide at pH 4.1 and 8.1.*

pH	Current, µA			Time, s			n value		
	First wave	Second wave	Third wave	First wave	Second wave	Third wave	First wave	Second wave	Third wave
4.1	5.4	4.8	-	-	-	-	-	-	-
	4.4	4.0	-	7200	7200	-	3.2	3.2	-
8.1	3.4	3.2	-	10800	10800	-	3.0	3.2	-
	2.7	2.1	5.3	-	-	-	-	-	-
	2.4	1.9	3.5	7200	7200	7200	2.8	2.8	2.1
	2.1	1.7	2.5	10800	10800	10800	3.5	3.4	1.6

It was apparent from Table 1 in Supplementary material that the values of D, $E_{1/2}$/pH, α_{na} and I (diffusion current constant) were practically in the same range for entire reaction series under study. Thus it was possible to discuss the effect of substituents quantitatively in terms of the Hammett equation [39]. The values of the Hammett substituent constants were taken from the literature [39]. $E_{1/2}$–σ plots in media of pH 4.1 and 9.1 for all the compounds under study are shown in Figure 10. The values of specific reaction constant (ρ) calculated from the graphs were found to be in the range of 0.15-0.85. The specific reaction constant values are all positive [40,41] (Table 11) and low indicating that the nucleophilic reaction was taking place. This confirms that the electron uptake was the potential rate determining step [42].

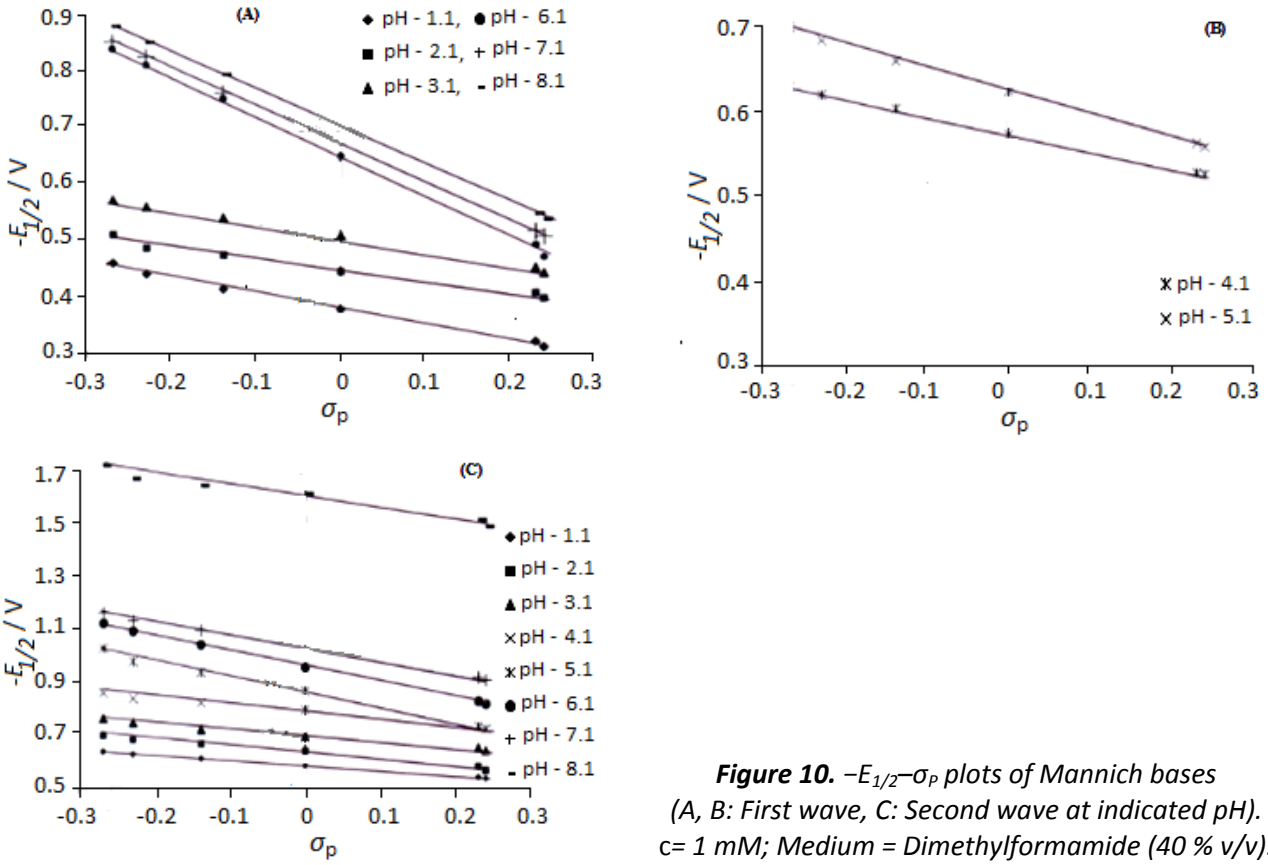


Figure 10. *$-E_{1/2}$–σ_P plots of Mannich bases (A, B: First wave, C: Second wave at indicated pH). c= 1 mM; Medium = Dimethylformamide (40 % v/v).*

Cyclic voltammetric studies of {4-[3-methyl-5-oxo-4(4^{l}-substituted phenyl hyarazono)-4,5-dihydro-pyrazol-1-yl]phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide (V a-f) at hanging mercury drop electrode

The cyclic voltammetric data of compounds Va-f at pH 2.1, 4.1, 6.1, 8.1 and 10.1 are given in Tables 2-7 in Supplementary material. The voltammograms contain two cathodic peaks in acidic solutions and three cathodic peaks in basic solutions at all sweep rates. The cyclicvoltammograms of Va is shown in the Figure 11.

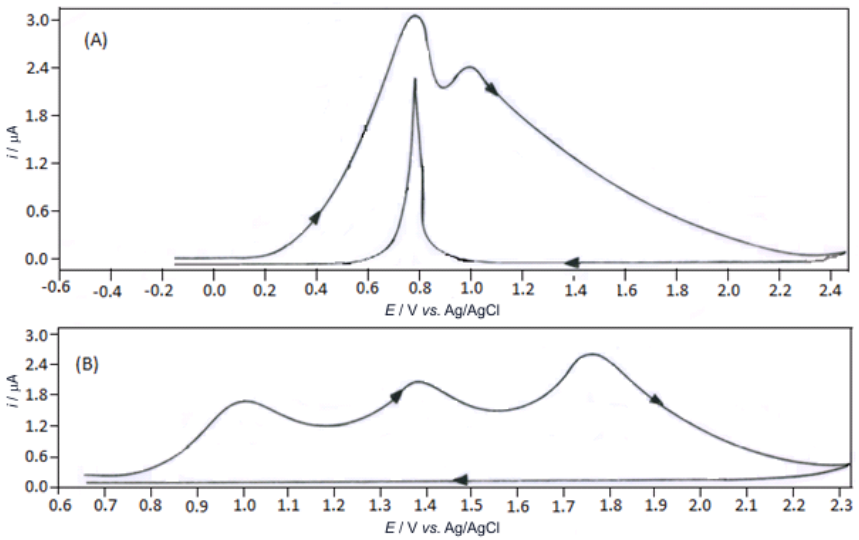


Figure 11. *Cyclic Voltammograms of {4-[3-Methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]--phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide; A represents the cyclicvoltammogram at pH 4.1 and B that at pH 8.1.* c *= 1 mM; Medium: Aqueous dimethylformamide (40 % v/v); sweep rate 100 mv/s.*

Influence of scan rate on peak potential and peak current

The cathodic peak potentials were shifted to more negative values with the increase in scan rate. The cathodic peak currents increase with the increase in scan rate. The results are shown in Tables 2-7 in Supplementary material.

Nature of the electrode process

i_{pc} *vs.* $\gamma^{1/2}$ was a linear plot passing through the origin for the cathodic peaks. This suggests the diffusion controlled nature of the reduction process. This fact was further confirmed by the increase of peak currents with the increase in the concentration of the depolarizer.

The irreversible nature of the electrode process was indicated by following observations.

1. The anodic peak was absent in the reverse scan.
2. The value of ($E_{pc/2}$ – E_{pc}) was greater than 56.5/n mV, where n represents number of electronics involved in the corresponding electrode process.
3. The E_{pc} shifted towards more negative potentials with increase in the concentration of the depolarizer.
4. The current function ($i_{pc}/\gamma^{1/2}C$) was independent of scan rate and
5. ($i_{pc}/\gamma^{1/2}$) *vs.* υ graph was similar to the one expected for case II of Nicholson-Shain Criteria [43].

Table 11. *Effect of pH (Britton-Robinson buffers) on the reaction constant for the reduction of {4-(3-methyl-5-oxo-4-(4^{l}-substituted phenyl hydrozono)-4,5 dihydro-1-yl]-phenoxy}-acetic acid (2-oxo-1 piperidine – 1- ylmethyl-1,2-dihydro-indol-3-ylidene)-hydrazide.*

pH	ρ value	
	First wave	Second wave
1.1	0.29	0.20
2.1	0.25	0.25
3.1	0.25	0.25
4.1	0.20	0.20
5.1	0.33	0.58
6.1	0.66	0.66
7.1	0.58	0.58
8.1	0.66	0.50
9.1	0.66	0.50
10.1	0.66	0.50

Effect of pH on the peak potential and peak current

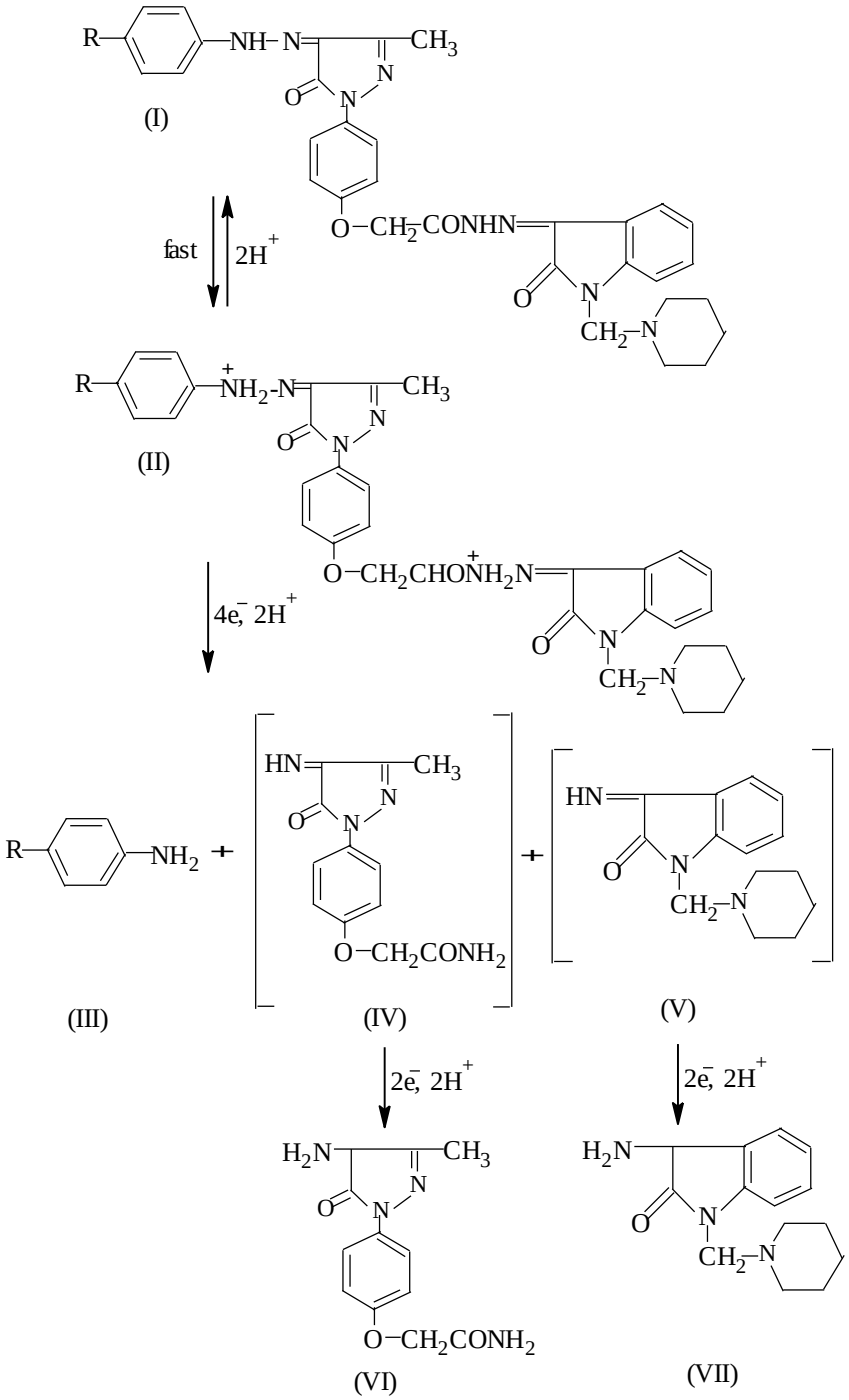
The results presented in ***Tables 2-7*** in Supplementary material show that the cathodic peak potential shifts towards more negative values with the increase in pH of the solution.

The first and the second cathodic peak currents decrease with increase in pH of solutions from 2.1 to 10.1, while peak current corresponding to the third wave noticed in alkaline solutions remains constant. The results were similar to those observed in polarographic studies. Hence the reduction mechanism at HMDE was assumed to be same as that noticed at DME.

Voltammograms recorded in media of pH 4.1 under repeated cycles showed that the peak height decreases with increase of repetition of cycles. However, no significant change was noticed in the shape of the voltammogram. This may be ascribed to the adsorption of the depolarizer on the mercury solution interface.

Reduction pattern in acidic media

From the position of the peak on potential axis, it was proposed that first and second cathodic peaks obtained in acidic solutions were due to the reduction of azomethine group to amines. The reduction mechanism is shown in Scheme 3.



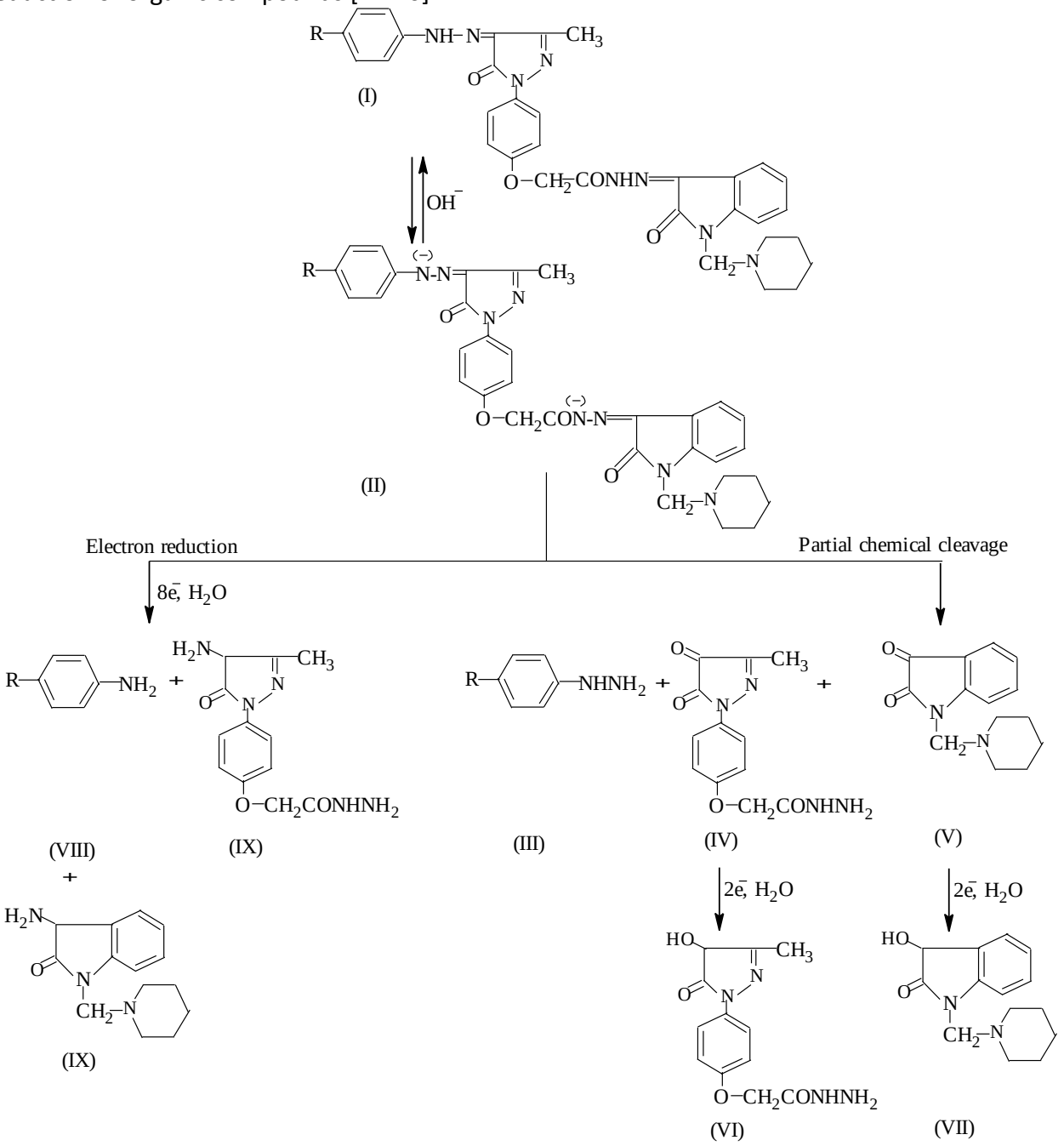
Scheme 3. *Reduction in acidic medium*

Reduction pattern in alkaline media

The position of peaks on potential axis in alkaline medium indicates that the first and second peaks were due to two 4-electron reduction processes of azomethine anionic form and third peak was due to reduction of carbonyl group to carbinol. The protons required for the ketone reduction were obtained from aqueous solution (Scheme 4).

Inverted peaks

Except in solutions of pH 8.1-10.1 and in 0.1 M NaOH, the compounds of V series exhibit inverted peaks (Figure 11). The inverted peak is a common phenomenon in electrochemical reduction of organic compounds [44-46].



Scheme 4. *Reduction in basic medium*

In present studies, the peak potentials were unaltered at lower sweep rates (10-50 V s^{-1}). At higher sweep rates (100-500 V s^{-1}), peak current increases with increases in sweep rate. However a cathodic peak during anodic cycle (Inverted peak) was noticed in buffer solutions of pH 2.1-6.10.

Inverted peaks are generally attributed to

- The movement of mercury surface due to uneven drop polarisation. This bears similarity to the explanation of polarographic maximum of the first kind [47-49] or
- the inhibition of electrode reaction as a consequence of coverage of the electrode by a product of the electrode reaction [50-52]

If the peak is attributed to the second possibility, its intensity is expected to increase with decrease in scan rate. Hence the results in the present studies were not attributed to the second possibility. Moreover, a significant polarographic maximum was observed for the compounds under the experimental conditions of study. It is clear therefore that the inverted peak was attributed to the movement of the mercury surface due to uneven drop polarization.

Effect of substituents on the cyclic voltammetric behaviour of {4-[3- methyl-5-oxo-4(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]phenoxy}-acetic acid (2-oxo-1-piperidene-1-ylmethyl- 1,2-dihydro indol-3-ylidene)-hydrazide.

To investigate the influence of the substituent on cathodic peaks corresponding to the azo group reduction, Hammett's linear free energy relations were applied. The plots drawn between the cathodic peak potential and the Hammett's substituent constant were presented in Figure 12. The slope (ρ) of the linear plots so obtained was positive and confirms the nucleophilic reduction. The values are presented in Table 12.

Table 12. *Effect of pH on the reaction constant for the reduction of {4-[3-Methyl-5-oxo-4-(4^{l}-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl] phenoxy}-acetic acid (2-oxo-1-piperidine-1-yl methyl)-1.2 di-hydro-indol-3-ylidene)- hydrazide.*

pH	ρ	
	I wave	II wave
2.1	0.33	0.33
4.1	0.25	0.25
6.1	0.25	0.25
8.1	0.33	0.33
10.1	0.33	0.33

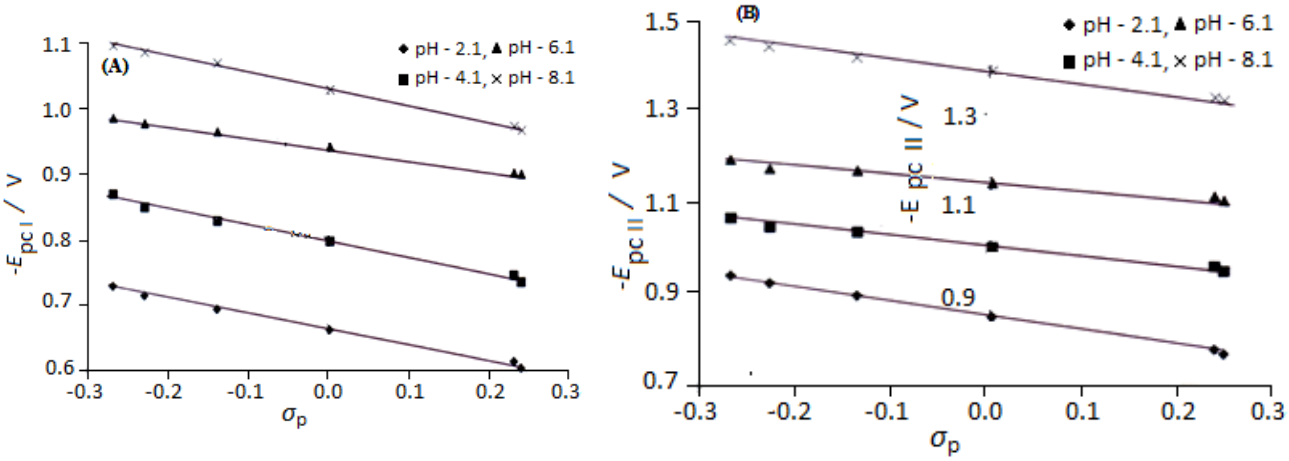


Figure 12. *$-E_{1/2}$–σ_P plots of Mannich bases (A: First wave, B: Second wave).* c *= 1 mM; Medium = Dimethylformamide (40% v/v).*

Cyclic voltammetric studies of {4-[3-methyl-5-oxo-4-(4$^{|}$-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)-hydrazide (Mannich bases V a-f) with a crown–ether modified carbon paste electrode.

Cyclic voltammetric studies of {4-[3-methyl-5-oxo-4-(4$^{|}$-substituted phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl]-phenoxy}-acetic acid (2-oxo-1-piperidine-1-ylmethyl-1,2-dihydro–indol-3-ylidene)-hydrazide (V a-f) were carried out at modified carbon paste electrode in buffer solutions of pH value 2.1, 4.1, 6.1, 8.1 and 10.1 at different scan rates *i.e.* 10 mV s^{-1}, 20 mV s^{-1}, and 50 mV s^{-1}, 100 mV s^{-1}, 200 mV s^{-1}, 300 mV s^{-1}, 500 mV s^{-1}. At all scan rates, the compounds exhibit two well defined cathodic peaks in solutions of pH 2.1-6.1 and three cathodic peaks in alkaline solutions of pH 8.1 - 10.1. An extra anodic peak was noticed in the acidic solutions of pH 2.1 – 6.1.

Effect of scan rate on peak potential and peak current

Peak potentials and peak currents change with the change of scan rates. The cathodic peak potentials become more negative and cathodic peak currents increase with increase in scan rate (Tables 2-7 in Supplementary material).

Effect of pH on peak potentials and peak current

The cathodic peak potentials were shifted to more negative values with the increase in pH. The peak currents decrease with increase in pH of the medium. The data is given in the Tables 2-7 in Supplementary material.

Nature of electrode process

The irreversible nature of electrode process was established by the fact that a plot of $i_{pc}/\upsilon^{1/2}$ versus sweep rate was a straight line parallel to sweep rate axis**.** The irreversible nature of electrode process was confirmed by

- dependence of peak potential on sweep rate,
- the separation of anodic peak and cathodic peak potential (E_{pa}–E_{pc} = ΔE_p) was not equal to 60 / *n* mV at 25°C[53], where *n* represents number of electronics involved in the corresponding electrode process.
- the shape of $i_{pc}/\upsilon^{1/2}$ versus υ plot was in accordance with the Nicholson and Shain criteria [43].

The linear plots of i_{pc} versus $\upsilon^{1/2}$ suggest the diffusion controlled nature of the electrode process. This was further supported by the negative shift of peak potential with increase in sweep rate. The plots of i_{pc} *vs* concentration and i_{pc} *vs* $\upsilon^{½}$ fulfil the criteria for the diffusion controlled nature of the electrode process. The plots of Epc *vs* pH were similar to $E_{½}$ *vs.* pH plots and this supports the findings and conclusion drawn from DC polorography.

Comparison between polarographic studies and cyclic voltammetric studies

Equal number of polarographic waves and cyclic voltammetric peaks noticed in DC polarographic and cyclic voltammetric studies respectively suggest similar behavior in both the studies. However, an additional anodic peak was noticed in solutions of pH 2.1 – 6.1 may be attributed to oxidation of amine formed in the previous reduction step.

Conclusions

A series of six novel Mannich bases were synthesized and characterized by IR, ^{1}H NMR, mass spectral data and elemental analysis. The compounds under study gave two well defined

polarographic waves in the media pH 1.1-7.1 and three waves in the media pH 8.1-10.1. The results were compared with those obtained in cyclic voltammetry at hanging mercury drop electrode and modified carbon paste electrode. The mechanism for the reduction process in acidic as well as basic medium is proposed.

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