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Synthesis and Characterization of Some Imidazolinones and Their Schiff Bases

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Some amino substituted imidazolinones were synthesized from respective oxazolinones and their schiff bases were also synthesized by the treatment with the benzaldehydes. The structures and substitution of different groups were characterized by their UV data and pK_a values, which were observed in methanol: water = 1:1 system and determined by potentiometric method at 20ºC in acetone +10 % water solvent system, respectively. The electronic transitions and inductive effects of different groups were prominently established.

Key Words: Imidazolinone, Schiff base, UV-data, pK_a.

INTRODUCTION

The imidazoles include many substances of both biological and chemical interest[1]. In view of the obvious importance of the naturally occuring imidazoles in biological systems, it is surprising to find that a vast number of synthetic imidazoles have been prepared as potential pharmacological reagents[2-8]. Of these, a number of nitroimidazoles appear to have a considerable application as established anti-infective agents such as metronidazole, clotrimazole, miconazole and ketoconazole[9,10]. Furthermore, misomidazole is an important anticancer drug. Other imidazolines such as naphazoline, xylometazoline, tolazoline are valuable vasodilating and vasoconstricting drugs. The established number of antagonists to histamine, useful in treatment of several allergic manifestations, such as anserine and cimetidine which are also imidazoles[9]. Therefore, as a step in the direction of synthetic drugs, the synthesis of some acetylidene/benzylideneaminoethyl/phenyl imidazolinones (**I**: **1-8**) and their schiff bases (**II**: **9-32**) have been carried out and the structures were confirmed by IR, NMR and MS spectral analysis[11].

Drug action is based on a sequence of several complicated physicochemical events such on drug absorption, durg distribution, its binding to macromolecules, metabolic processes involving bioactivation, degradation

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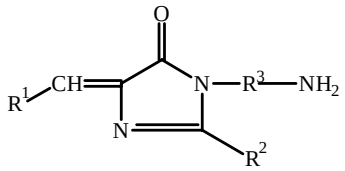
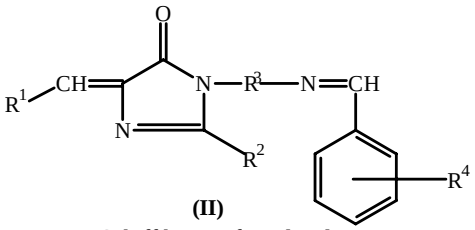
and excretion as well as bioavailability of the drug in active form to reach the sites of action and to interact to produce a response. For each of these processes, certain conditions in the physico-chemical properties which are necessary to be considered for biological action can be divided into two groups: parameters which describe mainly physical properties of the compound such as solubility, partition-coefficient, molar absorptivity, *etc*. and the parameters which are more related to the chemical properties such as dissociation constant, substituent constant, electronic and steric effects. It was found that a change in substitution pattern in any part of an organic compound produces a great variation in activity leading to relating the physico-chemical properties with biological activity. The dissociation constant and lipid solubility of the drug as well as the pH at the absorption site often dictate the absorption characteristics of a drug from solution. The inter-relationship among these parameters is known as the pH-partition theory of drug absorption. The fraction of drug in solution that exist in the non-ionized form is a function of both the dissociation constant of the drug and the pH of the solution. The dissociation constant is often expressed for both acid and bases as pK_a (negative logarithm of the acidic dissociation constant). The relationship between pH and pK_a and the extent of ionization is given by the Henderson-Hesselbach equation: pK_a-pH = log [Fu/Fi] and pK_a-pH = log [Fi/Fu]. For an acidic drug and a basic drug, respectively; where Fu and Fi are the fractions of the drug present in the non-ionized and ionized forms, respectively. The methods those are regularly adopted to determine the pKa value of the compounds are: potentiometric method, spectrophotometric method, solubility method and conductometric method. Studies revealed that weak acids and strong bases have a large pKa value, whereas weak bases and strong acids have a small pK_a value[12].



(I)

Imidazolinones



(II)

Schiff bases of imidazolinones

Taking in account of all the facts, it was contemplated to observe the λ_{max}, ε_{max} and to determine the pKa values of all synthesized compounds in consideration of the interesting chemical features of imidazolinone moiety and schiff bases. The λ_{max}, ε_{max} of the compounds[5] in the solvent system water: methanol = 1:1 were observed in the range of 200-400 nm. The pK_a value determination[12] was carried out by adopting potentiometric method

in acetone +10 % water solvent system at 20ºC. The results *i.e.* the average pKa value of individual compound along with the pH and UV-data are displayed in Table-1 and accordingly the structural features of all synthesized compounds were characterized.

TABLE-1
UV DATA, pH AND pK_a VALUES OF SYNTHESIZED COMPOUNDS (**1-32**)

Compd. No.	Substituents				UV data		In acetone + 10 % water at 20ºC	
	R^1	R^2	R^3	R^4	λ_{max} (nm)	ε_{max} (dm^3/mol/cm)	pH	pK_a
1	CH_3	CH_3	CH_2CH_2	-	229	5434.400	6.03	3.2658
2	CH_3	C_6H_5	CH_2CH_2	-	233	7428.795	8.40	5.2120
3	C_6H_5	CH_3	CH_2CH_2	-	235	7382.938	6.50	4.9470
4	C_6H_5	C_6H_5	CH_2CH_2	-	240	9148.556	6.40	5.8095
5	CH_3	CH_3	C_6H_4	-	297	10834.861	4.00	4.9968
6	CH_3	C_6H_5	C_6H_4	-	300	24354.418	3.72	5.4668
7	C_6H_5	CH_3	C_6H_4	-	302	23797.745	3.90	5.1828
8	C_6H_5	C_6H_5	C_6H_4	-	303	28764.451	4.64	6.1148
9	CH_3	CH_3	CH_2CH_2	H	243	9983.032	3.08	3.5698
10	CH_3	C_6H_5	CH_2CH_2	H	246	7934.703	3.31	4.1088
11	C_6H_5	CH_3	CH_2CH_2	H	244	9394.688	3.28	3.7148
12	C_6H_5	C_6H_5	CH_2CH_2	H	248	11421.897	4.54	6.9568
13	CH_3	CH_3	C_6H_4	H	295	20332.210	3.89	5.1798
14	CH_3	C_6H_5	C_6H_4	H	298	25211.478	4.67	5.7638
15	C_6H_5	CH_3	C_6H_4	H	301	31257.835	3.73	5.2488
16	C_6H_5	C_6H_5	C_6H_4	H	299	41951.853	6.34	7.0338
17	CH_3	CH_3	CH_2CH_2	*m*-NO_2	380	43245.504	4.76	4.9666
18	CH_3	C_6H_5	CH_2CH_2	*m*-NO_2	396	63598.919	6.61	7.0966
19	C_6H_5	CH_3	CH_2CH_2	*m*-NO_2	383	65700.761	4.25	4.9366
20	C_6H_5	C_6H_5	CH_2CH_2	*m*-NO_2	417	888815.050	3.92	4.6846
21	CH_3	CH_3	C_6H_4	*m*-NO_2	416	57514.236	5.45	6.0549
22	CH_3	C_6H_5	C_6H_4	*m*-NO_2	418	84425.657	5.20	8.0606
23	C_6H_5	CH_3	C_6H_4	*m*-NO_2	421	114879.640	5.20	5.5696
24	C_6H_5	C_6H_5	C_6H_4	*m*-NO_2	419	133245.560	3.75	4.5426
25	CH_3	CH_3	CH_2CH_2	*p*-OCH_3	283	44941.838	6.86	7.3126
26	CH_3	C_6H_5	CH_2CH_2	*p*-OCH_3	289	61145.216	6.56	7.9516
27	C_6H_5	CH_3	CH_2CH_2	*p*-OCH_3	286	78168.600	6.01	6.7326
28	C_6H_5	C_6H_5	CH_2CH_2	*p*-OCH_3	310	113919.280	5.63	6.4078
29	CH_3	CH_3	C_6H_4	*p*-OCH_3	392	61877.184	5.15	5.7616
30	CH_3	C_6H_5	C_6H_4	*p*-OCH_3	393	88978.500	5.52	7.8726
31	C_6H_5	CH_3	C_6H_4	*p*-OCH_3	399	92300.364	4.90	5.4016
32	C_6H_5	C_6H_5	C_6H_4	*p*-OCH_3	396	104317.070	3.45	4.3826

EXPERIMENTAL

The UV-analysis of all synthesized compounds[11] were carried out on Shimadzu UV1201 spectrophotometer using methanol: water = 1:1 for base line correction in the range of 200-400 nm.

The pK_a values were observed on pH meter, Toshniwal Instrument Mfg. Pvt. Ltd., Ajmer, India, CAT No. CL 54.

(a) 0.01 M solution of the compound were preared in 50 mL in a solvent system (acetone +10% water), (b) 0.1 N aqueous KOH solution (for weakly acidic drugs) or 0.1 N aqueous HCl solution (for weakly basic drugs) were prepared and standardized accordingly, (c) The pH meter was calibrated by the pH tablets before 0.5 h of the titration (d) A burette containing solution(b) was then fitted, (e) 47.5 mL of solution(a) in titrating vessel was taken and pH was recorded at 20ºC, (f) The titration was performed by addition of 0.5 mL portion of solution (b) from burette and the pH after each addition of titration was measured, (g) Addition of titrant volumes were continued up to 5 mL (10 nos. addition) and (h) The pK_a was then calculated by applying Henderson Hasselbach equation for each addition of titrant and the mean value was thus reported.

For a weakly acidic drug; $pK_a = pH + \log [HA]/[A^-]$ and for a weakly basic drug; $pK_a = pH + \log [BH^+]/[B]$, where HA is the unionized form of acid, A^- is the ionized form of acid, BH^+ is ionized form of base and B is the unionized form of the base.

RESULTS AND DISCUSSION

The UV-data of all compounds were observed to show satisfactory results. It is to be noted that all the observations were of allowed electronic transition of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, not forbidden, as the ε_{max} of all were not found less than 100. The value of ε_{max} of all the compounds were obtained with desirable observation, that depending on the molecular weight and substitution of $-C_6H_5$ in position R^2 and that is why R^1, $R^2 = -C_6H_5$ showed highest ε_{max} value $R^1 = -CH_3$, $R^2 = -C_6H_5$ and then $R^1 = -C_6H_5$, $R^2 = -CH_3$ and R^1,$R^2 = -CH_3$; except in the case of schiff base. In the bases the effect of substitution of $-C_6H_5$ in position R^1 for ε_{max}, in almost cases were prominent. Again, the ε_{max} was found more prominent in the case of common group of substitution *i.e.* $-C_6H_5 = R^1$, R^2 in 12 compounds showed highest than $-CH_3 = R^1$, R^2 and in the series also, the prominent effect of C_6H_5 substitution at position R^1 was observed. Compounds **5-8** showed bathochromic shift than compounds **1-4** due to $n \rightarrow \pi^*$ (predominating), support by π-electrons of $R^3 = -C_6H_4$ having been connected by two nitrogen atom in para position and it has been observed in individual series **1** to **4** and **5** to **8**; that R^1, $R^2 = -C_6H_5$ was highest than $R^1 = -C_6H_5$, $R^2 = -CH_3$ and

then R^1 = -CH_3, R^2 = -C_6H_5 and later R^1, R^2 = -CH_3. The same effect the predomination of $\pi\rightarrow\pi^*$ more than $n\rightarrow\pi^*$ transition of compounds **13-16** synthesized from amino phenyl imidazolinones (**5-8**), where as the amino ethyl schiff bases (**9-12**) showed $n\rightarrow\pi^*$ predomination synthesized from compounds **1-4**. The predomination of $\pi\rightarrow\pi^*$ in case of compounds **13-16** was found might be due to the support of phenylidene group of bases to the amino phenyl. Again, bathochromic shift due to the prominent effect of -C_6H_5 substitution at position R^2 was found in compounds **9-12**, whereas R^1 was found in compounds **13-16**. Bathochromic shift due to the -NO_2 substitution in the schiff bases were found highest and than the -OCH_3, due to the predominating $n\rightarrow\pi^*$ transition. The characterized electronic transition for compounds **17-32** were found in similar to the series of respective other synthesized schiff bases.

The pK_a values of synthesized imidazolinones were compared with the pK_a values of the respective oxazolines. The aminoethyl (**1-4**) and aminophenyl (**5-8**) imidazolines (**I**) were synthesized separately from respective oxazolinones and the pK_a values of oxazolinones, respectively found as 5.1657 ($R^1 = R^2$ = -CH_3), 5.4894 (R^1 = -CH_3, R^2 = -C_6H_5), 5.4850 (R^1 = -C_6H_5, R^2 = -CH_3) and 5.807 ($R^1 = R^2$ = -C_6H_5) at 20ºC in (acetone + 10 % water) solvent system. From the observation of pK_a determination, the structural features of synthesized compounds were marked that they were heteronitrogenous aromatic[13,14]. It has been found that for all synthesized compounds the log of ionic and non-ionic ratio in few observations showed negative value at 20ºC on addition of more titrant, might be due to the ion formation taken place in = N-, as like as at 25ºC the formation of hydrazinium ion shows pK_1 value = -0.88 [15], which could be understood on detailed analysis of stepwise data. Synthesized imidazolinones (**1-4** and **5-8**) were found to show less pK_a value than the respective oxazolinones, which was desirable except **4** and **8**, as they were containing -C_6H_5 in both the positions R^1 and R^2. In all the cases, it has been observed that the addition of -C_6H_5 in any position ($R^1/R^2/R^3$ or schiff base formation by addition of benzaldehyde) were showing the increase of pK_a value, which was expected due to the positive inductive effect of -C_6H_5; such as compounds **13-16** showed more than compounds **9-12**, compounds **13-16** more than compounds **5-8**, 5-8 more than compounds **1-4** and **1**,**4** more than compounds **9**,**12**. Only exception in the case of Schiff bases of compounds **10**,**11** were found, that synthesized from compounds **2**,**3** respectively might be due to some unknown ionic or steric hindrances. Almost all Schiff bases of having R^4 = *m*-NO_2 and *p*-OCH_3 found to show increased pK_a value than respective precursors excpet $R^1 = R^2$ = -C_6H_5 and again Schiff bases of R^4 = H showed less pK_a value than other at R^4 except $R^1 = R^2$ = -C_6H_5, which were nothing but the appropriate effect of inductivity of different groups.

Expected pK_a values of the Schiff bases of *m*-nitro- and *p*-methoxy benzaldehydes were observed and it was also recorded the opposite trend among the two series of imidazolinones *i.e.* due to the substitution at R^3 and moreover it was also found that the mild positive inductive effect of $-OCH_3$ were followed, which were not observed in the cae of $R^3 = -C_6H_4$, might be the inductivity of respectively characterized groups were diminished. Again a through investigation of individual series *i.e.* compounds **1-4**, **5-8**, **9-12** and **13-16** claimed the importance of substitution in the position R^1 and particularly in R^2 position in valuation of pKa; that it has been found that R^1, $R^2 = -C_6H_5$ showed highest pK_a values than $R^1 = -CH_3$, $R^2 = -C_6H_5$, then gradually reduced in the cases of $R^1 = -C_6H_5$ and $R^2 = -C_6H_5$ and R^1, $R^2 = -CH_3$. But in the cases of compounds **17-32**, it was found that R^1, $R^2 = -C_6H_5$ showed least pK_a values and gradually they were increased in case of $R^1 = -C_6H_5$, $R^2 = -CH_3$, R^1, $R^2 = -CH_3$, $R^1 = -CH_3$, $R^2 = -C_6H_5$, which proved the prominent electronic activities of $-NO_2$ and $-OCH_3$.

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