Indian Journal of Chemistry
Vol. 45B, November 2006, pp. 2580-2582

Note

Correlation between the *p*Ka and pharmacological properties of some imidazolin-5(4*H*)-ones, their precursors and Schiff's bases

J K Gupta[1], Biplab De* & V S Saravanan[1]
[1]Deptt. of Pharm Tech, Jadavpur University, Kolkata, West Bengal 700 032, India
Regional Institute of Pharmaceutical Science And Technology, Abhoynagar, Agartala, Tripura 799 005, India
E-mail : biplab_32@yahoo.co.in

Received 7 October 2004; accepted (revised) 5 September 2006

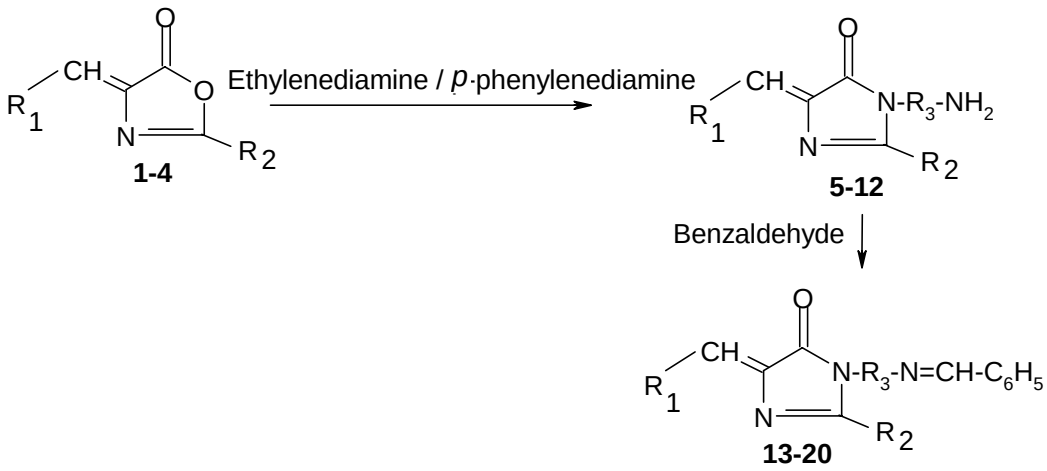
The *p*Ka value of some synthesized imidazolin-5(4*H*)-ones and their precursors, Schiff's bases are determined by potentiometric method and the analgesic activity and CNS depressant property are evaluated, which are correlated with the *p*Ka values. It is found that a correlation established in best fit curve of 3rd order polynomial equation.

Keywords: Imidazolin-5(4*H*)-ones, Schiff bases, potentiometric method, analgesic activity, CNS depressant property
IPC Code: Int. Cl.[8] C07D

In continuation of our search[1] on the correlation between *p*Ka and pharmacological properties of imidazole derivatives, we are presently analyzing the correlation between *p*Ka and the analgesic, CNS depressant property of some synthesized imidazolin -5(4*H*)-ones, their precursors and Schiff's bases. Synthesis of the title compounds is depicted in **Scheme I**.

In recent years, several imidazolin–5(4*H*)-ones and their derivatives are gaining prominence for their potential pharmacodynamic properties. In view of these observations, it was contemplated to synthesize some novel imidazolinone derivatives **5-12** from respective oxazolinones[2,3] **1-4** and upon the treatment with benzaldehyde, their Schiff's bases **13-20** were also synthesized and characterized[4] with spectral and analytical data as 4-acetylidene/benzylidene-2-methyl/phenyl oxazol-5(4*H*)-ones **1-4**, 1-amino ethyl/phenyl-2-methyl/phenyl-4-acetylidene/benzylidene-imidazolin-5(4*H*)-ones **5-12** and 1-phenylidene-amino-ethyl/phenyl-2-methyl/-phenyl-4-acetylidene/-benzylidene-imidazolin -5(4*H*) ones **13-20**. The IR spectra was recorded in KBr pellet, on Perkin-Elmer Infra Red-283 and Bomen DA-8FTIR, of imidazolinones and their Schiff's bases were also recorded as C-H str of CH_3 at 2870-3067 cm^{-1} (except **8, 12, 16** and **20**); Ar C=C skeletal vibration recorded at (except **5**) 1411-1522 cm^{-1} and Ar-H deformation at 1179-1232; characteristic stretching for C=O of imidazolinones at 1652-1689; C=O str at 1710-1797 cm^{-1}; C=N str of imidazolinones at 1618-1638; CH= C str at 1518-1584; N=C-N at 1349-1425;-CH_2-CH_2- str of compounds **5-8** and **13-16** recorded at 782-810 cm^{-1}; due to *trans* ethylenic group spectra recorded at 961-975 and at 873-907 cm^{-1}; and Schiff's bases showed peak in particular for –N= i.e., 3º aromatic amine at 1314-1327 cm^{-1}; moreover C-H deformation of aromatic ring in Schiff's base found at 1139-1187 cm^{-1}. The UV–analysis were carried out on a Shimadzu UV 1201 spectrophotometer using methanol + water = 1:1 for base line correction. The λ_{max} (ε_{max} in dm^3/mol/cm) of compounds **5-20** were recorded as 229(5434.400), 233(7428.795), 235(7382.938), 240(9148.556), 297(10834.861), 300(24354.418), 302(23797.745), 303(28764.451), 243-(9983.032), 246(7934.703), 244(9394.688), 248(11421.897), 295(20332.210), 298(25211.478), 301(31257.835) and 299(41951.853) respectively. The *p*Ka value (in 10% water + acetone solvent system at 20°C) and pharmacodynamic properties[5] such as analgesic activity and CNS depressant property were determined by potentiometric method[6], acetic acid induced writhing method (% protection)[7] and by measuring locomotors activity[8] using actophotometer in mice, respectively. For evaluation of every pharmacological property 6 Nos. healthy adult albino Swiss mice weighing between 20-25 gm separately were taken for each compound and administered intraperitoneally in the dose of 100 mg/kg body weight. The observation was presented in **Table I**.

Drug absorption and drug action is influenced by many physico-chemical characteristics, the *p*Ka value is one of the important physico-chemical parameter that influences the pharmacological activities of the drug. The pharmacological properties i.e. analgesic activity and CNS depressant property of the synthesized compounds were co-related with their



Scheme I

Table I—*p*Ka, analgesic activity and CNS depressant property of compounds **1-20**

Compd	Substituents			Type of Compd	*p*Ka (10%water+acetone)at 20°C	Analgesic: % Protection to writhings	CNS depressant:% change of decreasing activity (movement)
	R_1	R_2	R_3				
1	CH_3	CH_3	-	Acetylidene oxazolinone	5.1657125	30.14	-
2	CH_3	C_6H_5	-	’’	5.4894625	45.72	-
3	C_6H_5	CH_3	-	Benzylidene oxazolinone	5.4850875	68.32	-
4	C_6H_5	C_6H_5	-	’’	5.807225	65.24	-
5	CH_3	CH_3	CH_2CH_2	Acetylidene-aminoethyl imidazolinone	3.2658263	44.18	52.09
6	CH_3	C_6H_5	CH_2CH_2	’’	5.2120763	35.96	39.48
7	C_6H_5	CH_3	CH_2CH_2	Benzylidene-aminoethyl imidazolinone	4.9470763	65.75	42.43
8	C_6H_5	C_6H_5	CH_2CH_2	’’	5.8095763	39.73	38.60
9	CH_3	CH_3	C_6H_4	Acetylidene-aminoethyl imidazolinone	4.9968082	34.25	56.29
10	CH_3	C_6H_5	C_6H_4	’’	5.4668082	19.86	55.85
11	C_6H_5	CH_3	C_6H_4	Benzylidene-aminoethyl imidazolinone	5.1828082	56.16	56.15
12	C_6H_5	C_6H_5	C_6H_4	’’	6.1148082	22.26	52.37
13	CH_3	CH_3	CH_2CH_2	Schiff base of 5	3.5698082	48.29	53.92
14	CH_3	C_6H_5	CH_2CH_2	’’ 6	4.1088082	41.10	51.32
15	C_6H_5	CH_3	CH_2CH_2	’’ 7	3.7148082	69.52	52.38
16	C_6H_5	C_6H_5	CH_2CH_2	’’ 8	6.9568082	42.47	50.77
17	CH_3	CH_3	C_6H_4	’’ 9	5.1798082	26.03	52.03
18	CH_3	C_6H_5	C_6H_4	’’ 10	5.7638082	12.67	41.96
19	C_6H_5	CH_3	C_6H_4	’’ 11	5.2488082	47.60	42.24
20	C_6H_5	C_6H_5	C_6H_4	’’ 12	7.0338082	18.49	40.04

*p*Ka values by drawing the plots taking *p*Ka value in x-axis and pharmacological activities in y-axis. Each plot was plotted in 3rd order polynomial using computer software MS-Office’97: MS-EXCEL Program and the equation for obtained line was reported along with the multiple correlation co-efficient square (R^2) value.

, r = correlation co-efficient

$R^2 = 1 - \omega/\omega_{11}$, $\omega = \begin{vmatrix} 1 & r_{12} & r_{13} \\ r_{21} & 1 & r_{23} \\ r_{31} & r_{32} & 1 \end{vmatrix}$, r = correlation co-efficient

Results and Discussion

From the observation of *p*Ka determination, the structural features of synthesized compounds were

marked that they were heteronitrogenous aromatic as *p*Ka of all were found in between 3.2 to 7.2 (refs.9 and 10). It has been found that for all synthesized compounds the log of ionic and non-ionic ratio in few observations showed negative value (e.g. upon addition of 2.5 mL basic standardized solution in the case of weakly acidic compound such as compound **6**, log [unionized] / [ionized] = ─0.026065) at 20ºC, might be due to the ion formation in = N-, similarly at 25ºC, the formation of hydrazinium ion on proton - transfer reactions of materials in water shows pK_1 value = ─0.88 (ref.11). The keen observation of *p*Ka value was undoubtedly supporting the formation of respectively characterized compounds. From the observation of analgesic activity, it has been found that imidazole derivatives containing $R_1 = C_6H_5$ and $R_2 = CH_3$ showed better activity than any other and $R_2 = CH_3$ might be the essential part in increase/decrease of analgesic activity. No significant CNS depressant property observed in oxazolinones (**1-4**). The CNS depressant activity of imidazolines found highest in case of substitution of CH_3 in position R_1 and R_2 – both and it was gradually decreased upon the substitution of C_6H_5 on those positions. In the case of Schiff's bases the activity was more, when $R_3 = CH_2CH_2$, but again it was observed that amino phenyl ($R_3 = C_6H_4$) showed more activity than amino ethyl ($R_3 = CH_2\ CH_2$) imidazolinones.

The square of multiple correlation co-efficient value (R^2) are observed. In each case it is recorded that $R^2 = 1$, that is the pharmacological activities evaluated were to have the correlation with their *p*Ka value i.e. the individual structural features. In studying of the curve equations, one can predict very easily the pattern of correlation. It is found that except in the case of Schiff's bases of acetylidene imidazolinones, all the curves indicate the same type of correlations in co-relation between *p*Ka and analgesic activity.

Conclusion

The determined *p*Ka values of all synthesized compounds revealed the structural relationship. The correlation between *p*Ka and pharmacological properties of all synthesized compounds were established in best fit curve of 3rd order polynomial equation.

References

1 De B & Ramasarma G V S, *Indian Drugs*, 36, **1999**, 583.

2 Furniss B S, Hannaford A J, Smith P W G & Tatchell A R, *Practical Organic Chemistry* (ELBS-Longman, Singapore) **1996**, pp. 1155 - 1156.

3 Sarvanan V S, De B & Gupta J K, Synthesis and antimicrobial activity of some 4-substituted-2-phenyl oxazol-5(4*H*)-one derivative, in *91st The Indian Science Congress* (Punjab University Campus, Chandigarh) 3-7 January **2004**.

4 De B, Gupta J K & Sarvanan V S, *Acta Pharmaceutica*, **55**, **2005**, 287.

5 De B, Gupta J K & Sarvanan V S, *Indian J Pharm Scs*, **67**, **2005**, 373.

6 De B & Gupta J K, *Indian J Pharm Educ*, **37**, **2003**, 100.

7 Wittkin L B, Heubuer C F, Galdi F, O'keefe E, Spitaletta P & Plummer A J, *J Pharmacol Expt Therap*, **133**, **1961**, 400.

8 Kulkarni S K, *Hand book of Pharmacology* (Vallabh Prakashan, Delhi) **1996**, pp. 41-43.

9 Albert A & Serjeant E P, *The determination of ionization constants–a laboratory Manual* (Chapman & Hall, New-York) **1984**.

10 Dean A J, *Analytical Chemistry Hand Book* (Mc-Graw Hill Inc., New-Delhi) **1995**, 3.57.

11 Willard H H, Merritt L L, Dean J A & Settle F A, *Instrumental methods of analysis* (CBS Publishers & Distributors, Delhi) **1986**, 872.