Synthesis, Characterization and Anticonvulsive Evaluation of Pyridine & Pyrimidine Hydantoins

Dr. Sangeeta Kamthan
Associate Professor, Department of Chemistry, Bareilly College, Bareilly

Abstract **- Heterocyclic compounds having Nitrogen as hetero-atom are highly reactive and possess various pharmacological activities. Hydantoins of pyridine and pyrimidine were synthesized via chloro-acetyl derivatives. The synthesized compounds were characterized by means of their IR and purity checked by the analysis. The compounds were evaluated for anticonvulsant activity by maximal electro-shock method and chemo-shock. They were found to possess significant activity.**

Index Terms: anticonvulsive activity, hydantoins, Pyridine, Pyrimidine.

I. INTRODUCTION

Derivatives of pyridine and pyrimidine are known to possess anticonvulsant, antidepressant, anorexic and tranquilizing activity [1] [2].They have attracted significant interest in medical chemistry in recent years [3]

Pyridine derivatives have shown to exhibit anticonvulsant activity. Their preparation has been characterized in last few years, Trizolopyridines [4], Hexahydropyridines [5] and Benzopyranol pyridines [6]. Pyridyl analogs of Diphenyl hydantoin were found to have considerable anticonvulsant activity as compared to Diphenyl hydantoin [7].

Pyrimidine is also an aromatic compound similar to pyrimidine with two nitrogen atoms in the ring, at position 1 and 3. Pyrimidines that have broad spectrum of bioactivities (antibacterial, anticancer, anti-inflammatory and so on) are an important one of heterocyclic compounds [8] - [10].

Pyrimidine derivatives with manipulation at various positions have been showed to possess considerable anticonvulsant activity [11] -] [15].

In the present communication, attempt has been made to report the synthesis of newer hydantoin derivatives via chloro-acetylation of 2-amino pyridine, 3-amino pyridine, 4-amino pyridine and 2-amino pyrimidine followed by condensation with an alkali metal cyanate in presence of quaternary ammonium salt and polar solvent [16]. The structures of the synthesized compounds were assigned on the basis of IR and PMR spectra data. They were screened for their anticonvulsant activity by MES method [17] using male albino mice and the results were tabulated.

II.MATERIAL AND METHODS

N^3–(pyrid-2-yl) hydantoin, N^3–(pyrid-3-yl) hydantoin, N^3 – (pyrid-4-yl) hydantoin and N^3 – (primid-2-yl) hydantoin were synthesized by the method discussed below and their melting points were determined in the open capillaries using Boitus melting point apparatus and expressed in ℃ (Table-1). IR spectra were recorded either on Perkin-Elmer

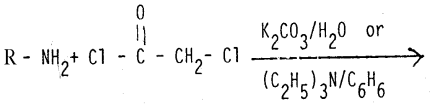
FT-IR 881 or Bruker Alpha FT-IR Spectrophotometer using KBr disc.

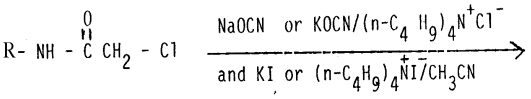
A. Synthesis of chloroacetyl pyridines / pyrimidine

Equimolor quantity 2-chloroacetyl Pyridine (0.01 M) of freshly distilled 2- chloroacetyl chloride and 2-amino pyridine in dry benzene containing Potassium carbonate was added with constant stirring the reaction mixture and was refluxed on water bath at 72 ℃ for 2 hrs. Excess benzene was distilled off and the residue was washed successively with sodium carbonate solution and water and finally recrystallized with ethanol.Similarly, chlroacetyl derivatives of 3- amino pyridine, 4-amino pyridine and 2- amino pyrimidine were prepared.

B. Synthesis of N^3 – (pyrid-2-yl) hydantoin / N^3-(pyrimid-2-yl) hydantoin

Tetra–n–butly ammonium iodide (100 mg) was added to the solution of chloro-acelylated compound obtained in step 1 (1.71 gm, 0.01 mole) and potassium cyanate (0.8gm, 0.01mole) in acetonitrile. The mixture was stirred at 70 ℃ for 8 hrs. It was then cooled to room temperature and the solvent distilled off. The crude product was washed with water and recrystallised with ethanol.





Similarly, N^3- pyridine hydantoin analogs were synthesized. The general sequence of the chemical reaction is depicted as follows:

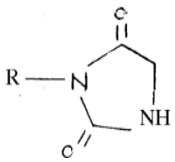


Table 1.The molecular formula, melting point & percentage yield of substituted hydantoins of Pyridines and Pyrimidine**.**

S. No.	Nature of R	Molecule formula	M.P ℃	Yield %
I	2-aminopyridine	$C_8H_7N_3O_2$	125	55
II	3-aminopyridine	$C_8H_7N_3O_2$	120	42
III	4-aminopyridine	$C_8H_7N_3O_2$	118	40
IV	2-aminopyrimidine	$C_7H_6N_4O_2$	110	52

The analysis of N (found and calculated) did not differ more than 0.4%

III. CHARACTERIZATION OF 2- CHLORO-ACETYL PYRIDINES AND PYRIMIDINE

The synthesized compound was satisfactorily characterized by IR spectra, PMR spectra, elemental analysis and tlc. The IR spectra (in KBr) was recorded which reveals characteristic absorption bands in the region of 1680 cm^{-1} corresponding to C=O group. In addition, the compound exhibited a strong band around 1720-1670 cm^{-1} characteristic of O=C-N band. Absorption band at 3280 cm^{-1} indicated -NH- stretching frequency. The PMR spectra reveals characteristic signal at frequency ẟ2.8-1.5 corresponding to the protons of $–COCH_2$ Cl group. The purity of the compound was checked by tlc.

IV. CHARACTERIZATION OF N^3–(PYRIDINYL) HYDANTOINS AND N^3–(PYRIMIDYL) HYDANTOIN

The IR spectra showed characteristic absorption peaks in the region of 1740-1700 cm^{-1} C=0 absorbance at position-4) and 1700-1650 cm^{-1} (C=0 absorbance position-2). A broad spectrum is noticed between 3180-3150 cm^{-1} due to –NH- stretching at position-3 (Characteristic of –CONHCO- bond in cyclic system). An absorption peak in the region of 1340-1310 cm^{-1} corresponds to C-N bond.

The PMR spectra exhibits –NH- stretching frequency by a broad, weak and variable resonance signal at frequency ẟ 9.92-7.01 cm^{-1} (determined by D_2O exchange).

V. EVALUATION OF ANTICONVULSANT ACTIVITY

Male albino mice weighing 20-25 mg were used in the present study. They were maintained at an ambient temperature of 22 ± 1 ℃ and had food and water ad.libitum. The mice were divided into groups of six animals each except otherwise mentioned. The test compounds were dissolved in polysorbate (Tween 80) and diluted with distilled water and were injected i.p.in a dose of 100 mg/kg to the mice. One group received standard drug, Diphenyl hydantoin sodium in a dose of 25 mg/kg i.p. The control group received vehicle only. The animals were observed for behavioral changes, if any, up to 1 hour of drug administration.

The anticonvulsant activity was studied by maximum electroshock seizures (MES). The electro-shock (48mA, 0.2 sec.) was delivered 1 hr. after the drug

administration through a convulsiometer (Techno) by using ear electrodes according to the method of Swinyard et.al. (1952) [17]. Female mice were excluded for screening due to the fact that oestrous cycle influences the seizures – threshold. After the delivery of shocks, duration of various phases of MES (tonic flexion, tonic extensor and clonus) and of post seizure depression, defined as the time required to regain the righting-reflux (RR), was taken as the index for protection. The statistical significance of the difference in the mean values were calculated by the student's't' test.

Table-2. Effect of substituted hydantoins of Pyridines and Pyrimidine on components of electroshock-induced seizures in male albino mice.

Compound No.	No. of Animals	Mean duration in seconds ± SEM			
		Flexor	Extensor	Clonus	Stupor
Vehicle Control	11	2.29 ± 0.16	15.09 ± 1.35	11.80 ± 3.19	53.80 ± 10.06
I	6	1.66 ± 0.14	21.4 ± 1.57***	4.14 ± 1.28*	58.8 ± 21.4
II	6	1.76 ± 0.41	21.8 ± 1.64****	4.71 ± 1.37*	59.4 ± 22.8
III	6	1.94 ± 0.71	22.64 ± 1.78***	5.28 ± 1.61*	61.2 ± 22.8
IV	6	1.6 ± 0.08***	10.0 ± 4.46	13.48 ± 4.20	107.72 ± 26.3
Diphenyl hydantoin sodium	6	1.63 ± 0.24*	0.00 ± 0.00****	2.20 ± 1.04****	4.73 ± 1.79***

P value in comparison to control group -*P: - < 0.05, **P :-< 0.025, ***P :-< 0.01, ****P: -< 0.001'a' : Dose of 25 mg/kg i.p

VI. RESULTS

Substituted hydantoins of pyridines and pyrimidine were synthesized and their structure, physical and chemical properties are summarized in Table 1.

All the newly synthesized hydantoin derivatives of pyridines and pyrimidine were found to show satisfactory anticonvulsant activity when compared with Diphenyl hydantoin sodium which was used as standard drug. The MES convulsions were divided into four phases (i) Flexion (ii) Extensor (iii) Clonus (iv) Stupor. The observations are shown in Table-2.

The compound I showed maximum anticonvulsant activity.

VII. DISCUSSION

The compounds containing single Nitrogen, as hetero atom in heterocyclic moiety in hydantoin derivative, in general, have shown considerable anticonvulsant effect as indicated by its high stupor value.

VIII. CONCLUSION

Pyridine and Pyrimidine hydantoin derivatives are chemically reactive and endorse various substitutions on the heterocyclic ring capable of exhibiting biological activities potentially. They explore the range of the pharmaceutical chemist to synthesize and develop new hydantoin derivatives as lead molecules.

IX. ACKNOWLEDGEMENT

The author is thankful to Principal, Bareilly College, Bareilly, Director IVRI, Izatnagar and Head, Division of Pharmacology and Toxicology, IVRI, Izatnagar, Bareilly for providing necessary lab facilities

REFERENCES

[1] Van Gebler, L.H. Josephus, Alfons Raeymackers, F.G. Leopold, J. Willy: U.S. 3, 936, 718(Cl.260-256, 4H; CO 7D 239/14) (1976) Chem. Abstr. 85 525 (1976).

[2] BassieLevitt and Morris Stolar: Eur. Pat. (Cl. C07D 239/62) (1985) Chem. Abstr. 103, 593 (1985)

[3] Naeem S., Akhtar S., Mushtaq N., Kamil A., Zafar S., Anwar S., Arif M. Synthesis of novel derivatives of 4-Pyridine carboxylic acid hydrazide and their activity on central nervous system. *Pak. J. Pharm. Sci.* 2014; 27:1401–1408. [PubMed] [Google Scholar]

[4] M.M. Vohra, S.M. Pradhan, P.C. Jain, S.K. Chatterjee, Nitya Anand: J. Med.Chem., 296, 8 (1965)

[5] Rudolf Kunstmann, Lerch Ulrich, Hermann Yerhards and Ulrich Schacht: J. Med., 432, 27 (1984)

[6] Jean A. Yauthier, Lestie G.Humber and Clara Revesz:U.S. 4, 132,710 (Cl. 546-63 CO7D491/04) (1979)
[7] E. Campaigne and H.L.Thomas: J. Am. Chem. Soc., 77 5365 (1955)
[8] Kaur R., Kaur P., Sharma S., Singh G., Mehndiratta S., Nepali K. Anti-Cancer Pyrimidines in Diverse Scaffolds: A Review of Patent Literature. *Recent Pat. Anticancer Drug Discov.* 2015; 10:23–71. doi: 10.2174/1574892809666140917104502. [PubMed] [CrossRef] [Google Scholar]
[9] Nofal Z.M., Fahmy H.H., Zarea E.S., El-Eraky W. Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities. *Acta Pol. Pharm.* 2011; 68:507–517. [PubMed] [Google Scholar]
[10] Rahaman S.A., Rajendra Prasad Y., Kumar P., Kumar B. Synthesis and anti-histaminic activity of some novel pyrimidines. *Saudi Pharm. J.* 2009; 17:255–258. doi: 10.1016/j.jsps.2009.08.001. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[11] W. Wiegrebe, Fore Wehrhahn and U.P. Schluneggar: Pharm. Acta. Helv. 261, 50 (1975)
[12] Ueda Tohru and jack J. Fox: J. Org. Chem., 1762, 29 (1864)
[13] Greenhalgh Norman and Charles H. Vasey: Brit., 711, 618 (1954)
[14] Wm. R. Boon, Greenhalgh Norman, Eric London and Charles H. Vasey: U.S., 2, 637. 730 (1953)
[15] Charles H. Vasey: U.S., 2, 676/76 (1954)
[16] Kim, S.C. and Kwon, B.M. (1982). A new convenient synthesis of hydantoin derivatives by phase transfer method. Synthesis 795-796
[17] Swinyard, E.A. Brown, W.C. and Goodman, L.S. (1952). Comparative assays of antiepileptic drugs in mice and rats, J. Phamac. exp. Ther. 106: 319-330.