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Synthesis of Some New Hydantoin Derivatives with Possible Anticonvulsant And Analgesic Activities

Dr. Roopali Tandon, Dr. Ved Prakash Singh, Dr. S. C. Mehra

Department of Chemistry, Bareilly College, Bareilly

Abstract:-

Literature survey on hydantoin derivatives shows various pharmacological activities, thus various hydantoin derivatives with cyclic modification of the parent structure were synthesized as possible anticonvulsant and analgesic activities. These Compounds were prepared by condensation of

3–N-p-substituted phenyl hydantoin with phenyl cyanamide to form 3-N-(p-substituted phenyl) – 1-N-(N-phenyl guanidyl) amidino hydantoin.

The purity of the compounds were checked on thin layer chromatography (TLC). The compounds were analyzed for elemental analysis, the structure of compounds were characterized by Infra-red (IR) spectroscopy and nuclear magnetic spectroscopy (NMR). The compounds were screened for anticonvulsant and analgesic activities.

Keywords: hydantoin, synthesis, anticonvulsant, analgesic, activity.

1. Introduction-

Hydantoins and its derivatives besides effective anticonvulsants[2] are also remarkably successful drug in variety of chemotherapeutics fields like

antibacterial, antitubercular, antitumor[3], antithyroids[4], antineoplastics[5], analgesic, antihistamine, and antiarrhythmic[7], antispasmodic[9] and anthelmintics activities etc. Some of its derivatives are highly effective as fungicides, insecticides, and roderticides[12].The most recent application of hydantoin derivatives is antiviral[12-13], antiradiation[14], and hypoglycemic[15], agent. Various 3-N- (Substituted) hydantoin reported in literature possess marked anticonvulsant activity[17-19]. Keeping this view various new hydantoin derivative have been synthesize which might have the potential anticonvulsant activities.

2. Experimental

2.1 Preparation of N-p-substituted phenyl acetanilide-

Freshly distilled chloroacetyl chloride (1.2 ml) in dry benzene was added drop by drop to freshly distilled anilie (1 ml) dissolved in dry benzene containing 2gms of potassium carbonate with stirring. The stirring. The stirring of the reaction mixture was continued for four hours. Excess of benzene was then distilled of and the residue mixture was treated with sodium bicarbonate and water to remove acid impurities. The product was washed with water dried and finally recrystallized from ethanol.

The compound so obtained was characterized by elemental analysis tlc ir pmr spectra.

IR (KBr) = 1738-1740 cm^{-1} (due to C=O absorption), 3390-3122 cm^{-1} (due to CH-stretching vibration of benzel), 1610-1720 cm^{-1} (Characteristic absorption in band showing the presence of -C-CH_2-Cl

$$\overset{\overset{O}{\|}}{}$$

PMR= 2.1 - 2.2 (2H, s- Co CH_2cl)

7.39 - 8.12 (5H.m. Ar-H), 8.01 (1H, b- NH)

2.2. Preparation of 3- N-p- substituted phenyl hydantoin -(2)

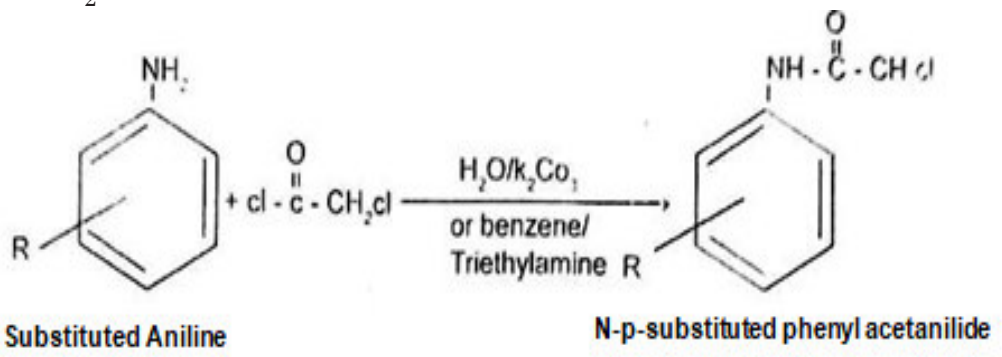
Chloroacetanilide where treated with an alkali metal cyanate in presence of phase transfer catalyst give corresponding hydantoin. 1.6 gm of chloroacetanilide was dissolved in 25 ml of acetonitrile containing KOCN (0.8 gm) and 0.1 gm of tetra n-butyl ammonium iodide was added to it. The temperature was maintained between 60-80^{0}C and was continuously stirred for 8-10 hrs. The mixture was then cooled at room temperature and evaporated to dryness on a water bath. The crude product so obtained was washed with distilled water and finally recrystallized from ethanol.

The compound 3-N-substituted phenyl hydantoin was characterized by elemental analysis, tlc i.r. and p.m.r. spectra. The tlc gave single spot I.R. (KBr) = 1760 - 1740 cm^{-1} (due to c = o gp at position - 4 of hydantoin ring 1710=1700 cm^{-1} (due to c = o gp at position - 2 of hydantoin ring) 3230 3210 cm^{-1} (broad spectrum peak due to -NH at position -3 3100 2998 cm^{-1} (due to CH stretching frequency of aryl gp.

PMR = 7.39 (5H-m Ar-H)

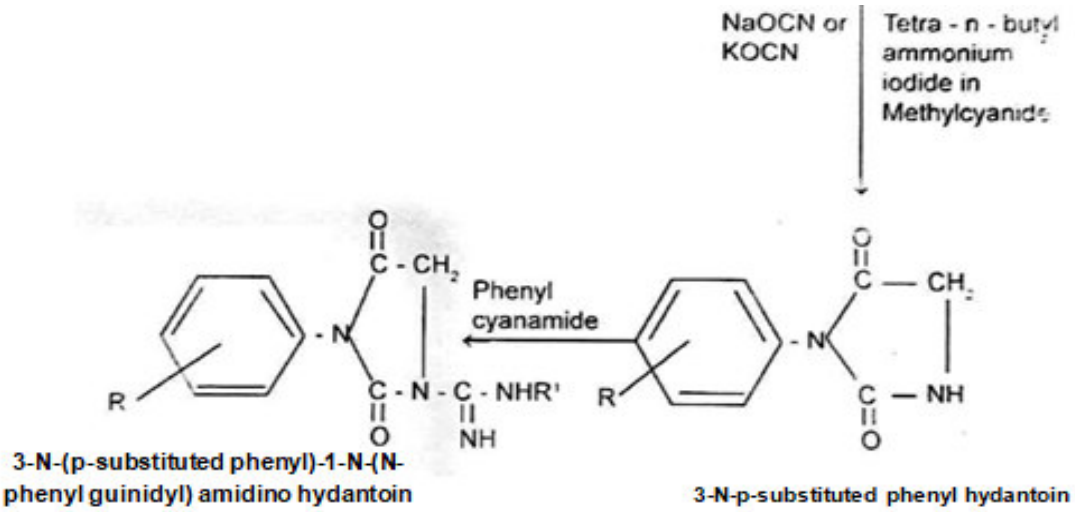
7.39 - 8.01) Correspond to NH gp of hydantoin ring i.e. - 1H-NH)

4.03 (2H.d-CH_2 - N)



Substituted Aniline

N-p-substituted phenyl acetanilide



2.3. Condensation of 3-N-p- substituted phenyl hydantoin with phenyl cyanamide- Formation of 3-N- (p-substituted phenyl)- 1-N-(N-phenylguinidyl) amidino hydantoin

To an ice cooled ethereal solution of phenyl cyanamide (0.01m) dry HCl gas was passed for about 3 minutes. The phenylamidine chloride which separate as a sticky mass was dissolved in acetonol. To above solution was added a solution of N-P-substituted phenyl hydantoin (0.01m) in acetone. Almost immediately 3-N-(substituted phenyl)-1-N-alkyl guanidyl hydantoin separated which was filtered and washed with warm acetone and recrystallized from ethanol/water (1.1) on rendering the solution of the hydrochloride basic with NH_3. The pre bases was obtained which was recrystallized from ethanol/H_2O (2.1).

The compound 3-N-substituted phenyl hydantoin was characterized by elemental analysis. tlc i.r. and p.m.r. spectra. The tlc gave single spot.

IR (KBr) = 1760-1740 cm^{-1} due to c = 0 gp at position - 4 of hydantoin ring). 1710-1700 cm^{-1} (due to c = o gp at position - 2 of hydantoin) 3100 - 2998 cm-1 (die to CH stretching frequency of aryl gp) 1200 - 1190 cm (due to NH).

PMR = 7.39 (5H, m, Ar - H),

9.1 (1H. s C = NH), 4.1- 4.3

(1H, s. - NH), 4.14 (2H, - CH_2).

Structure: 3-N-(p-substituted phenyl)-1-N-(N-phenyl guanidyl) amidino hydantoin

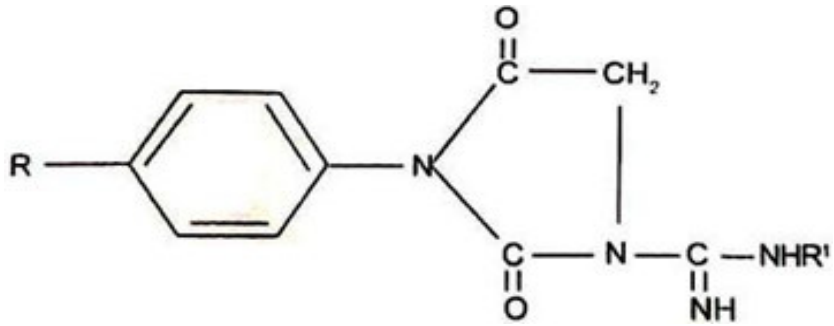


Table - 1 : Showing Nature of R, R

Nature of R	Nature of R'	M.P. ^0C	Yield	Mol. Formula	C	H	N
P – H	$-C_6H_5$	161	50	$C_{16}H_{14}N_4O_2$	61.73,(61.62)	4.18,(4.02)	13.50,(13.41)
P – cl	$-C_6H_5$	165	55	$C_{16}H_{13}N_4O_2cl$	55.57,(61.62)	3.47,(3.35)	12.15,(12.01)
$P–CH_3$	$-C_6H_5$	152	52	$C_{17}H_{16}N_4O_2$	62.76,(62.62)	4.61,(4.55)	12.92,(12.82)
$P-OCH_3$	$-C_6H_5$	168	56	$C_{17}H_{16}N_4O_3$	59.82,(59.71)	4.39, (4.24)	12.31,(12.22)
$P-OC_2H_5$	$-C_6H_5$	170	54	$C_{18}H_{16}N_4O_3$	60.84,(60.72)	4.78, (4.62)	11.83,(11.72)
$P-NO_2$	$-C_6H_5$	157	58	$C_{16}H_{13}N_5O_4$	53.93,(53.82)	3.37, (3.25)	15.73,(15.62)
P – H	$-C_6H_4cl$	156	51	$C_{16}H_{13}N_4O_2cl$	55.57,(55.42)	3.47, (3.32)	12.15,(12.03)
P – cl	$-C_6H_4cl$	172	56	$C_{16}H_{12}N_4O_2cl_2$	50.52,(50.42)	2.89, (2.72)	11.05,(10.92)
$P–CH_3$	$-C_6H_4cl$	180	54	$C_{17}H_{15}N_4O_2cl$	56.74,(56.64)	3.89, (3.73)	11.68,(10.52)
$P-OCH_3$	$-C_6H_4cl$	169	52	$C_{17}H_{15}N_4O_3cl$	54.32,(54.28)	3.72, (3.62)	11.18,(11.00)
$P-OC_2H_5$	$-C_6H_4cl$	155	53	$C_{18}H_{17}N_4O_3cl$	55.45,(55.32)	4.10, (3.95)	10.78,(10.62)
$P-NO_2$	$-C_6H_4cl$	170	50	$C_{16}H_{12}N_5O_4cl$	49.16,(49.02)	2.81,(2.71)	14.34,(14.24)
P – H	$-C_6H_4CH_3$	161	56	$C_{17}H_{16}N_4O_2$	62.76,(62.60)	4.61,(4.52)	12.92,(12.82)
P – cl	$-C_6H_4CH_3$	152	59	$C_{17}H_{15}N_4O_2cl$	56.74,(56.62)	3.89, (3.72)	11.68,(11.52)
$P–CH_3$	$-C_6H_4CH_3$	170	50	$C_{18}H_{18}N_4O_2$	63.71,(63.59)	5.01, (4.95)	12.38,(12.25)
$P-OCH_3$	$-C_6H_4CH_3$	157	60	$C_{18}H_{18}N_4O_3$	60.84,(60.72)	4.78, (4.62)	11.83,(11.72)
$P-OC_2H_5$	$-C_6H_4CH_3$	175	61	$C_{19}H_{20}N_4O_3$	61.78,(61.64)	5.14, (5.04)	11.38,(11.25)
$P-NO_2$	$-C_6H_4CH_3$	163	54	$C_{17}H_{15}N_5O_4$	55.13,(55.00)	3.78, (3.62)	15.13,(14.98)
P – H	$-C_6H_4OCH_3$	172	50	$C_{17}H_{16}N_4O_3$	59.82,(59.75)	4.39, (4.22)	12.31,(12.15)
P – cl	$-C_6H_4OCH_3$	180	51	$C_{17}H_{15}N_4O_3cl$	54.32,(54.18)	3.72, (3.62)	11.18,(11.02)
$P–CH_3$	$-C_6H_4OCH_3$	169	50	$C_{18}H_{18}N_4O_3$	60.84,(60.72)	4.78, (4.62)	11.83,(11.70)
$P-OCH_3$	$-C_6H_4OCH_3$	174	52	$C_{18}H_{18}N_4O_4$	58.22,(58.12)	4.58, (4.43)	11.40,(11.28)
$P-OC_2H_5$	$-C_6H_4OCH_3$	180	52	$C_{19}H_{20}N_4O_4$	59.22,(59.06)	4.93, (4.81)	10.90,(10.78)
$P-NO_2$	$-C_6H_4OCH_3$	169	50	$C_{17}H_{15}N_5O_5$	52.84,(52.72)	3.62, (3.59)	14.50,(14.38)
P – H	$-C_6H_4OC_2CH_3$	173	50	$C_{18}H_{18}N_4O_3$	60.84,(60.72)	4.78, (4.62)	11.83,(11.71)
P – cl	$-C_6H_4OC_2CH_3$	164	52	$C_{18}H_{17}N_4O_3cl$	55.45,(55.32)	4.10, (3.87)	10.78,(10.62)
$P–CH_3$	$-C_6H_4OC_2CH_3$	188	50	$C_{19}H_{20}N_4O_3$	61.78,(61.62)	5.14, (5.02)	11.38,(11.27)
$P-OCH_3$	$-C_6H_4OC_2CH_3$	170	55	$C_{19}H_{20}N_4O_4$	59.22,(59.11)	4.93, (4.79)	10.90,(10.78)
$P-OC_2H_5$	$-C_6H_4OC_2CH_3$	189	50	$C_{20}H_{22}N_4O_4$	60.15,(60.01)	5.26, (5.12)	10.52,(10.43)
$P-NO_2$	$-C_6H_4OC_2CH_3$	181	55	$C_{18}H_{17}N_5O_5$	54.00,(53.89)	4.00, (3.87)	14.00,(13.39)
P – H	$-C_6H_4NO_2$	177	45	$C_{16}H_{13}N_5O_4$	53.95,(53.82)	3.37, (3.28)	15.73,(15.62)
P – cl	$-C_6H_4NO_2$	187	49	$C_{16}H_{12}N_5O_4cl$	49.16,(49.00)	2.81, (2.74)	14.34,(14.22)
$P–CH_3$	$-C_6H_4NO_2$	190	50	$C_{17}H_{15}N_5O_4$	55.13,(55.01)	3.78, (3.64)	15.13,(15.03)
$P-OCH_3$	$-C_6H_4NO_2$	164	52	$C_{17}H_{15}N_5O_5$	52.84,(52.72)	3.62, (3.55)	14.50,(14.42)
$P-OC_2H_5$	$-C_6H_4NO_2$	173	55	$C_{18}H_{17}N_5O_5$	54.00,(53.89)	4.00, (3.88)	14.00,(13.92)
$P-NO_2$	$-C_6H_4NO_2$	181	50	$C_{16}H_{12}N_6O_6$	47.88,(47.72)	2.74, (2.62)	17.45,(17.34)

3.Conclusion-

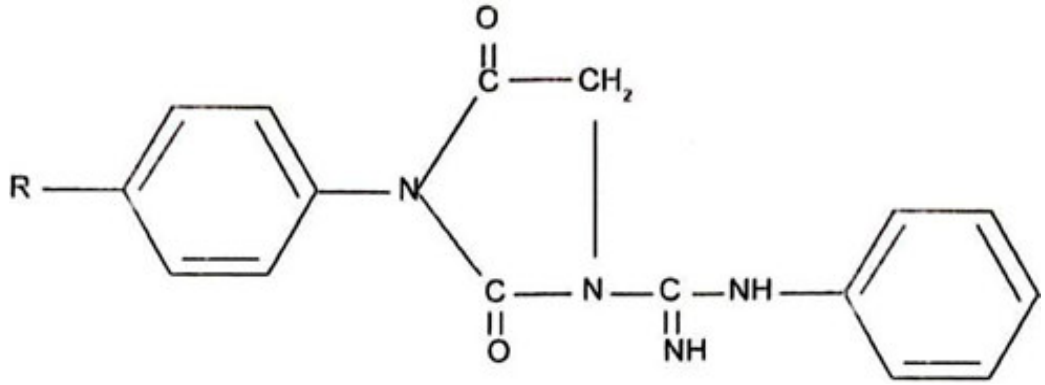
In the present investigation the anticonvulsant activity of each compound was evaluated by chenoshock procedure adult albino mise weighing 20-25 gms were used as experimental animals they were maintained at ambient temperature of 20 1^0C on an adequate diet and had free access of food and water except during the short period when they were removed from their cages for testing.

In table I compound II and IV were found to be inactive while compound I and III showed 33.33% and 50% protection respectively in table II compound II and IV were found to be inactive compound II showed maximum protection and lowest mortality rate at 24 hours and seems to possess comparatively satisfactory anticonvulsant activity.

The Observations of the present study indicate that the hydantoin derivatives which were subjected to pharmacological screening do not exhibit significant anticonvulsant activity. Only compound III table I showed comparatively satisfactory anticonvulsant actively as it gave maximum protection against leptazole induced convulsions and had the lowest mortality rate from the present study it seems that in general there should be at least one substituent present at C5 in the hydantoin ring in order that it may have pronounced anticonvulsant activity It may there fore be concluded that I –N, 3 – N disubstituted derivatives possess slight anticonvulsant activity. But do no show any analgesic activity.

Table No. 2

4. SCREENING RESULT OF 3-N-(p- substituted phenyl) 1-N-(N- phenyl guinidyl) amidino hydantoin



Compound No.	Nature of R	No. of Animals	Anticonvulsant Activity					Analgesic activity/mean of reaction time in min
			Mean of onset of convulsion in Min (Mean+SE)	% Protection against convulsion	% Death in 1 hrs	% Mortality after 1 hrs	% Mortality after 24 hrs	
I	-H	6	5.00±1.15	33.33	16.66	33.33	33.33	0.5±0.42
II	-Cl	6	7.20±1.65	0	33.33	66.66	66.66	0.50±0.20
III	$-CH_3$	6	8.15±1.72	50.00	16.66	16.66	16.66	0.36±0.12
IV	$-OC_2H_5$	6	6.80±1.21	0	66.66	66.66	66.66	1.32±1.06
	Control	6	7.30±1.80	0	100	100	100	3.70±1.63

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