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Synthesis of some new compounds with possible anticonvulsant and analgesics activities

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Abstract

Anticonvulsants may be defined as agents that prevent or diminish severity of convulsive seizures. The anticonvulsnats principal therapeutic application is in the treatment of the different varieties of epilepsy. Substituted Barbiturates posses anti convulsant activity. Series of Amides and Imids has also been found to be anticonvulsants. Quinazolinones when prepared and tested pharmacologically possessed anti convulsant activity.

In addition to above compounds, a few other compounds have been prepared and found active against convulsive seizures. Imidazoles, Imidazolidinones and Imidazolones showed moderate activity in control of epileptic seizures. Oxadiazoles, thiazoles, thiadiazole derivatives were prepared and tested for their effectiveness. Various N^3 substituted hydantoin and their sodium salts were reported to possess anticonvulsant activity.

Analgesics are the drugs which subside pain partially or completely without the loss of consiousness. Morphine which was isolated from opmum was the oldest alkaloid used as pain relieving substance.

Thus 2-aminothiazole when treated with chloro acetyl chloride to get chloroacetyl derivative which on treatment with an alkalimetalcyanate in pressure of phase transfer catalyst gave N^{3-} (thiazol-2-yl)-hydantoin, the product is then treated with chloroacetyl chlodride to get N'-(chloro-acetyl)-,N'-(3-chloropropinonyl)- and N'- (4-chlorobutryl)-N^{3-} (thiazol-2-yl)-hydantoins. The disubstituted hydantoin were finally condensed with various amines to get various derivatives of disubstituted hydantoins which may found to possess anticonvulsant and analgesic activity.

Key words : Anticonvulsants, analgesics, epilepsy, phase transfer catalyst, alkaloids, convulsive seizures, therapeutic.

Introduction

Barbituric acid and its derivatives are known to possess anticonvulsant and hypnotic at a cellular level and in whole organism[1-4] Oxazolidinedinone[5], Succinimides[6], Primidone[7] and Acylureas[8] have also been found to have significant anticonvulsant activity. A review of literature shows that hydantoins which resemble the above mentioned heterocyclic compounds in having the prerequisite structure, -CONH-CH- with X=0 or H2 for a compound to be an effective antipileptic also exhibit marked pharmacological properties[9].

Hydantoins and allied derivatives are of great interest to medicinal chemists due to their diverse biological activities, like lowering of blood sugar in mammals[10], antiarrhythemic[11, 12], antitubercular[13], antiinflammatory[14], antitumar[15,16] and anticonvulsant properties[17,18]. The hydantoin ring shows nucleophillic activity at the nitrogen atoms. In most cases N-3 substitution is preferred over N-1 because of the polarizability of the N-H bond at N-3 and the ready formationi of the N-3 anion which is more nucleophillic than the unionized N-1 nitrogen. The activity and polarizability associated with N-3 are caused by the two adjacent electron withdrawing carbonyl groups. N-1 has only one such group and, therefore, behaves much like a norman amide or lactam. Workers have demonstrated that certain fluorine containing 1,3,5-trisubotituted hydantoins show anticonvulsant and analgesic properties[19]. A perusal of literature revealed sufficient scope for further studies on bioactive hydantoins and allied derivatives. N-1 and N-3 disubstituted derivatives of phenytoin and 5-phenyl-5-alkyl hydantoins can be prepared and activity strongly dependent on the type of substitution[20-23].

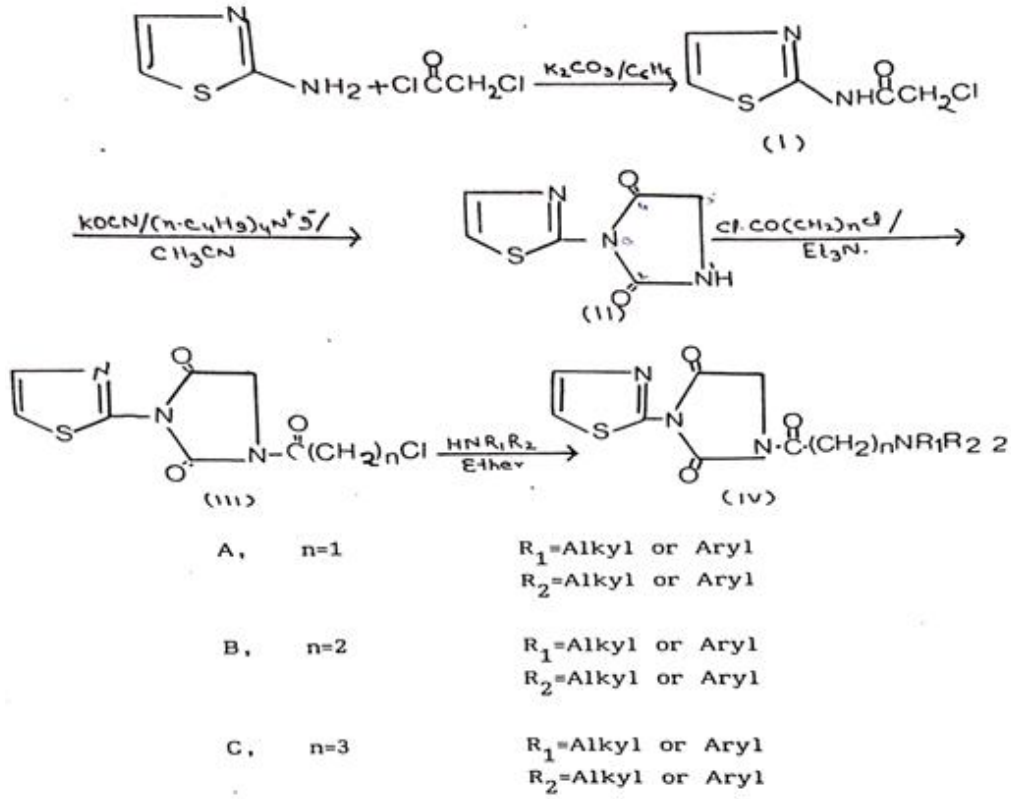
In view of the great therapeutic activity of N-1 and N-3-disubstituted hydanoins, it seemed desireable to synthesize some N-1 and N-3-disubstituted hydantoins.

Thus 2-aminothiazole when treated with chloroacetyl chloride to get chloroacetyl derivatives which on treatment with an alkalimetalcyanate in presence of phase transfer catalyst gave N3-(thiazol-2-yl)-hydantoin, so obtained was further treated with chloroacetyl chloride, 3-chlorpropionyl chloride and 4-chlorobutryl chloride to get N'-(chloro-acetyl)-, N'-(3-chloropropionyl)- and N'-(4-chlorobutryl)-N3-(thiazol-2-yl)-hydantoins. The disubstituted hydantoins were finally condensed with various amines to get various derivatives of disubstituted hydantoins which may found to possess anticonvulsant and analgesic activity.

Keeping in view these facts it was thought worthwhile to prepare various compounds whch may prove to be fruitful anticonvulsant and analgesic with lesser toxicity.

The amines used in the condensation are diethyl amine, dipropylamine, di-isopropylamine, morpholine and 2-aminopyridine.

The precursor for (IV) is 2-aminothiazole. These compounds (IV) have been characterized on the basis of i.r. spectra, elemental analysis and the purity of compounds have also been checked by tlc.



Experimental

Preparation of chloroacetyl-2-aminothiazole :

Freshly distilled chloroacetyl chloride (0.1M) in dry benzene was gradually added to 2-aminothiazole (0.1M) dissolved in drybenzene (60ML) containing potassium carbonate with constant stiring. The reaction mixture was refluxed on water- bath at 70^{0}C for 2 hrs. Excess benzene was distilled off and the residue was treated with sodium bicarbonate solution and washed with water to remove acid impurities. The product was recrystallized from ethanol.

Yield: 60%	m.pt. : 188^{0}C	
Anal found	N: 15.91% S	18.07%
Calc. for $C_5H_5N_2SOCl$	N: 15.86% S	18.13%

Compound was characterized on the basis of elemental analysis and i.r. spectra. Purity of this compound was also checked by tlc. The i.r. spectra showed characteristic absorption peaks in the region of 1650-1580 cm^{-1} and 1355-1310 cm^{-1} corresponding to C=0 group and C-N bond respectively. In addition, compound exhibited a strong band around 1705-1665 cm^{-1} characteristic of O=C-N group. Absorption band in the region of 3230-3160cm^{-1} indicated NH-stretching frequency. Compound have also been characterized by appearance of additional new resonance signal as singlet at 21-22 corresponds to protons of –$COCH_2Cl$ group.

Preparation of N_3-(thiazol-2-yl)-hydantoin :

Tetra-n-butyl ammonium iodide (500 mg) was added to a solution of chloroacetyl-2-aminothiazole (0.05 mol) and potassium cyanate (0.05 M) in acetonitrile and the mixture was stirred at 60-80^{0}C for 8 hrs. The mixture was then cooled to room temperature, the solvent evaporated and the crude product was washed with water three times. The residual solid was then dissolved in methanol and the insoluble solid was filtered off. The solvent was evaporated to give the product.

Yield:	48%	mpt. 96^{0}C
Anal found	N, 25.10%	S, 19.21%
Calc. for $C_6H_5N_3SO$;	N 25.14%	S 19.16%

The i.r. spectra of this compound showed characteristic absorption peaks in the region of 1760-1740 cm^{-1} (C=O absorbance at position-4) and 1710-1700 cm^{-1} (C=O absorbance at position-2). A broad absorption peak is noticed between 3210-3210 cm^{-1} due to –NH- at position-3 (characteristic of –CONHCO-bond in the cyclic system). An absorption peak in the region of 1355-1310 cm^{-1} corresponds to C-N band. The PMR spectra exhibit NH-stretching frequency by a broad, weak variable resonance signal at 924-576 (determined by D_2O exchange).

Preparation of N'-(Chloracetyl) – N^3-(thiazol-2-yl)-hydantoin[19] :

Distilled chloroacetyl chloride (0.1M) in dry toluene was gradually added to N^3-(thiazol-2-yl)-hydantoin(0.1M) dissolved in dry toluene, containing triethyl amine with constant stirring. The reaction mixture was refluxed for 8 hrs. The dark brown reaction mixture on cooling, gave desired product which was filtered, washed ten times with petroleum ether (40-60^{0}C) and finally recrystallized with ethyl acetate.

Yield : 48% mpt. 216.217^{0}C

Similarly N'-(3-chloropropionyl)-N^3-(thiazol-2-yl)-hydantoin and N'-(4-chlorobutyl)-N^3-(thiazol-2-yl)-hydantoin were prepared and are summarized in Table 1. Purity of these compounds were also checked by tlc.

Preparation of N'-(dipropylamine acetyl)-N3-(thiazol-2-yl)-hydantoin[19] :

To a solution of N'-(chloroacetyl)-N^3-(thiazol-2-yl) hydantoin (0.01M) in ether, dipropylamine (0.03M) was gradually added at 0^{0}C and the reaction mixture was refluxed for 2 hrs. After reaction mixture was filtered and recrystallized from solvent ether.

Similarly, N'-(Diisopropyl aminoacetyl), N'-(morpholine acetyl), N'-(pyridino-2-amino acetyl)-N^3- (thiazol-2-yl) hydantoins were prepared and are summarized in Table 2.

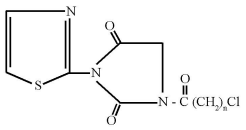
Preparation of N'-[3-(diethylamino) propionyl) – N3- (thiazol-2-yl) hydantoin[19]

The diethyl amine (0.03M) in ether was added dropwise to a ethereal solution of N' (3-chloropropionyl)-N3- (thiazol-2-yl)-hydantoin (0.01 M) at 0^{0}C. The resulting mixture was refluxed for 8 hrs to give desired product which was filtered and recrystallized from solvent ether.

Similarly, N'-[3-(dipropylamino) propionyl]-, N'-[3-diisopropylamino) propionyl]-, N'-[3-(morpholino) propionyl]-N'-[3-(pyridine-2-amino) propionyl]-N^3-(thiazol-2-yl)-hydantoins were prepared and are summarized in Table-3.

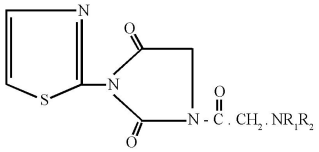
Similarly N'-[4-(dipropylamino)butryl]-and N'-[4-(di-isopropylamino) butryl]-N3 – (thiazol-2-yl)-hydantoins were also prepared and are summarized in Table 4.

Table-1 : Formation of N'-(ω-CHLOROACYL)-N^3-(THIAZOL-2-YL)-HYDANTOIN



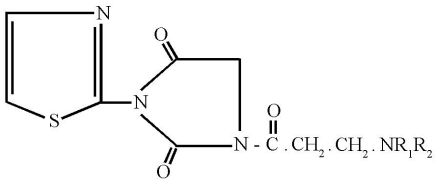
Nature of n	Molecular Formula	Melting point	Yield (%)	Elemental Analysis		
				Nitrogen		Sulphur
1	$C_8H_6N_3SO_3Cl$	216-217	48	Cal.	16.18	12.33
				Found	16.24	12.48
2	$C_9H_8N_3SO_3Cl$	124	48	Cal.	15.36	11.70
				Found	15.28	11.8
3	$C_{10}H_{10}N_3SO_3Cl$	264	45	Cal.	14.61	11.13
				Found	14.58	11.10

Table-2 : Formation of N'-(ALKYL-ARYL-ACETYL) -N^3-(THIAZOL-2-YL)-HYDANTOIN



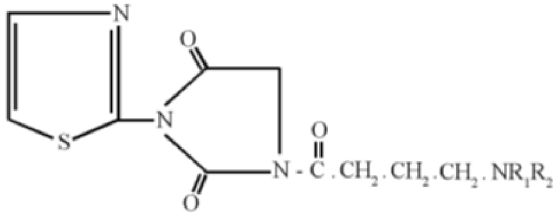
Nature of NR_1R_2	Molecular Formula	Melting point	Yield (%)	Elemental Analysis		
				Nitrogen		Sulphur
Dipropyl	$C_{14}H_{20}N_4SO_3$	216	41	Cal.	17.28	9.88
				Found	17.20	9.92
Di-isopropyl	$C_{14}H_{20}N_4SO_3$	206	42	Cal.	17.28	9.88
				Found	17.22	9.80
Morpholino	$C_{12}H_{14}N_4SO_4$	186	46	Cal.	18.06	10.32
				Found	18.00	10.26
Pyridino-2	$C_{13}H_{11}N_5SO_3$	101-103	42	Cal.	22.08	10.09
				Found	20.10	10.11

Table-3 : Formation of N'-3-[3-(ALKYL-ARYLAMINO) –PROPIONYL]-N3- (THIAZOL-2-YL)-HYDANTOIN



Nature of NR_1R_2	Molecular Formula	Melting point	Yield (%)	Elemental Analysis		
				Nitrogen		Sulphur
Diethyl	$C_{13}H_{18}N_4SO_3$	110	42	Cal. Found	18.06 18.14	10.32 10.46
Dipropyl	$C_{15}H_{22}N_4SO_3$	114	40	Cal. Found	16.57 16.49	9.47 9.40
Di-isopropyl	$C_{15}H_{22}N_4SO_3$	106-107	43	Cal. Found	16.57 16.68	9.47 9.31
Morpholino	$C_{13}H_{16}N_4SO_4$	118-120	36	Cal. Found	17.28 17.20	9.88 9.90
Pyridino-2	$C_{14}H_{13}N_5SO_3$	90	35	Cal. Found	21.15 21.23	9.67 9.52

Table-4 : Formation of N'- [4-(DIALKYLAMINO)–BUTRYL-N^3- (THIAZOL-2-YL)-HYDANTOIN



Nature of NR_1R_2	Molecular Formula	Melting point	Yield (%)	Elemental Analysis		
				Nitrogen		Sulphur
Di-propyl	$C_{16}H_{24}N_4SO_3$	117	41	Cal. Found	15.91 15.86	9.09 9.00
Di-isopropyl	$C_{16}H_{24}N_4SO_3$	126-128	43	Cal. Found	15.91 15.99	9.09 10.10

Result

N^1-N^3-disubstituted hydantoins were synthesized and screened for anticonvulsant and analgesic

activity. Nature of substitution at position of hydantoin ring was thiazole moiety, while at position 3 alkylaryl aminoacyl chain was used for replacing H atom of hydantoin ring.

Anticonvulsant activity of these compounds was determined against leptazole-induced seizures in mice. The number of animals not exhibiting convulsions during 60 min after injection of leptazole were expressed in terms of percentage protection. The details of screening results of compounds are summarized in Table 1 to 3.

Compounds afforded no significant protection against convulsions induced by leptazole in mice. The percent protection in animals was found to be 16.67 to 66.67%. Compound I, II (Table 1) and VIII (Table 3) were found to be inactive. Compound I of Table 2 showed 66.67% protection in mice. Compound II (Table 2) and II (Table 3) have lowest percentage of protection i.e. 16.67%. Compound (IV) (Table 1) and V (Table 2) showed minimum mortality at 24 hr. Various compounds offer varied degree of protection against death in first hr following leptazole administration in comparison to control. All compounds did not shown analgesic activity in tail pinc test in mice.

Discussion

In the present study, a series of N1–N3 disubstituted hydantoin derivatives containing thiazole moiety were successfully synthesized and characterized using spectral and analytical techniques. The synthesized compounds were evaluated for their anticonvulsant and analgesic activities. The pharmacological screening results indicated that most of the compounds exhibited weak to moderate anticonvulsant activity against leptazole-induced seizures in mice, while none of the compounds showed significant analgesic activity in the tail pinch test.

Structure–activity relationship studies suggested that substitution at the N-3 position of the hydantoin ring plays an important role in modulating anticonvulsant activity. It was observed that lower molecular weight derivatives showed relatively better activity, whereas increasing the alkyl chain length generally led to a decrease in activity. Among all synthesized compounds, selected derivatives demonstrated comparatively better anticonvulsant potential, indicating that hydantoin scaffold remains a promising pharmacophore.

Overall, the study highlights that although the synthesized compounds possess limited biological activity, they provide a useful foundation for further structural modifications toward the development of more potent anticonvulsant agents.

Scope of future Research :

The present work opens several avenues for future research in the development of biologically active hydantoin derivatives. Further studies can be focused on structural modification of the hydantoin nucleus by introducing different electron-donating and electron-withdrawing substituents to enhance pharmacological activity. Optimization of substitution at N-1 and N-3 positions may lead to compounds with improved anticonvulsant potency and reduced toxicity.

In addition, advanced pharmacological studies including different seizure models (such as MES model), neurotoxicity evaluation, and mechanism-based studies (*e.g.*, GABAergic pathway interaction) should be carried out to better understand the mode of action of these compounds. Molecular docking and computational studies can also be employed to predict receptor binding affinity and guide rational drug design.

Further, exploring hybrid molecules by combining hydantoin scaffold with other biologically active heterocycles (such as oxadiazoles, triazoles, or quinazolinones) may result in compounds with dual or enhanced therapeutic activity. Finally, detailed pharmacokinetic and in vivo studies are necessary to assess drug-likeness and clinical applicability of these compounds.

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