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Microwave Assisted Synthesis and Biological Evaluation of Hydantoin Derivatives

DINESH D. RISHIPATHAK, S.C. PAL and D.P. BELSARE*
Department of Pharmaceutical Chemistry, N.D.M.V.P. Samaj's College of Pharmacy
Gangapur Road, Nashik-422 002, India
E-mail: drishipathak@rediffmail.com

In the present investigation different substituted hydantoins and their N-Mannich bases were synthesized under microwave and evaluated for their anticonvulsant activity. The rapid and highly efficient synthesis of hydantoin derivative can be achieved under microwave irradiation which results in the improvement in yield and reduction in time of reaction. Among the 5,5-disubstituted 2,4-imidazolidinedione (hydantoin) derivatives, the compounds having both alkyl substituents are less active *i.e.* the latency to induce convulsions is less than that of the compounds having substituent either phenyl or substituted phenyl. [**S-2** $p < 0.05$ and **S-4** $p < 0.001$] Among the N^3-aminomethylated derivatives (N-Mannich bases), The compound (**S-4B**) derived by using unsubstituted primary aromatic amine, is more active than the compound (**S-2B**) derived by using substituted primary aromatic amine.

Key Words: Hydantoins, N-Mannich bases, Convulsions.

INTRODUCTION

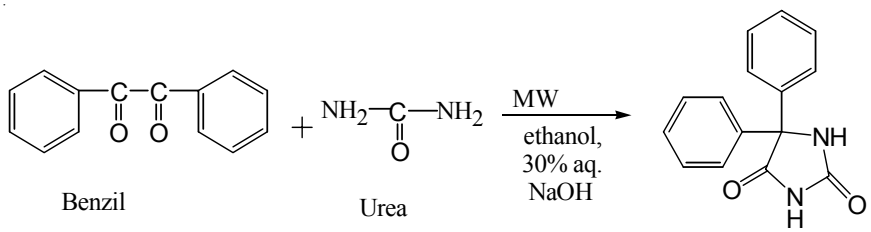
Epilepsy is one of the most common disorders of the central nervous system, worldwide. There is an ever-increasing need of research into the newer molecules for treating the epileptic seizures[1]. Epilepsy is a syndrome, characterized by paroxysmal, excessive and hypersynchronus discharges of large number of neurons. Primary use of anticonvulsant drugs is in the prevention and control of epileptic seizures. Hydantoins are the most common choice for the treatment of epileptic seizures[2-4].

The purpose of present investigation was to synthesize different substituted hydantoins and their N-Mannich bases under microwave as well as by conventional method and their evaluation for anticonvulsant activity.

N-Mannich bases have been proposed as potentially useful prodrug candidates for NH-acidic compounds such as various amides, imides, carbamates, hydantoins and urea derivatives as well as for aliphatic or aromatic amines. The concept of Mannich bases (Mannich aminomethylation) may be useful for improving the dissolution behavior of poorly soluble drug in an effort to improve the oral bioavailability[5-7]. Microwave assisted

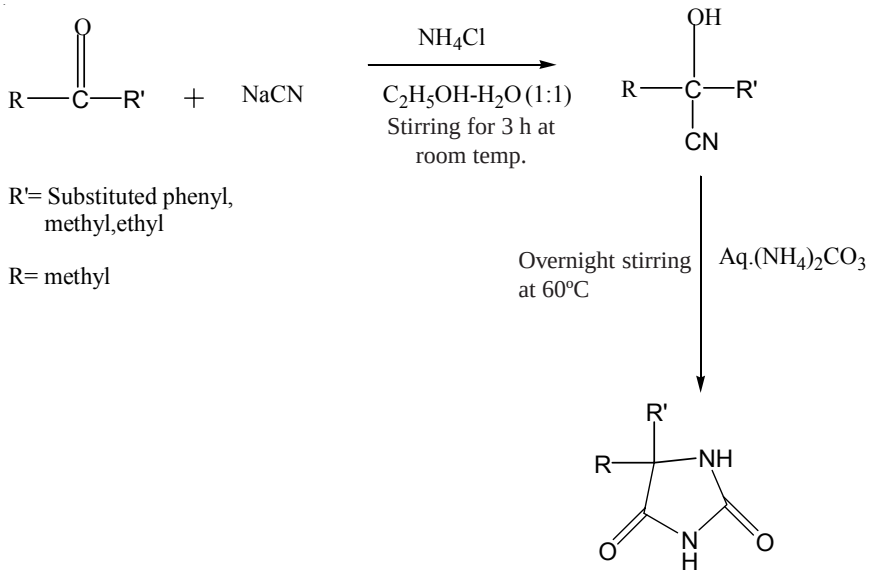
organic reaction enhancement (MORE) chemistry offers a simple, non-conventional technique for the synthesis of a wide variety of compounds having medicinal, pharmaceutical and commercial importance. Highly accelerated reaction rate is the main advantage, which enables chemist to carry out a synthesis in much lesser time and in reasonably good yields[8]. Now a days a modification of commercial equipment can be used having maximum power of 900 watts with power setting arrangement as P-1 to P-9 and H in increasing order. It also has temperature settings and a sensor for measuring the temperature of reaction mixture.

The various schemes adapted for the synthesis of hydantoin derivatives are outlined here,



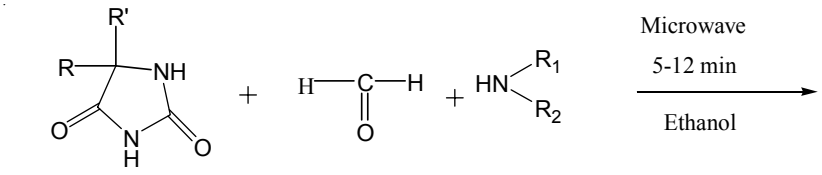
Benzil + Urea → 5,5-Diphenyl-2,4-imidazolidinedione

Scheme-I (Ref. 9)



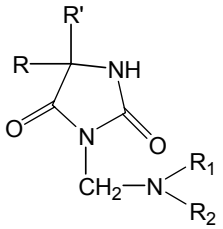
5,5-Disubstituted hydantoin

Scheme-II (Ref. 10)



5,5-disubstituted Hydantoin Aq.formaldehyde an amine

R′ = phenyl, substituted phenyl, methyl, ethyl
R = methyl, phenyl, *n*-propyl



N^3(substituted aminomethyl)-5,5-di-substituted-hydantoin

Scheme-III

EXPERIMENTAL

Melting points were taken in open glass capillary using Elico melting point apparatus and are uncorrected. Thin layer chromatography was done with silica gel G as adsorbant. The spots were detected by exposure to iodine vapours. Infrared spectra of compounds were recorded on Schimadzu IR 408 spectrophotometer model using Nujol as medium. Proton (^{1}H) NMR spectra of compounds were recorded on BROOT spectrophotometer (800 MHz) using DMSO-d_6 as solvent, at Analytical Center, University of Pune. The elemental analysis (CHN) of compounds was carried out at SAIF IIT-Mumbai. All microwave reactions were carried on Raga's Electromagnetic System with automatic power setting from P-1 to P-10. The reactions were started at power P-5 for initial 2 min and after every 2 min reaction mixtures was monitored for completion of the reaction with the help of TLC.

Synthesis of hydantoins under microwave[11,12]

A) 5,5-Diphenyl-2, 4-imidazolidinedione (Phenytoin) (S-1): Compound **S-1** was synthesized according to **Scheme-I** by using a mixture of 5.3 g (0.025 mol) of benzil, 3.0 g (0.05 mol) urea, 15 mL 30 % aqueous sodium hydroxide and 75 mL of ethanol.

IR (Nujol, ν_{max}, cm^{-1})[13] 730 (C-H deformation) 1490-1430 (phenyl ring breathing), 1720 (C=O stretching-C_4), 1780 (C=O stretching-C_2), 3200 (N-H stretching).

B) 5,5-Dimethyl-2, 4-imidazolidinedione (S-2): Compound **S-2** was synthesized by using 7.13 g (0.123 mol) acetone and 5 g (0.1 mol) of sodium cyanide in 12 mL water to give the cyanohydrin derivative as a intermediate. Then the cyanohydrin 4.25 g (0.05 mol) and freshly powdered ammonium carbonate 9.6 g (0.1 mol) were placed in reaction vessel and the mixture was ground until a fine powder was obtained (0.5 mol), then the reaction mixture was irradiated in the microwave oven at full power. On completion of the reaction, the mixture was poured in 20 mL water, the product obtained was filtered and recrystallized from water.

IR (Nujol, ν_{max}, cm^{-1})[14] 1150 (C-$(CH_3)_2$ stretching) 1450 (C-H deformation) 1710 (C=O stretching C_4) 1780 (C=O stretching-C_2) 3030 (C-H stretching). ^{1}H NMR (DMSO-d_6)[15] δ ppm 1.22 (s, 6H), 3.50 (s, 1Ha), 8.00 (s, 1Hb).

C) 5-Methyl-5-phenyl-2,4-imidazolidinedione (S-4): Compound **S-4** was synthesized by using acetophenone (0.0625 mol), ammonium chloride (5 g), sodium cyanide (0.094 mol) and ammonium carbonate (0.5 mol) according to **Scheme-II**.

IR (Nujol, ν_{max}, cm^{-1}) 1480 (C-C stretching), 1720 (C=O stretching-C_4), 1790 (C=O stretching-C_2), 2980 (C-H stretching), 3300 (N-H stretching). ^{1}H NMR (DMSO-d_6) δ ppm 1.15 (s, 3H), 6.90 (s, 5H) 3.40 (s, 1Ha), 8.10 (s, 1Hb).

D) 5-Methyl-5-(*p*-hydroxyphenyl)2,4-imidazolidinedione (S-5): Compound **S-5** was synthesized by using *p*-hydroxy acetophenone. IR (Nujol, ν_{max}, cm^{-1}) 1400 (C-O stretching) 1700 (C=O stretching-C_4) 1790 (C=O stretching-C_2) 3350 (N-H deformation) 3530 (O-H stretching). ^{1}H NMR (DMSO-d_6) δ ppm 1.20 (s, 3H), 6.85 (d, 2H), 6.75 (d, 2H), 4.55 (s 1H,OH) 3.55 (s, 1Ha), 8.15 (s, 1Hb).

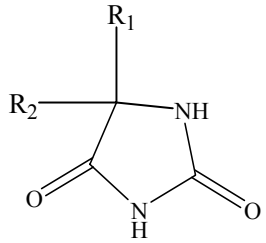
The physicochemical characteristics of these N^3-aminomethylated derivatives **S-1A** to **S-5C** are reported in Table-1.

Synthesis of N-Mannich bases of hydantoins under microwave

A) N^3-[(*p*-methoxyanilino)methyl]-5,5-diphenyl-2,4-imidazolidinedione (S-1A): 5,5-Diphenyl-2,4-imidazolidinedione, 1.26 g (0.005 mol) was dissolved in 20 mL of hot ethanol. To this solution 0.63 g (0.0051 mol) of *p*-methoxy aniline dissolved in small amount of ethanol and 0.42 mL (0051 mol) of 37 % formaldehyde were added. The reaction mixture was irradiated under MW, filtered hot and then cooled to room temperature. The solvent was allowed to evaporate and the product was collected, washed with small amount of cold aqueous ethanol and recrystallized from acetone.

IR (Nujol, ν_{max}, cm^{-1}) 1230 (C-N stretching, Ar-N), 1010 (C-O stretching alkyl-O), 1250 (C-O stretching aryl-O), 1080 (C- N stretching, aliphatic), 670-760 (C-H Aromatic), 1720 (C=O stretching-C_4), 1780 (C=O stretching-C_2), 3300 (N-H stretching).

TABLE-1
COMPARISON BETWEEN CONVENTIONAL AND MICROWAVE METHOD IN SYNTHESIS OF HYDANTOINS



Code	R_1/R_2	Reaction time		Yield (%) / m.p. (ºC)		Lit. m.p.[13]
		A (min)	B (min)	A	B	
S-1	$-C_6H_5$ / $-C_6H_5$	120	2.0	60.00 (296-297)	91.71 (297.298)	298
S-2	$-CH_3$ / $-CH_3$	O/N	3.0	70.23 (174-178)	95.23 (176.178)	174-177
S-3	$-CH_3$ / $-C_2H_5$	O/N	3.5	64.00 (144-146)	94.85 (146.148)	144-150
S-4	$-CH_3$ / $-C_6H_5$	O/N	–	75.85 (198-200)	–	199-201
S-5	$-CH_3$ / *p*-OH-C_6H_5	O/N	–	87.09 (258-260)	–	–

A = Conventional, B = Microwave, O/N = Overnight stirring at 60ºC.

B) N^3-[(*p*-methylanilino)methyl]-5,5-diphenyl-2,4-imidazolidinedione (S-1B): IR (Nujol, ν_{max}, cm^{-1}) 1240 (C-N stretching, Ar-N), 1080 (C-N stretching, aliphatic), 760-670 (C-H aromatic), 1720 (C=O stretching-C_4), 1790 (C=O stretching-C_2), 3290 (N-H stretching).

C) N^3-[(*p*-chloroanilino)methyl]-5,5-dimethyl-2,4-imidazolidinedione (S-2B): IR (Nujol, ν_{max}, cm^{-1}) 780 (C-Cl stretching), 1080 (C-N stretching, aliphatic), 1150 (C-(CH_3) stretching), 1710 (C=O stretching-C_4), 1790 (C=O stretching-C_2), 3390 (N-H stretching).

^{1}H NMR (DMSO-d_6) δ ppm 1.22 (s, 6H), 2.50 (d, 2H), 3.36 (s, 1Ha), 8.29 (s, 1Hb), 6.69 (d, 2Hc), 7.09 (d, 2Hd). Anal. ($C_{12}H_{14}N_3O_2Cl$), Calcd. (Found) %: C, 53.78 (52.68), H, 5.26 (5.36), N, 15.75 (14.92).

D) N^3-[(*p*-chloroanilino)methyl]-5-methyl-5-(*p*-hydroxyphenyl) 2,4-imidazolidinedione (S-5B): IR (Nujol, ν_{max}, cm^{-1}) 650 (C-Cl stretching), 1220 (C-O stretching), 1510 (N-H deformation), 1700(C=O stretching-C_4) 1790 (C=O stretching-C_2), 3400 (O-H stretching).

E) N^3-[(2,5-dichloroanilino)methyl]-5-methyl-5-(*p*-hydroxyphenyl) 2,4-imidazolidinedione (S-5C): IR (Nujol, ν_{max}, cm^{-1}) 720 (C-Cl stretching), 1380 (C-O stretching), 1710 (C=O stretching), 3410 (O-H stretching).

The N^3-aminomethylated derivatives (N-Mannich bases) **S-1B** to **S-5C** of the hydantoins, **S-1** to **S-5** were synthesized similarly as given in the procedure for compound **S-1A** by using 0.005 mol of the hydantoin derivative, 0.0051 mol of aqueous formaldehyde and 0.0051 mol of a primary or secondary amine such as aniline, substituted aniline or morpholine.

The physico-chemical characteristics of these N^3-aminomethylated derivatives **S-1A** to **S-5C** are reported in Table-2.

Biological evaluation

Anticonvulsant activity using pentylenetetrazole (PTZ) induced convulsions in mice[16,17]:

Animals: Swiss albino mice of either sex weighing 18-22 g were used for the study. Animals were housed for in group of five under standard laboratory condition and of temperature. (25 ± 2ºC) and humidity (55 ± 5 %) under 12:12 light dark cycle. They had free access to food and water. All experiments were done during the daytime. Food but not water was withheld 12 h before experimentation.

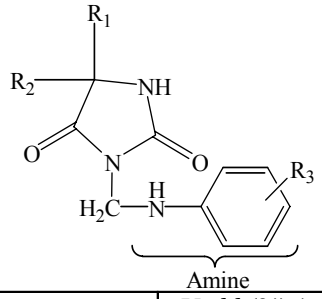
Procedure: The vehicle or the compounds were administered 0.5 h before administration of PTZ. Following observations were recorded immediately after administration of PTZ upto 0.5 h (**a**) latency to induce convulsions (**b**) number of convulsions (**c**) percent mortality.

Evaluation: (**a**) Increase in latency to induce convulsions and/or (**b**) decrease in number of convulsions and/or (**c**) decrease in per cent mortality indicates anticonvulsive potential of synthesized compound. Readings of synthesized compounds are compared with control.

RESULTS AND DISCUSSION

The starting material used for the synthesis of the different 5,5-disubstituted hydantoins was alkyl-alkyl/aryl/substituted aryl ketone through the formation of intermediate cyanohydrin derivative of the corresponding ketone. The N^3-aminomethylated derivatives of the different 5,5-disubstituted hydantoins were synthesized by the Mannich reaction for NH-acidic compounds using aqueous formaldehyde and different primary and secondary amines by conventional as well as microwave method[5,16]. The substitution occur at N-3 position, because the N_3-H acid dissociation constant (pK_a 9.12 for the hydantoin) much higher than that of N1-H (pK_a 14 or more)[18]. The reaction time by microwave method was considerably, in some cases drastically reduced as compared to the conventional method with a maximum 40 % increase in the yield of the compounds.

TABLE-2
COMPARISON BETWEEN CONVENTIONAL AND MICROWAVE METHOD IN SYNTHESIS OF N-MANNICH BASES OF HYDANTOINS



Code	$R_1/R_2/R_3$Amine	Reaction time		Yield (%) / m.p. (ºC)		Lit. m.p.[13]
		A (min)	B (min)	A	B	
S-1A	$-C_6H_5$/ $-C_6H_5$/ 4-OCH_3	60	12	54.00 (166-168)	83.00 (168-169)	167.5-169.5
S-1B	$-C_6H_5$/ $-C_6H_5$/ 4-CH_3	60	10	60.00 (170-172)	78.00 (170-172)	171.5-172.5
S-1C	$-C_6H_5$/ $-C_6H_5$/ Morpholine	120	–	50.00 (154-155)	–	153-155
S-2A	$-CH_3$/ $-CH_3$/ -H	180	7	75.10 (152-154)	88.50 154-155	154.5-155
S-2B	$-CH_3$/ $-CH_3$/ 4-Cl	–	10	–	75.00 (192-194)	193.5-194.5
S-3A	$-CH_3$/ $-C_2H_5$/ Morpholine	–	5	–	80.50 (144-146)	146-147
S-4A	$-CH_3$/ $-C_6H_5$/ -OH	–	10	–	90.00 (116-118)	–
S-4B	$-CH_3$/ $-C_6H_5$/ -H	60	7	64.20 (134-136)	86.60 (135-136)	136-136.5
S-5A	$-CH_3$/ *p*-OH-C_6H_4/ -H	–	8	–	89.10 (102-104)	–
S-5B	$-CH_3$/ *p*-OH-C_6H_4/ 4-Cl	–	10	–	92.00 (120-122)	–
S-5C	$-CH_3$/ *p*-OH-C_6H_4/ 2,5-dichloro	–	12	–	70.00 (132.134)	–

A = Conventional, B = Microwave.

The IR (Nujol) spectrum showed strong peak of carbonyls C_2 and C_4 of cyclic imide (CO-NH-CO) moiety at 1790-1770 and 1720-1700 cm^{-1}, respectively and the presence of a strong peak, that of N-H at 3490-3320 cm^{-1}, which are characteristic of hydantoin[14]. The presence of strong peak in the range of 1220-1020 cm^{-1}, those of aliphatic C-N stretch. is characteristic of aminomethylated compounds.

Anticonvulsant activity: Few of the synthesized hydantoins and N^3-aminomethylated derivatives of hydantoins were tested for anticonvulsant activity using pentylenetetrazole (PTZ) induced convulsions in mice.

In present study, all of the tested compounds showed: (**a**) increase in latency to induce convulsions (**b**) decrease in number of convulsions and (**c**) decrease in per cent mortality as compared to the control, pentylenetetrazole (PTZ).

Animals were pretreated with vehicle (polyethylene glycol, PEG-400, 0.1 mL, i.p.) or synthesized compounds (30/60/120 mg/kg) 0.5 h prior to PTZ (80 mg/kg, s.c.) latency and mortality recorded upto 0.5 after PTZ administration.

Animals treated with PTZ exhibited convulsions, the latency was 4.01 min. All the tested compounds showed anticonvulsant activity. Among these, the 5-methyl-5-phenylhydantoin (S-4) showed maximum activity reflected as significant increase in latency to induce convulsions ($p < 0.001$) (Table-3). The replacement of the phenyl ring by alkyl group *i.e.* 5,5-dimethyl-2,

TABLE-3
ANTICONVULSANT EFFECT OF SOME SYNTHESIZED HYDANTOIN DERIVATIVES IN MICE USING PENTYLENETETRAZOLE (PTZ) INDUCED CONVULSIONS

Code	Dose (mg/kg, i.p.)	Latency to induce convulsions (min)$^{\phi}$ (min ± SEM)	No. of convulsions	Mortality (%)
PTZ	80†	4.01 ± 0.38	4	80
Diazepam	2	–	–	0
S-2	60	6.75 ± 0.37‡	2	40
	120	9.03 ± 0.56	0	40
S-2B	30	9.49 ± 0.15*	2	40
	60	12.39 ± 1.26	0	0
S-4	30	14.40 ± 0.12*	1	20
	60	17.16 ± 1.28	0	0
S-4B	30	10.46 ± 0.83*	1	20
	60	13.10 ± 0.12	0	0

† = Subcutaneously i.p = Intraperitonially ϕ = Values are in mean ± SEM
‡ = $p < 0.05$, *$p < 0.001$ compared with control.

4-imidazolidinedione (**S-2**) decreases activity as indicated by decrease in latency to induce convulsions, (Table-3) which supports the literature data[3] that one of the substituent on the 5-position must be phenyl ring or aromatic group.

The activity study of N^3-aminomethylated derivatives showed that introduction of the aminomethyl function on N^3 increases the anticonvulsant activity *i.e.* for N^3-[(*p*-chloroanilino)methyl]-5,5-dimethyl-2,4-imidazol-idinedione (**S-2B**), the latency to induce convulsions was increased than that of **S-2**.

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