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Synthesis and Anticonvulsant Activity of Pyridazinone Derivatives

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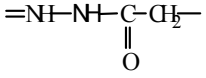
ABSTRACT: In the recent years there has been an increased interest in the pyridazinone ring system. Many investigations indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement is necessary for anticonvulsant activity. Many investigations indicated that the presence of at least one aryl group, one or two electron donor atoms and/or an NH group in a special spatial arrangement seems to be necessary for anticonvulsant activity. Therefore in the present article we report the synthesis of pyridazinone ring derivatives and their anticonvulsant screening through maximal electroshock seizure test.

KEY WORDS: Pyridazinone Derivatives, Anticonvulsant Activity

INTRODUCTION

Pyridazin-3(2H)-one derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activity ranging from cardiovascular properties, anti-inflammatory, antidiabetic, analgesic, anti AIDs, anticancer, antimicrobial and anticonvulsant activities[1]. In order to explore the activity associated with the structural moiety



various 6- substituted derivatives were synthesized and their anticonvulsant activity was tested[2]. A study of anticonvulsant agents reveals that the presence of an amide moiety, cyclic or not, is present in most anticonvulsants. The pyridazinone ring system agrees with this salient feature and many papers have reported anticonvulsant activities of pyridazine derivatives[3]. Hence this feature of the ring system was tapped for the presence of any anticonvulsant activity.

MATERIAL AND METHOD

All the chemicals used were of CDH and Merck. The melting points were determined in open capillary tubes on a Jyoti Laboratories Melting Point Apparatus and are uncorrected. The purity of the compounds was confirmed by TLC using silica gel G as stationary phase, using two solvent systems; by TLC using silica gel G as stationary phase, using two solvent systems; Benzene: Ethanol (9:1) and Toluene: Ethyl formate: Formic acid (5:4:1) and visualized in iodine. The IR spectra were recorded in potassium bromide on a Perkin Elmer IR spectrometer. The PMR spectra were recorded on R-32 (300MHz) instrument using $CDCl_3$ as solvent and tetra methyl silane as internal standard. Phenytoin was obtained as a gift sample from Cadilla Pharmaceuticals. The animal research study was approved by the animal ethical committee (CPCSEA).

Aroyl propionic acid (IIa-IIe) was synthesized by refluxing a mixture of benzene (30 ml) and anhydrous aluminium chloride (10 gm, 0.15 mole) was then added intermittently with continuous stirring to the refluxing mixture. The anhydrous condition was maintained throughout the reaction and the temperature was gradually increased to 60° C. the mixture was refluxed for 5 hours. The contents of the flask were then left overnight at room temperature. 2.5 % hydrochloric acid was added to the overnight kept mixture and subjected to steam distillation was complete; the contents were poured into a beaker, washed with hot water and immediately filtered off. To this 5 % sodium bicarbonate solution was added and filtered while hot. The clear filtrate was washed with an organic solvent (petroleum ether, chloroform). The aqueous layer (when washed with ether) was collected

and acidified with dilute hydrochloric acid to pH 1 to obtain the crude product. The aroyl propionic acid was collected, crystallized with aqueous ethanol and dried at room temperature.

6-aryl-2,3,4,5-tetrahydro-3-pyridazinone (IIa-IIe) was synthesized by dissolving the aroyl propionic acid in methanol and refluxing with hydrazine hydrate (0.1 mole) for 4 hours at a temperature of 15-20° C. the contents were concentrated and the poured into ice water. The crude product obtained was dried, recrystallised from ethanol and dried at 60° in oven.

6-aryl-2,3,4,5-tetrahydro-3-thiopyridazinone (IIIa-IIIe) was prepared by refluxing 0.1 mole of (II) dissolved in o-xylene, with phosphorus pentasulphide (0.1 mole) for 4 hours at a temperature of 150° C. The contents were poured into a beaker and concentrated to a small volume. Yellow colored crystals were collected, crystallized from ethanol and dried at room temperature. The two groups of compounds were obtained as a result of condensation with hydrazine hydrate of aroyl propionic acid and substitution with sulphur. The compounds were obtained in good yields. The compounds were characterized by elemental analysis, IR, PNMR spectral data (Table 1 & 2).

PHARMACOLOGICAL STUDIES

All the compounds (II a-IIe) and (IIIa-IIIe) were screened for anticonvulsant activity by maximal electroshock seizure test[4]. Test drugs and vehicles were administered orally 30 minutes before subjecting the animals to maximum electroshock through trans auricular electrodes. Protection against seizures is defined as the abolition of the hind limb tonic extensor component of seizures. Averaged to about 20-25 g. of mice was taken. They were numbered and divided into groups of five. Three such groups were taken, one for standard, one for, control and one for the test compound. The dose was given orally to the animals half an hour before the stimulus was given. The test compound was given orally to the animals of the third group. The animals were subjected to electroshock via ear electrodes after 30 minutes and the pattern of the resulting seizure was observed, and the various components were timed to the nearest half second with a stopwatch. The readings were taken for all the other animals of the group. The starting dose of the test compound was 10 mg/Kg, 25mg/Kg, 50mg/Kg, and 100mg/Kg.The reduction in the time of or the abolition of tonic extensor phase (as the case may be) of MES convulsions was noted. Similarly readings for control and standard (Phenytoin 25 mg/Kg) were also noted and the readings subjected to preliminary statistical analysis.

RESULTS AND DISCUSSION

Here we have reported the synthesis of a series of substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazinones (IIa-IIe)and 6-aryl-2,3,4,5-tetrahydro-3-thiopyridazinones (IIIa-IIIe) and their anticonvulsant activity. The reaction sequence leading to the formation of different title compounds is outlined in Scheme 1. Benzoyl propionic acid as a starting compound was synthesized by Friedel Craft's acylation of aromatic hydrocarbon with succinic anhydride in presence of $AlCl_3$ (I). This on reaction with hydrazine hydrate yielded substituted 6-aryl-2,3,4,5-tetrahydro-3-pyridazonone (IIa-IIe) followed by substitution with sulphur to yield the compounds (IIIa-IIIe). The purity of the compounds was checked by TLC and the structures were confirmed by spectral analysis. All the compounds IIa-IIe and IIIa-IIIe were screened for anticonvulsant activity. The anticonvulsant activity was evaluated by the maximal electroshock-induced seizure test[4]. Out of the ten compounds subjected to anticonvulsant screening by the M.E.S. method, two showed significant activity (Table 3). Rest showed moderate anticonvulsant activity.

Reaction Scheme 1

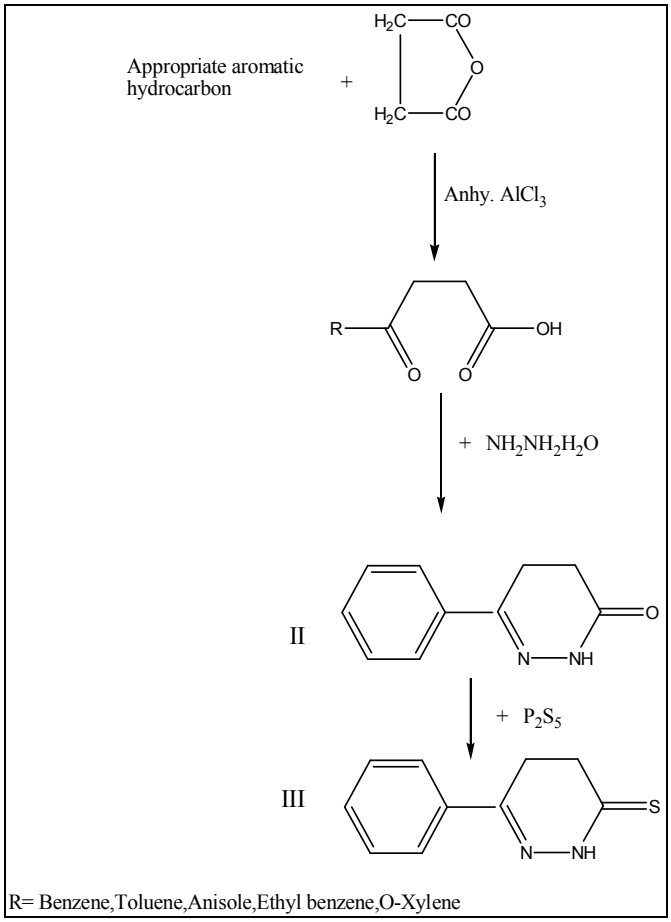


TABLE 1: Physical data of the compounds synthesized (reaction scheme 1)

Comp.	IUPAC Name	Starting aromatic hydrocarbon	m.p. ˚C	R_f	%Yield
IIa	6-phenyl 2,3,4,5-tetrahydro-3-pyridazinones	Benzene	245	0.38	80
IIb	6-p-tolyl 2,3,4,5-tetrahydro-3pyridazinones	Toluene	101	0.6	80
IIc	6-p-anisyl 2,3,4,5-tetrahydro-3-pyridazinones	Anisole	179	0.65	78
IId	6-p-ethyl phenyl 2,3,4,5-tetrahydro-3-pyridazinones	Ethyl benzene	125	0.67	65
IIe	6-3,4-dimethyl phenyl 2,3,4,5-tetrahydro-3-pyridazinones	0-xylene	133	0.69	75
IIIa	6-phenyl-2,3,4,5-tetrahydro-3-thiopyridazinones	Benzene	92	0.76	60
IIIb	6-p-tolyl-2,3,4,5-tetrahydro-3-thiopyridazinones	Toluene	92	0.76	60
IIIc	6-p-anisyl-2,3,4,5-tetrahydro-3-thiopyridazinones	Anisole	170	0.8	54
IIId	6-p-ethyl phenyl-2,3,4,5-tetrahydro-3-thiopyridazinones	Ethyl benzene	144	0.78	55
IIIe	6-3,4-dimethyl phenyl-2,3,4,5-tetrahydro-3-thiopyridazinones	0-xylene	180	0.86	58

TABLE 2: SPECTRAL DATA OF COMPOUNDS SYNTHESISED

Comp.	IR (cm^{-1})	NMR (δppm)
IIa	1667(C=O), 1426(C=N)	2.6(2H,m,CH_2),2.9(2H,m,CH_2), 7.5(3H,m,H-3', 4',5')7.8(2H,m,H-2',6'), 2(NH,s)
IIb	1658.8,3217.4,1510.8, 3095.6	2.38(s,3H,CH3),2.60(m,2H,), 2.97(T,2H,J=8.1Hz),7.26(t,2H,J=9Hz,H3',5'), 7.63(d,2H,H2',6'),8.79(s,NH)
IIc	1665.9,3208.7,1613.5, 1252.1	2.59(t,2H,J=8Hz),2.96(t,2H,J=8Hz), 3.86(,OCH3),6.94(d,2H,H3',5'),7.68(m,2H,H2',6'),8.81(s,NH)
IId	1665.8,3427.7,1595.3, 2928.4	1.25(t,3H,J=7Hz),1.59(s), 2.64(m,2H)3.01(m,2H),7.26(d,2H,J=8.1HzH3',5') 7.65(d,2H,J=8.1Hz,H2',6'),8.54(s,NH)
IIe	1666.8,3218.0,1507.9, 1204.1	2.38(t,3H),2.63(m,2H),3.01(m,2H,),7.44(d,H5'), 7.66(d,H6'),7.52(s,H2'),8.69(s,NH)
IIIa	3398(NH),1600(C=N), 1287(C=S)	7.49(m,3H,H3',4',5'),7.829m,2H,H2',6')
IIIb	1289.6,1598.2,3412.6	2.41(s,3H),3.42(s,H,ArSH),7.28(t,2H,H3',5'),7.74(m,2H,H2',6')
IIIc	1301.3,1605.7,3401.8, 1259.9	2.764(m,2H),2.276(m,2H), 7.47(d,2H,H3',5'),7.77(m,2H,H2',6')
IIId	1285.2,1598.2,3429.7, 2917.9	1.27(t,3H),2.72(m,2H), 3.80(m,2H),7.52(d,2H,H2',6'),7.77(m,5H),7.33(d,2H,H3',5'), 3.5(m,ArSH)
IIIe	1300.3,1605.1,3429.4, 1259.5	2.32(m,2H),2.76(m,2H), 2.55(s,3H),3.50(ArSH),7.60(s,1H,H2'),7.33(d,1H,H5'), 7.28(d,1H,H6')

TABLE 3: ANTICONVULSANT SCREENING RESULT

S. No.	Compound	Dose (mg/Kg) P/O (mg)	Mean±SEM	%Protection
1	3b	100	4.7±0.27	59.48
2	3c	100	7.1±0.51	38.79
3	Control	-	11.6±0.26	-
4	Standard	25	1.0±0.07	91.38

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