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Anticonvulsant properties of N-cyclopentylphthalimide and N-benzylphthalimide

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ABSTRACT

Synthetic heterocyclic compounds have been found to possess important biological properties including anticonvulsant effects in man and animals.This study was aimed at highlighting the anticonvulsant properties of two phthalimide derivatives (N-cyclopentylphthalimide and N-benzylphthalimide). N-Cyclopentylphthalimide and N-benzylphthalimide were synthesized and screened for anticonvulsant properties using adult Swiss mice. Convulsion was induced using maximum electroshock therapy. The compounds were found to be seizure protective and protection was observed even after forty eight hours.

Keywords: anticonvulsant, N-cyclopentylphthalimide and N-benzylphthalimide, seizures.

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INTRODUCTION

Synthetic heterocyclic compounds have been found to possess important physiological properties in man and animals including anticonvulsant effects [1,2]. Cyclic enaminone esters for example have been synthesized, characterized, and evaluated for anticonvulsant activities [3].

Epilepsy is one the most frequent diseases of the central nervous system and the characteristic feature is occurrence of seizures and twenty to forty million people worldwide are affected [4,5] Since anticonvulsant therapy is only effective in 60-70% of patients, further investigation of new antiepileptic dugs with specific effects remain a challenge [6]. In addition to this limitation, available anticonvulsants do not treat the disease but control the symptoms and fail to adequately control 50% of patients with severe complete partial seizures.

Few anticonvulsant drugs are available for paediatric use and therapy to prevent epileptogenesis is lacking thus patients with head injury or infarcts with febrile seizures will subsequently develop epileptic syndrome. Treatment of life threatening *status epilepticus* is to some extent inadequate and some highly effective drugs produce tolerance and side effects which result in poor patients' compliance [7,8].

Though several drugs drugs such as felbamate, fosphenytoin, gabapentin, lamotrigine, vigabatrin and zonisamide were approved in the last decade [9] none of the available antiepileptic drug is ideal as they can be associated with chronic and adverse side effects [10].

This study highlights the synthesis and anticonvulsant screening of phthalimide derivatives (N-cyclopentylphthalimide and N-benzylphthalimide) as a way of searching for new, specific and more effective anticonvulsant agents. No previous anticonvulsant screening to the best of our knowledge has been carried out on these compounds.

MATERIALS AND METHODS

Adult Swiss mice weighing 18-25g, dimethysulphoxide (DMSO), potassium phthalimide, benzyl bromide, cyclopentyl bromide, distilled water, chloroform, thin layer chromatographic plates (silica gel 60-F_{254} Merck), Ugo Basil Electroshock equipment, electrodes.

Chemistry

N-Benzylphthalimide was synthesized from potassium phthalimide and benzyl bromide in DMSO [11]. N-Cyclopentyl phthalimide was synthesized from potassium phthalimide and cyclopentyl bromide in DMSO [12].

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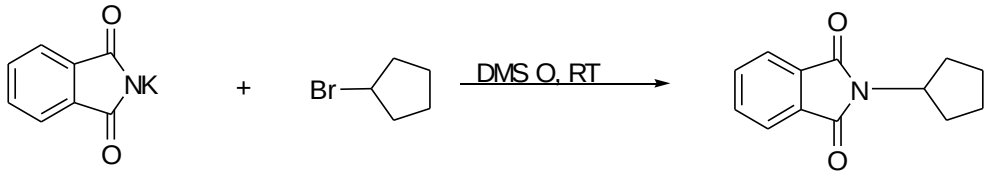
Figure 1

Synthesis of N-Cyclopentylphthalimide.



Phthalimide Cyclopentyl bromide N-Cyclopentylbromide

Synthesis of N-Benzylphthalimide

Phthalimide Benzylbromide N-Benzylphathalimide

DMSO Dimethysulphoxide
RT Room temperature

Pharmacology

Swiss male mice weighing 18-25g were used. Male mice were used to exclude the variations of endocrine secretions on brain excitability. The mice were maintained under standard environmental conditions and had access to standard diet and water.

The protocol used was approved by the Ethics Committee of the Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

The required doses corresponding to 300mg/kg, 100mg/kg and 30mg/kg body weight of mice were calculated and prepared in DMSO solutions. Each group (consisting of three mice each) received varying doses of N-cyclopentylphthalimide and N-benzylphthalimide intra-peritoneally. A control test group of three mice received DMSO solution only.

The electroshock equipment was calibrated to deliver an amount of electrical current adequate for inducing convulsions in mice. Thirty minutes after administration of the compounds (N-cyclopentylphthalimide or N-benzylphthalimide), each mouse was subjected to electric shock and observed for any reaction. This procedure was repeated at time intervals of 1hour, 2hours, 4hours, 8hours, 24hours and 48hours. The criterion of anticonvulsant activity was complete protection against convulsions characterized by tonic or clonic seizures of any kind.

RESULTS AND DISCUSSION

N-Benzylphthalimide was synthesized from potassium phthalimide and benzyl bromide in DMSO. The reaction was monitored with thin layer chromatography. The crude

product recrystallized from DMSO-water afforded crystals with a melting point of 119-120^{O}C. [11, 113-115 ^{O}C].

N-Cyclopentylphthalimide was synthesized from potassium phthalimide and cyclopentyl bromide in DMSO. Melting point of the resulting crystals was found to be 105-106 ^{O}C. [12, 99-102 ^{O}C].

Nuclear Magnetic Resonance (NMR), Infra Red (IR) and Mass Spectroscopy (MS) were used to unequivocally determine the structure and purity of synthesised compounds.

N-Cyclopentylphthalimide was found to be seizure protective when administered intraperitoneally to mice in test groups. Protection from seizures occured at a dose of 300mg/kg body weight of mice. This was observed at 30 minutes, 1hour, 2hours, 4hours, 8hours, 24hours and 48hours when electroconvulsive therapy was applied post drug administration. At a dose of 100mg/kg and 30mg/kg body weight of mice protection was seizures was also observed at 30minutes and up to 48 hours post drug administration.
Mice in the control group who received DMSO solution only exhibited tonic seizures when electroconvulsive therapy was applied.

Table 1: Results of mice in test group subjected electroconvulsive therapy post administration of N-cyclopentylphthalimide

Time Interval/ Dose	30minutes	1hour	2hours	4hours	8hours	24hours	48hours
300mg/kg	3/3	2/2*	2/2	2/2	2/2	2/2	2/2
100mg/kg	3/3	3/3	3/3	3/3	3/3	3/3	3/3
30mg/kg	3/3	3/3	3/3	3/3	3/3	3/3	3/3
Control (0.2ml)	0/3	0/3	0/3	0/3	0/3	0/3	0/3

* Death of one mouse

N-benzylphthalimide was also administered intraperitoneally to mice in test groups at a dose of 30mg/kg, 100mg/kg and 300mg/kg body weight of mice after which electroconvulsive therapy was applied. At 300mg/kg and at 100mg/kg the test animals did not exhibit tonic seizures at 30minutes, 1hour, 2hours, 4hours, 8hours, 24hours and 48hours when electroconvulsive therapy was applied but at 30mg/kg, protection was observed as from 2hours following drug administration and this lasted for 48hours.

Mice in the control group who received 0.2ml of DMSO only exhibited tonic seizures when electroconvulsive therapy was applied.

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Table 2: Results of mice in test group subjected electroconvulsive therapy post administration of N-benzylphthalimide

Time Interval/ Dose	30minutes	1hour	2hours	4hours	8hours	24hours	48hours
300mg/kg	3/3	3/3	3/3	3/3	3/3	2/2*	2/2
100mg/kg	3/3	3/3	3/3	3/3	3/3	1/1*	1/1
30mg/kg	0/3	0/3	3/3	3/3	3/3	3/3	3/3
Control (0.2ml)	0/3	0/3	0/3	0/3	0/3	0/3	0/3

* Death of mice

CONCLUSION

N-Cyclopentylphthalimide had a fast onset of action and long duration of action. N-Cyclopentylphthalimide could be neurotoxic at doses higher than 100mg/kg as shown by death of three mice.

N-Benzylphthalimide had a slower onset of action and a long duration of action. The slow onset of action of N-benzylphthalimide could be attributed to the bulky aromatic group. N-Benzyl phthalimide could also be neurotoxic at doses higher than 100mg/kg as three mice in that dosing group died.

N-Cyclopentylphthalimide and N-benzylphthalimide possess significant central nervous system properties and anti-convulsant properties.

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