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Der Pharma Chemica, 2012, 4 (3): 1133-1139  
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ISSN 0975-413X  
CODEN (USA): PCHHAX

## Synthesis of oxcarbazepine by newer method

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### ABSTRACT

Epilepsy is one other most common ailment of man with a prevalence of approximately 1%. It is estimated that 50 millions person's world wide may have this disorder. Although many are well controlled with available therapies, perhaps one quarter of the total continue to have seizures. Anticonvulsant drugs are the mainstay of epilepsy management and may have to be taken for life. In more than 20% of those affected, chronic intractable (refractory) epilepsy develops. This necessitates the use of combination therapy. But the use of these drugs in combination is plagued by cognitive impairment and drug interactions with the results that only about 10% of the patients with refractory epilepsy seem to benefit substantially from polypharmacy. Thus the new viable antiepileptic molecules are urgently needed. In an effort to improve the tolerability profile of the carbamazepine without affecting its epileptic potency, the keto analogue oxcarbazepine was developed. Oxcarbazepine has developed its efficacy and its improved safety profile and is now considered as epileptic drug of first choice. Some of the synthetic routes of oxcarbazepine described in the literature used costlier raw materials and the reported yield is less. Hence, an attempt was made to synthesize oxcarbazepine by modified route that reduces the costly raw materials, cost of production with high yield.

**Keywords:** Epilepsy, carbamazepine, oxcarbazepine, polypharmacy

### INTRODUCTION

The term epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures<sup>1,2</sup>. The term "seizures" refer to a transient alteration of behaviour due to abnormal excessive, hyper synchronous discharges from aggregate of CNS neurons.

Seizure can be

- Non epileptic –when evoked in a brain by treatment such as electric shock or chemical convulsants.
- Epileptic –when occur without evident provocation.

The epilepsies are common and frequently devastating disorders, affecting approximately 0.5% of the population. more than 40 distinct forms of epilepsy have been identified. the incidence increases again epilepsy begins before the age of 18 in over 75% population.

Seizures the characteristic event in epilepsy, is associated with the episodic high frequency discharges of impulses by a group of neurons in the brain. What starts as a local discharge may then spread to other areas of the brain. The site of primary discharge and extent of its spread determines the symptoms that are produced, which ranged from a brief lapse of attention to a full conclusive fit lasting for several minutes.

The particular symptoms produced depend on the function of the region of the brain that is affected thus involvement of the hypothalamus causes peripheral autonomic discharge and involvement of the reticular formation in the upper brain stem leads to loss of consciousness.

Oxcarbazepine is highly lipophilic thus easily pass the BBB and reach the site of action<sup>3</sup>. Hence, an attempt was made to prepare oxcarbazepine by modified route and screen for anticonvulsant activity.

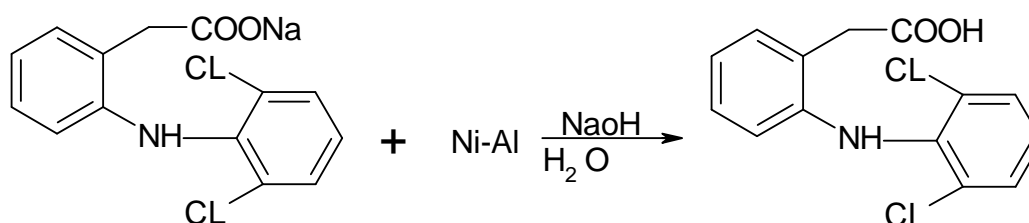
- ✓ Attempt was made to synthesize oxcarbazepine through different routes that may give good yield with acceptable purity
- ✓ Costly raw materials were avoided to make the process economical.
- ✓ Complicated procedures were avoided to achieve simpler techniques.
- ✓ Characterization of synthesized oxcarbazepine by made by TLC, IR, and NMR techniques.
- ✓ Pharmacological evaluation of oxcarbazepine by maximal electrical shock method which produce a selective anticonvulsant activity was studied.

## MATERIALS AND METHODS

The following steps were involved in the synthesis of oxcarbazepine:

1. Formation of 2-(2-phenylamino) benzene acetic acid.
2. Formation of 10-oxo-10, 11-dihydro-5H-dibenz (b,f)-azepine.
3. Formation of 10-oxo-10, 11-dihydro-5H-dibenz (b,f) -azepine-5-carbonyl chloride.
4. Formation of oxcarbazepine.

### 1. Formation of 2-(2-phenylamino) benzene acetic acid:



S.No	Chemicals	Mol weight	Weight	Mole	Ratio
1	Diclofenac Sodium	318	10 gm	0.0031(M)	1
2	Ni-Al	86	5 gm	0.062 (M)	2
3	NaoH	40	2 gm	0.05 (M)	-
4	H <sub>2</sub> O	18	150 ml	-	-
5	Methanol	-	40 ml	-	-

### Procedure

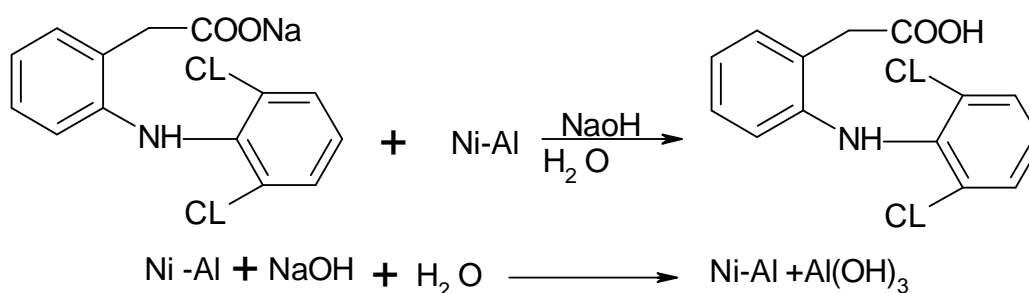
The above mention quantities of diclofenac sodium, NaoH, methanol and water were taken. Stir the reaction mixture at R.T. Then slowly added 5gm of Ni-Al alloy, over the period of 2-3 hrs. After addition of Ni-Al alloy, filtered the R.M over celite, acidified with dilute HCL to pH 2. Then extract with ethyl acetate (EA). Then finally distilled off EA and collected the reduced product.

Yield of 2-(phenylamino) benzene acetic acid was found to be 88%.  
M.P=180-181°C.

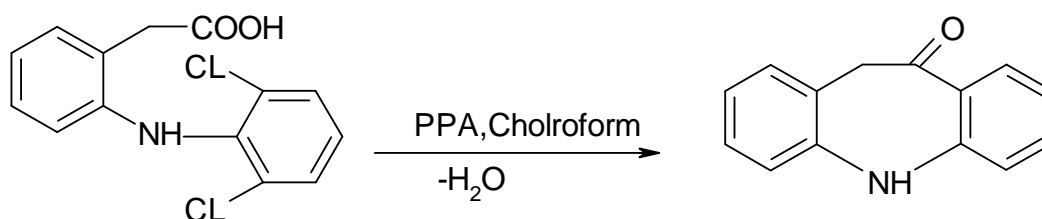
### Mechanism

In the first step the mechanism involved as follows:

Ni-Al alloy reacts with NaOH and form aluminium hydroxide, active nickel and hydrogen. The active nickel reacts with chloride atom of ring and form nickel chloride. Then after at making pH 2 acids separates out. This leads to the formation of desired compound.



## 2. Formation of 10-oxo-10,11-dihydro-5H-dibenz (b,f)-azepine:



S.No	Chemical used	Mol.wt	Wt	Mole	Ratio
1	2 (phenylamino) benzene acitic acid	227	5gm	0.022(M)	1
2	Polyphosphoric acid(PPA)	-	10gm	-	-
3	Cholorform	-	100ml	-	-

### Procedure

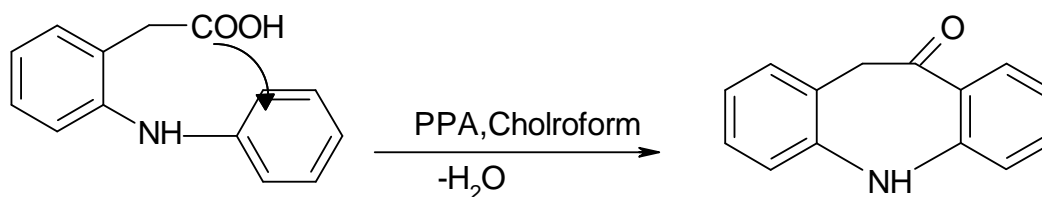
Take 5gm of 2-(phenylamine)benzene acitic acid ,100ml of choloroform and 10gm of (PPA).reflux the reaction mixture with stirring for 10-12hrs .after that checked TLC by using acetone and chloroform 1:1 as mobile phase .then after confirmation from TLC add H<sub>2</sub>O and neutralise PPA with Na<sub>2</sub>CO<sub>3</sub> .after neutralisation seprate the chloroform layer from Na<sub>2</sub>CO<sub>3</sub> .finally distilled off chloroform layer and collected 10-oxo-10,11-dihydro-5H-dibenz(b,f)-azepine and analysed by IR .

The yield of cyclized product found to be 80%

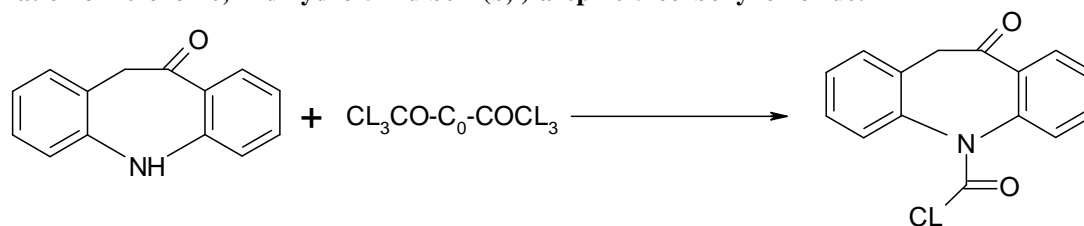
M.P =185-190°C.

### Mechanism

In the following reaction, polyphosphoric acid acts as a dehydrating agent. It removes the water molecule and thus leads to formation of desired compound.



## 3. Formation of 10-oxo-10,11-dihydro-5H-dibenz(b,f)-azepine-5-carbonyl chloride:



S.No	Chemical used	Mol wt	Wt	Mole	Ratio
1	10-oxo-10,11-dihydro-5H-dibenz(b,f)-azepine	209	3.5gm	0.016(M)	1
2	Hexachloro-dimethyl Carbonate	297	2.37gm	0.008(M)	0.5
3	Tetrahydrofuran	-	50ml	-	-

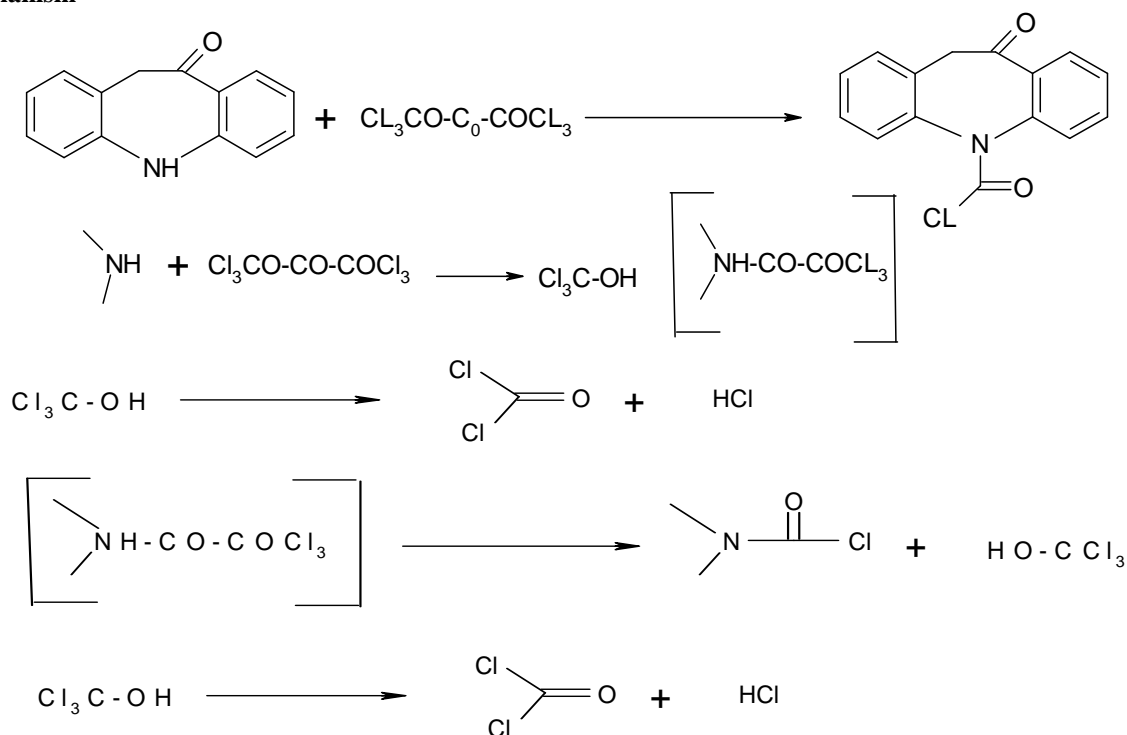
### Procedure

Take 3.5gm of 10-oxo-10, 11-dihydro-5H-dibenz (b, f) -azepine, 2.37gm of hexa-chlorodimethyl carbonate and 50 ml of THF. Stir the reaction mixture at R.T for 5to 6 hrs. Then checked the TLC by using EA:PE in 2:8 as mobile phase. Then after confirmation from TLC, distilled of THF and added H<sub>2</sub>O, solid came out. Filter the solid, dry and analyse by FTIR.

The % yield of 10-oxo-10, 11-dihydro-5H-dibenz (b, f) -azepine-5-carbonyl chloride product found to be 90%.

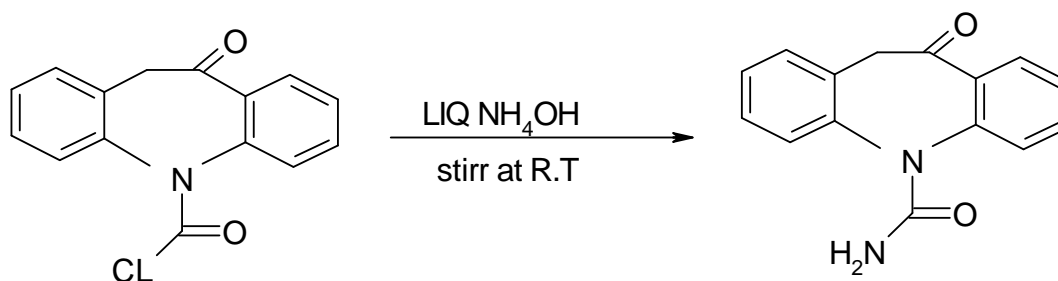
M.P=205-207°C.

## Mechanism



In the above reaction hexachlorodimethyl carbonate gives 2<sup>e</sup> equivalent phosgene moieties. This reacts with 10-oxo-10, 11-dihydro-5H- dibenz (b, f) - azepine to form, 10-oxo-10, 11-dihydro-5H-dibenze (b, f)-azepine -5-carbonyl chloride.

## 4. Formation of oxcarbazepine:

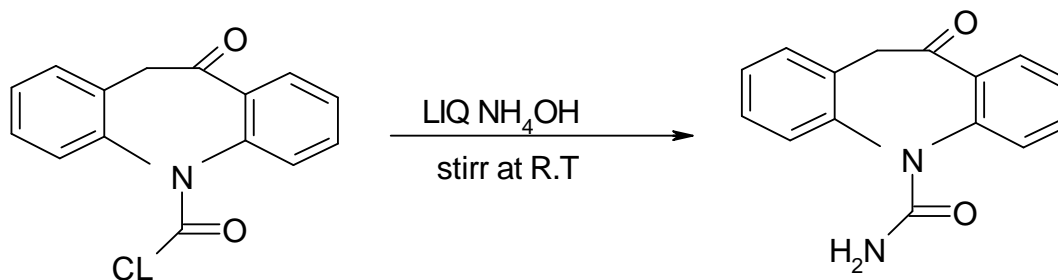


S.No	Chemical used	Mol.wt	Wt	Mole	Ratio
1	10-oxo-10,11-dihydro-5H-dibenz (b, f) -azepine-5-carbonyl chloride	271	3.5g	0.012(M)	1
2	Dilute $\text{NH}_4\text{OH}$	15	15%(5ml)	0.025(M)	2
3	Isopropyl Alcohol	-	40ml	-	-

## Procedure

Take 3.5gm of 10-oxo-10, 11-dihydro-5H-dibenz (b, f)-azepine-5-carbonyl chloride, 40 ml of IPA. Then added drop wise liquid  $\text{NH}_4\text{OH}$  with stirring at R.T. Stir the reaction mixture for 7 hrs. Checked TLC by using 50:50 EA:PE as mobile phase. After confirmation from TLC then added water to dissolved excess of  $\text{NH}_4\text{OH}$ . Then add EA layer. Distilled off the EA layer and collected the oxcarbazepine.

The % yield of oxcarbazepine found to be 85%.

**Mechanism**

In the above reaction ammonia reacts with carbonyl chloride moiety to form final product oxcarbazepine.

**PHYSICAL PROPERTIES**

PROPERTIES	OBSERVATION
Description	Yellow crystals and odourless
Solubility	Soluble in Acetone, chloroform, methanol, ethylacetate & Toluene Insoluble in water
Recrystallized	Ethanol
Melting point	220°C – 222°C
Percentage of yield	85%

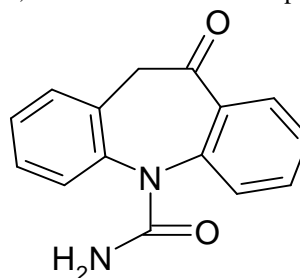
**IR SPECTRUM**

GROUPS	WAVE NUMBERS(Cm <sup>-1</sup> )
C=C Str	1653.8cm <sup>-1</sup>
C=O Str ketonic group	1685Cm <sup>-1</sup>
C=C Str of aromatic ring at	1592Cm <sup>-1</sup> and 1563Cm <sup>-1</sup>
Asymmetric and symmetric Str of NH <sub>2</sub> group of amide at	3467Cm <sup>-1</sup> and 3340Cm <sup>-1</sup>
NH deformation vibration at	1407Cm <sup>-1</sup>

**NMR SPECTRUM**

1. Aromatic protons between 7 to 8.5 δppm
2. Aliphatic CH<sub>2</sub> doublet at 3.8 and 4.4δppm
3. NH<sub>2</sub> protons at 5.0δppm

According to the IR and NMR spectral data obtained, the structure of the compound may be oxcarbazepine.

**OXCARBAZEPINE**

Attributed Molecular Formula :C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>

**ANTICONVULSANT ACTIVITY OF SYNTHESIZED OXCARBAZEPINE BY MAXIMAL ELECTROSHOCK METHOD<sup>4</sup>**

Institutional Animal Ethical Committee (IAEC) approval was taken before performing the animal studies.

In maximal electroshock (MES) electroshock is applied through the ear electrodes. The MES convulsions are divided into five phases such as

1. Tonic flexion
2. Tonic extensor
3. Clonic convulsion
4. Stupor and

## 5. Recovery or death

A substance is to possess anticonvulsant property if it reduces or abolished the extensor phase of MES convulsion.

**Procedure**

Swiss albino rats of either sex (170-250gm) were weighed and divided into 3 groups of 5 animals each. Of the 3 one group was used as control, to test the effect of MES alone and one group was used as STD administered with carbamazepine 14mg/kg<sup>1</sup> and one group was used for synthesized oxcarbazepine. The suspension of the drugs was prepared in 0.5% guargum solution in distilled water. To the control animals MES was given and time for onset of clonic convulsions was recorded. To the other groups 14mg/kg<sup>9</sup> of carbamazepine was given through oral route and after 1 hour MES was given and delay in the onset of action were recorded.

To the remaining one group synthesized oxcarbazepine was given through oral route and after one hour, the onset of convulsions was recorded. Results were statistically compared against the control.

Group no	Body Wt	Treatment (dose)	Time(sec) in various phase of convulsions				
			flexion	extensor	clonus	Stupor	Ror D
I	189	Control	6	9	3	90	R
	190		5	8	4	110	D
	195		4	11	2	96	R
	192		5	10	4	102	R
	193		7	9	2	98	D
II	200	carbamazepine 14mg/kg	2	6	2	70	R
	205		2	2	1	72	R
	203		0	4	2	66	R
	206		2	5	1	68	R
	198		1	6	1	72	R
III	185	oxcarbazepine 14mg/kg	2	6	2	60	R
	180		2	3	1	58	R
	175		0	3	1	71	R
	183		2	1	0	42	R
	182		0	2	2	48	R

R=RECOVERY, D=DEATH

The following table indicates the effects of synthesized oxcarbazepine and carbamazepine on the extensor phase of convulsions in albino rats.

S.No	Treatment dose (mg/kg)	Mean $\pm$ SEM	P value
1	Control	4.60 $\pm$ 0.748***	-
2	Standard	4.60 $\pm$ 0.836***	0.0007
3	Oxcarbazepine (14mg/kg)	3.00 $\pm$ 0.836***	0.0002

Statistics: unpaired 't' test n=5

\*P<0.05

\*\*P<0.01

\*\*\*P<0.001

**RESULTS**

The synthesized oxcarbazepine was compared with that of carbamazepine and control for anticonvulsant activity. The synthesized oxcarbazepine was found to be very active because of its reduced time of extensor phase as compared to carbamazepine and control. The values are statistically significant too as compared to control and carbamazepine.

The new modified route of oxcarbazepine synthesis involved following steps:

**STEP 1:** Reaction of 2-(2,6-dichlorophenylamino) benzene acetic acid monosodium salt with Ni-Al alloy gave 2-(2,6- dichlorophenylamino) benzene acetic acid

**STEP 2:** Reaction of 2-(2,6-dichlorophenylamino) benzene acetic acid with polyphosphoric acid led to cyclization.

**STEP 3:** Reaction of cyclized product with hexachlorodiethyl carbonate gave carbonyl chloride compound.

**STEP 4:** Finally, reaction of carbonyl chloride compound when refluxed with ammonia gave oxcarbamazepine with better yield and yield was 85%.

**DISCUSSION AND CONCLUSION**

In an effort to improve the tolerability profile of the carbamazepine without affecting its epileptic potency, the keto analogue oxcarbazepine was developed. Oxcarbazepine has developed its efficacy and its improved safety profile and is now considered as epileptic drug of first choice.

Some of the synthetic routes of oxcarbazepine described in the literature, used costlier raw materials and the reported yield is less.<sup>5,6,7,8</sup>

Hence an attempt was made to synthesize oxcarbazepine by a modified route that reduces the costly raw materials, cost of production with high yield.

The procedure is simple involving just four steps, with cheaper raw materials. Hence, the method is cost effective. Further the synthesized oxcarbazepine was characterized by TLC, IR, NMR and melting point techniques. Log P value is directly related to bioavailability and it is an important value to be considered for CNS drugs.

The synthesized oxcarbazepine was screened for anticonvulsant activity by Maximal electrical shock method (MES). The animal studies have been performed with respect to carbamazepine as the STD, using 14mg/kg<sup>8,9</sup>.

The animal studies proved that the anticonvulsant activity of synthesized oxcarbazepine is very significant.

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