CHAPTER I

INTRODUCTION

Definition and Epidemiology.

The term *seizure disorders*, *convulsions*, and *epilepsy* are often used interchangeably, although they do not really mean the same thing. *Convulsions* are involuntary spasmodic contractions of muscles. Most people probably think that a convulsion is the generalized tonic-clonic reaction that occurs with grand mal or major motor epilepsy, although it occurs in other situations as well. A *seizure* is a sudden attack of epilepsy or another disorder and may or may not involve a generalized convulsion. For example, with absence seizures (petit mal seizures), there may be no abnormal movements at all; in some other types of seizures, only a part of the body may be affected by abnormal movements. A convulsion or seizure may occur as an isolated incident, such as one set off by fever in a young child (Collin, 1983). The term *epilepsy* is used collectively to include a group of syndromes of central nervous system (CNS) disorders characterized by sudden, transitory, and recurring seizures involving one or more of the following systems: motor (convulsion), sensory, autonomic, or psychic. Most investigators do not include single isolated seizures in the definition of epilepsy. Abnormal and excessive discharges in the

electroencephalogram (EEG) nearly always accompany the seizures (Chan, 1992).

Epilpsy affects approximately 1% of the worldwide population and is the second most common neurologic disorder after stroke. It is estimated that one of every 11 persons in the United States will experience a seizure at some time during life. The incidence is highest in the first 10 years of life and declines thereafter through the age of 50 until the elderly years, when again the incidence increases. Epilepsy begins before the age of 18 years in over 75% of patients (Alldredge, 1992).

Classification.

Seizures are classified on the basis of distinctive behavioral features as well as on ictal and interictal eletroencephalographic (EEG) findings (Commission on classification and terminology of the International League Againt Epilepsy, 1981) and are devided broadly into two groups: partial and generalized (see Table 1) (Ambre et al., 1994).

Partial seizures arise in part of the cerebral hemispere and are often accompanied by focal EEG abnormalities. They are subdivided according to the whether consciousness is maintained (simple) or impaired (complex). The manifestations of partial seizures are determined by the

TABLE 1.

EPILEPTIC SEIZURES: CLASSIFICATION

I. Partial seizures. (Focal seizures).
   A. Simple partial seizures.
      1. with motor signs.
      2. with somatosensory or special sensory symptoms.
      3. with autonomic symptoms.
      4. with psychic symptoms.
   B. Complex partial seizures.
      1. simple partial onset followed by impairment of consciousness.
      2. with impairment of consciousness at the onset.
   C. Partial seizures evolving to secondarily generalized seizures.
      1. simple partial seizures (A) evolving to generalized seizures.
      2. complex partial seizures (B) evolving to generalized seizures.
      3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures.

II. Generalized seizures. (Convulsive or nonconvulsive).
   A. (1). Typical absence seizures (petit mal seizures).
      (2). Atypical.
   B. Myoclonic seizures.
   C. Clonic seizures.
   D. Tonic seizures.
   E. Tonic-Clonic seizures.
   F. Atonic seizures.

III. Unclassified epileptic seizures including neonatal seizures

(Adapted from Commission on Classification and Terminology of the International League Against Epiepsy, 1981).

particular brain area involved. Either type of partial seizure may become secondarily generalized. Generalized seizures are characterized by impaired consciousness with clinical or EEG evidence indicating involvement of both hemispheres initially; they are classified as non-convulsive or convulsive subtypes. In case of unclassified epileptic seizures, this type of seizures includes all seizures that cannot be classified because of inadequate or incomplete data. Neonatal seizures differ greatly from those in older patients and often represent the initial symptom of a serious neurologic disorder. A range of behaviors (including abnea and autonomic phenomena) may be seizures, but not all are reflected in the EEG findings (electroclinical dissociation). Thus, neonatal seizures may be difficult to diagnose and classify (Ambre et al., 1994).

Recurrent seizures are the presenting symptom of the neurologic disorder, epilepsy. Because the International Classification of Epileptic Seizures (ICES) is limited to a description of individual seizure types, epileptic syndromes, which permit the appropriate classification of patients, are classified separately (Commission on Classification and terminology of the International League Againt Epilepsy, 1989). An epileptic syndrome is characterized by a clustering of signs and symptoms that regularly occur together; the seizure type(s), etiology, precipitating factors, hereditary components, and natural history (e.g. age of onset, chronicity, severity) are considered in this classification. Delineating epileptic syndromes permits a greater precision of diagnosis and prognosis than simply classifying seizure types, because the same type of seizure can occur in various syndromes. Some syndromes are well defined and

unequivocal while others are heterogeneous. For many patients, a specific syndrome cannot yet be assigned.

The epilepsies are classified on the basis of seizure type (localization-related or generalized) and seizure etiology (idiopathic or symptomatic) (see Table 2). Idiopathic epilepsies have no definable cause; they often are familial, and onset is age-related. Benign familial neonatal convulsions and juvenile myoclonic epilepsy are two of the idiopathic epilepsies with putative gene assignments. These epilepsies are more likely than symptomatic epilepsies to be associated with normal development, responsiveness to antiepileptic drugs, and remission. Symptomatic epilepsies and syndromes are caused by diagnosable central nervous system (CNS) disorders although, in some patients with presumed symptomatic epilepsy, the underlying cause remains obscure (cryptogenic). In these epilepsies, the interictal EEG is more likely to be abnormal, the prognosis is less favorable, and the response to antiepileptic drugs is variable.

Symptomatic partial epilepsies and idiopathic generalized epilepsy are the most common syndromes observed in adults. In the pediatric population, the spectrum of syndromes is large and is age dependent. Prevalence increases with age during childhood and adolescence, is stable in adult years, and increases again in elderly individuals.

TABLE 2.

EPILEPSIES AND EPILEPTIC SYNDROMES: CLASSIFICATION.

1. Localization- related (focal, local, partial) epilepsies and syndromes.
   A. Idiopathic (with age-related onset).
      1. Benign childhood epilepsy with centrotemporal spike.
      2. Childhood epilepsy with occipital paroxysms.
      3. Primary reading epilepsy.
   B. Symptomatic.
      1. Chronic progressive epilepsia partialis continue of childhood.
      2. Syndromes characterized by seizures with specific modes of precipitation.
      3. Temporal lobe epilepsies.
      4. Frontal lobe epilepsies.
      5. Parietal lobe epilepsies.
      6. Occipital lobe epilepsies.
   C. Cryptogenic.

II. Generalized epilepsies and syndromes.
   A. Idiopathic (with age-related onset).
      1. Benign neonatal familial convulsions.
      2. Benign neonatal convulsions.
      3. Childhood absence epilepsy.
      4. Juvenile myoclonic epilepsy.
      5. Epilepsy with grand mal (GTCS) seizures on awakening.
      6. Epilepsies with seizures precipitated by specific modes of activation.

(table continued on next page)

TABLE 2 (continued).

B. Crytogenic or symptomatic.
   1. West syndrome.
   2. Lennox-Gastaut syndrome.
   3. Epilepsy with myoclonic-astatic seizures.
   4. Epilepsy with myoclonic absences.

C. Symptomatic.
   1. Nonspecific etiology.
      a. Early myoclonic encephalopathy.
      b. Early infantile epileptic encephalopathy with suppression burst.
   2. Specific syndromes.
      a. Epileptic seizures may complicate many disease states.

III. Epilepsies and syndromes undetermined whether focal or generalized.
   A. With both generalized and focal seizures.
      1. Neonatal seizures.
      2. Severe myoclonic epilepsy of infancy.
      3. Epilepsy with continuous spike waves during slow-wave sleep.
      4. Acquired epileptic aphasia.
   B. Without unequivocal generalized or focal features.

IV. Special syndromes
   A. Situation-related seizures
      1. Febrile convulsions
      2. Isolated seizures or isolated status epilepticus
      3. Seizures occurring only when there is an acute matabolic or toxic events.

(Adapted from Commission on Classification and Terminology of the International League Against Epiepsy, 1981).

Basic Mechanisms of Epilepsy.

It would be a gross oversimplification to suggest a single mechanism or cause of epilepsy. Because of the diversity of seizure types, it is understandable that a common denominator has so far not been found; rather, there is likely to be more than one neurophysiological and biochemical mechanism for seizure disorders. Because the most prominent feature of an epileptic seizure is sustained synchronous neuronal discharges, and plausible mechanism needs to account for such a phenomenon. Some investigators have proposed that synchronous firing may require specifically timed inhibitory and excitatory neuronal activity. However, the specific mechanism for sustaining the synchronous firing is still unknown. It has been suggested that most seizures begin with, and are sustained by, the synchronous firing of relatively localized group of neurons, namely, the seizure focus. A reduction in inhibitory neurons in the focus may be a plausible explanation. Alternatively, the primary seizure focus may originate or be triggered by factors such as congenital defects, hypoxia at birth, local biochemical changes, neoplasm, head trauma, ischemia, or endocrine disorders. The seizure focus may remain quiescent over long periods of time, discharging only intermittently as revealed by surface EEG analysis, and may not lead to overt clinical seizures. What is not known is the exact mechanism for the transition from a dormant focus to one that can initiate the spread of synchronous electrical discharges to neighboring areas. Presumably, inhibitory pathways and mechanisms exist that prevent the spread of abnormal

discharges. The notion of positive feedback loops has been proposed also, but there has been little evidence to support this idea (Chan, 1992).

Physiological and biochemical factors that may also facilitate the spread of abnormal electrical activity to other parts (presumably normal) of the brain include changes in blood gas tension, blood glucose levels, plasma pH, and electrolyte composition of extracellular fluid; fatigue; sleep deprivation; drug withdrawal; nutritional deficiencies; emotional stress; and endocrine changes. Other less common triggering factors include hot water baths, music, reading books, brushing teeth, eating, watching TV, and doing mathematics.

Alterations in the membrane or metabolic properties of individual neurons may render the neurons pathologically hyperexcitable. Such changes may in turn affect Ca^{2+} and Na^{+} conductances. The microenvironment surrounding neurons may effect neuronal discharges. Elevated extracellular potassium may be associated with seizure activity. Some finding indicate that such changes in extracellular potassium are preceded by a decrease in extracellular calcium concentration. This series of events may increase neuronal excitability by decreasing synaptically mediated inhibition and by decreasing the inhibitory influence of calcium-dependent potassium efflux. Another mechanism involves a reduced level of Na^{+} + K^{+}ATPase found in the synaptosomal membrane derived from a freeze-lesion focus; this may lead to a reduced capability to reclaim lost K^{+}.

Biochemical lesions affecting the synthesis, storage, release, and reuptake of inhibitory amino acid neurotransmitters may be another possible mechanism for enhancing neuronal excitability. A major inhibitory neurotransmitter is γ-aminobutyric acid (GABA). Many convulsive agents are known to affect GABA metabolism. Some agents related to GABA metabolism and its receptors have been shown to possess some antiepileptic activity. Some of the antiepileptic properties of benzodiazepines may be related to the receptor complex involving both benzodiazepine and GABA receptors that are linked intimately to conductance and synaptic inhibition.

Animal models of epilepsy indicate that there is at least one initiation site for seizures in the rat brain, the area tempestus, and at least two policing areas, the substantia nigra and the anterior thalamus. It remains to be determined whether the same brain regions in the human brain regulate seizure activity. Other animal models of seizure disorders also provide basic information about epilepsy. For example, the method of kinding involves inducing seizures with chronically administered repetitive low intensity and below-threshold electrical stimuli. The relevance of kinding to human epileptogenesis has been debated.

General Features of Antiepileptic Drug Therapy.

Antiepileptic drug therapy is the mainstay of epilepsy treatment. The goals are to reduce the frequency of recurrent seizures and minimize

the adverse effects associated with antiepileptic drug therapy. Specific therapeutic and points must be individualized for each patient. The choice of antiepileptic drug therapy should be based on the seizure classification, the age and sex of the patient, concurent medical conditions, potential adverse effects, and the pharmacokinetic features of the individual drugs. When these factors are considered and the guiding principles of antiepileptic drug therapy are followed, good-to-excellent seizures control can be attained in most patients. Nonetheless, some patients may continue to suffer from frequent seizures despite appropriate drug treatment (Collins, 1983)

Before discovery of the antiepileptic drugs, Treatment of the epilepsy consisted of trephining, cupping, and the use of herbal medicines and animal extracts. In 1857, Sir Charles Locock reported the successful use of potassium bromide in the treatment of what is now known as catamenial epilepsy. In 1912, phenobarbital was first use for epilepsy, and in the next 25 years, 35 analogues of phenobarbital were studied as anticonvulsants. In 1938, phenytoin was found to be effective against experimental seizures in cats (Chan, 1992).

Between 1935 and 1960, tremendous strides were made both in the development of experimental models and in methods for screening and testing new antiepileptic drugs. During that period, 13 new antiepileptic drugs were developed and marketed. Following the enactment of requirements for proof of drug efficacy in 1962, antiepileptic drug

development slowed dramatically. In the last 25 years, only a few antiepileptic drugs have reached the marketplace (Chan, 1992)

The antiepileptic drugs use nowadays belong to several chemical classes. Most of the drugs can be classified by the chemical structure into many groups as the following (Burgen and Mitchell, 1978). The structures of compounds I - XIX are shown in figure 1.

1. barbiturates e. g. phenobarbital (I), mephobarbital (II), metharbital (III)
2. deoxybarbiturates e. g. primidone (IV)
3. hydantoins e. g. phenytoin (V), mephenytoin (VI), ethotoin (VII)
4. oxazolidinediones e. g. trimethadione (VIII), paramethadione (IX)
5. succinimides e. g. ethosuccimide (X), phensuximide (XI)
6. acylureas e. g. phenacemide (XII), ethylphenacemide (XIII)
7. iminostilbenes e. g. carbamazepine (XIV)
8. benzodizepines e. g. diazepam (XV), clonazepam (XVI), clorazepate (XVII)
9. branched-chain carboxylic acid e. g. valproic acid (XVIII)
10. carbonic anhydrase inhibitors e. g. acetazolamide (XIX)

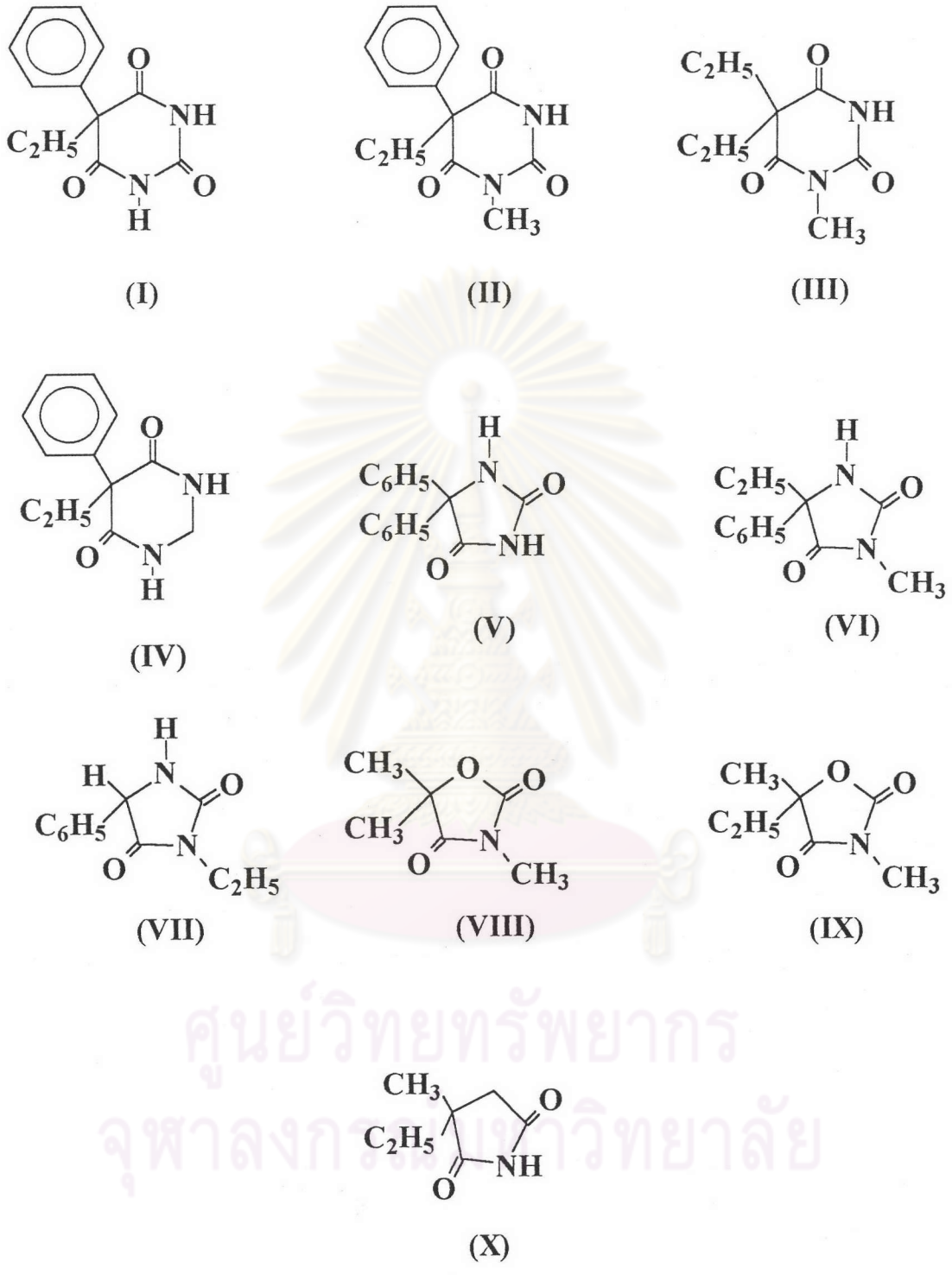


Figure 1. The chemical structures of anticonvulsant drugs.

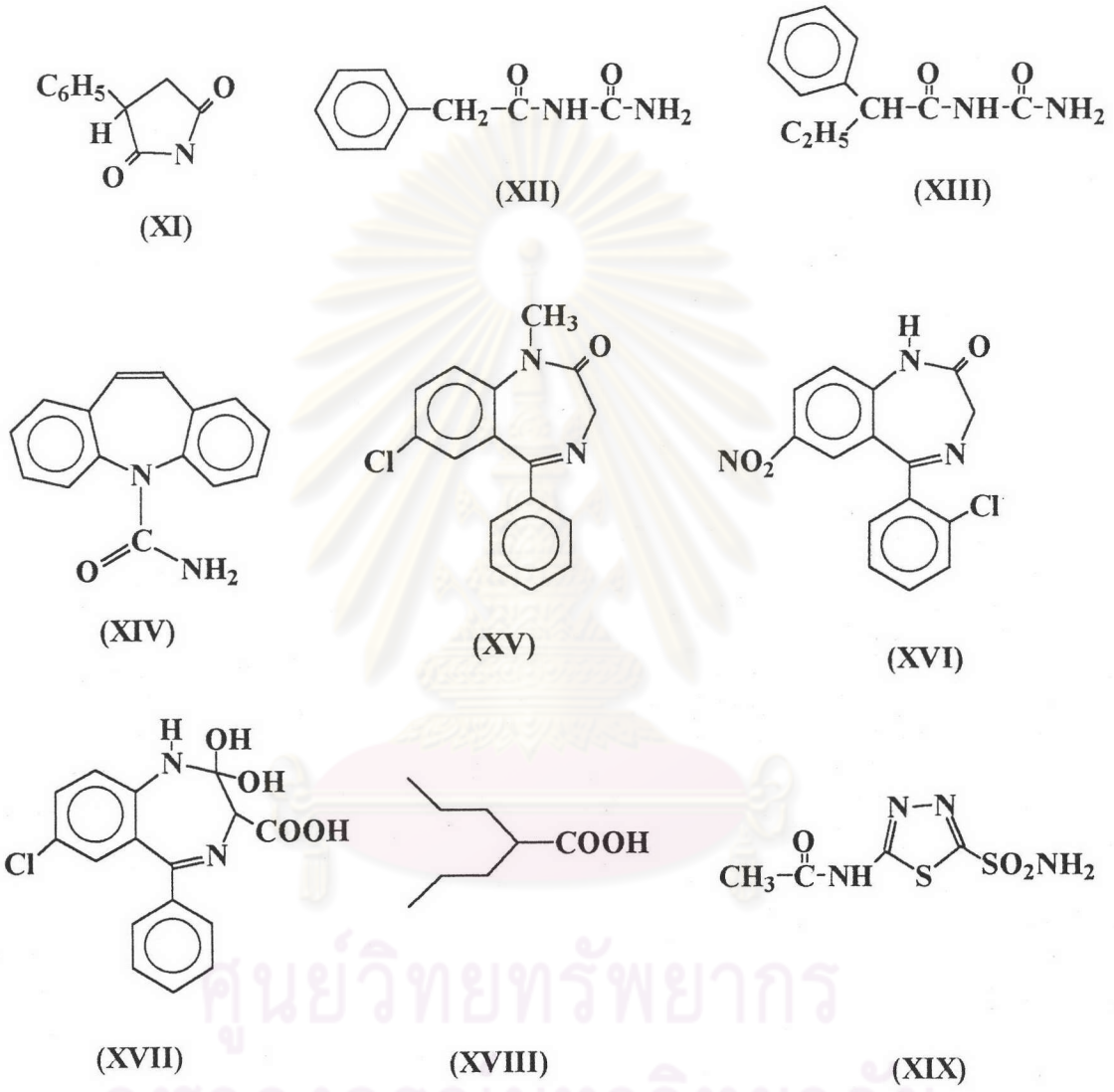


Figure 1. (continued) The chemical structures of some anticonvulsant drugs.

Mechanism of Action of Anticonvulsants.

Working hypotheses for the actions of anticonvulsants arise from the idea that drug-induced changes in permeability to specific ions may stabilize membranes, interfere with Ca^{++} -mediated release of neurotransmitters, and so forth. There is considerable information about electrophysiologic effects of antiepileptic agents and about their effects on ion fluxes. Nevertheless, the relevance of the experimental observations to the therapeutic benefit remains somewhat speculative.

Phenytoin and carbamazepine are used in management of generalized tonic-clonic and partial seizures. They block Na^+ channels in voltage-, frequency-, and time dependent fashion, probably by binding to and stabilizing the channels in their inactive, rather than their resting or open, state. In a routine screening procedure, they raise the threshold for electroshock-induced convulsions. At the neurophysiologic level, these agents decrease the spread of seizure discharge (Clark, 1992).

Phenobarbital and benzodiazepines promote Cl^- influx and hyperpolarization through interactions with the $GABA_a/Cl^-$ channel complex. Phenobarbital appears to act at the so-called picrotoxin site. Benzodiazepines bind at a different site. Valproic acid, a broad-spectrum antiepileptic drug, in some way facilitates GABA-mediated inhibition and also blocks Na^+ channels.

Agents such as ethosuximide and trimethadione, which are primarily useful for treatment of absence seizures, block a specific type (T) of Ca^{++} channel and are relatively effective in preventing seizure production by pentylenetetrazol.

Many other agents that interact with the GABA complex (vigabatrin or γ-vinyl GABA, progabide), Na^{+} or Ca^{++} channels, or excitatory amino acid receptors are under investigation for potential use in management of epilepsy. Analogues of adenosine, a putative neurotransmitter with anticonvulsant activity, may provide yet another avenue for improved antiepileptic compounds (Clark, 1992)

Need for New Drugs.

There are several compelling reasons for the development of new antiepiliptic drugs. Although antiepileptic drugs permit many patients to lead rewarding lives, clinical data do not support the widely held but erroneous belief that a large percentage of epileptic patients are adequately controlled by drug therapy. However, it should be noted that the major cause of poor seizure control is patient noncompliance with regularly taking their medication. Another consideration is that chronic toxicity is associated often with the prolonged administration of antiepileptic drugs. therefore, the need for new drugs is clear, and the search for more effective and safer antiepileptic drugs continues, with nearly 20 new agents currently under going clinical evaluation and several new

compounds with novel structures undergoing preclinical evaluation (Chan, 1992).

Development of Novel Unsaturated N-(2-Propylpentanoyl) urea

To understand the development of novel unsaturated N-(2-propylpentanoyl) urea derivatives which were synthesized in this research, valproic acid and its derivatives and acylurea analogues such as phenacemide (XII) have been considered. Hereby, these compounds have been concluded, as followed.

Valproic acid, (2-propylpentanoic acid) (XVIII) is an established antiepileptic drugs with a simple chemical structure but an unusally broad spectrum of action which includes tonic-clonic, partial complex, and absence seizures. Although the use of valproate in the treatment of epilepsy has grown during recent years, two major side-effects, teratogenicity and hepatotoxicity, have been associated with valproate therapy. Comparative analysis of anticonvalsant potency and safety margin; utilizing the classical animal model for anticonvulsant screening, shows that valproic acid is less potent than phenobarbital, phenytoin and carbamazepine. Consequently, and due to the shortage of new antiepileptic drugs, there is a substatial need to develop improved derivatives of valproic acid (Bialer, 1993). For instance, the following valproic acid derivatives were evaluated in comparison with the parent compound (see figure 2).

-the primary amide of valproic acid. i.e. valpromide (XX) and its isomers and analogoues (Bialer et al., 1993).

-monoester prodrugs of valproic acid. i.e. n-propyl valproate (XXI) (Hadad et al., 1993).

-unsaturated analogues of valproic acid. i.e. 2-propyl-2-pentenoic acid (XXII) (Abbott and Palaty, 1995).

-monoureids analogues of valproic acid. i.e. N-(2-propylpentanoyl) urea (XXIII) (Saisorn et al., 1992).

In 1993, Twelve analogues of valproic acid were primarily synthesized for study of structure-teratogenicity relationships and evaluated the anticonvulsant and neurotoxic effects by Elmazar, Hau and Nua. One of the investigated compounds, 4-Methyl-2-propyl-4-pentenoic acid (XXIV) as illustrated in figure 3, showed higher protective index (TD_{50}/ED_{50}) and safety ratio (TD_3/ED_{97}) than that of valproic acid, indicating that its maximum anticonvulsant protection is achieved in non-neurotoxic dose. Compare with valproic acid, compound XXIV produced lower teratogenicity and embryolethality in the mouse model. (Elmazar et. al., 1993).

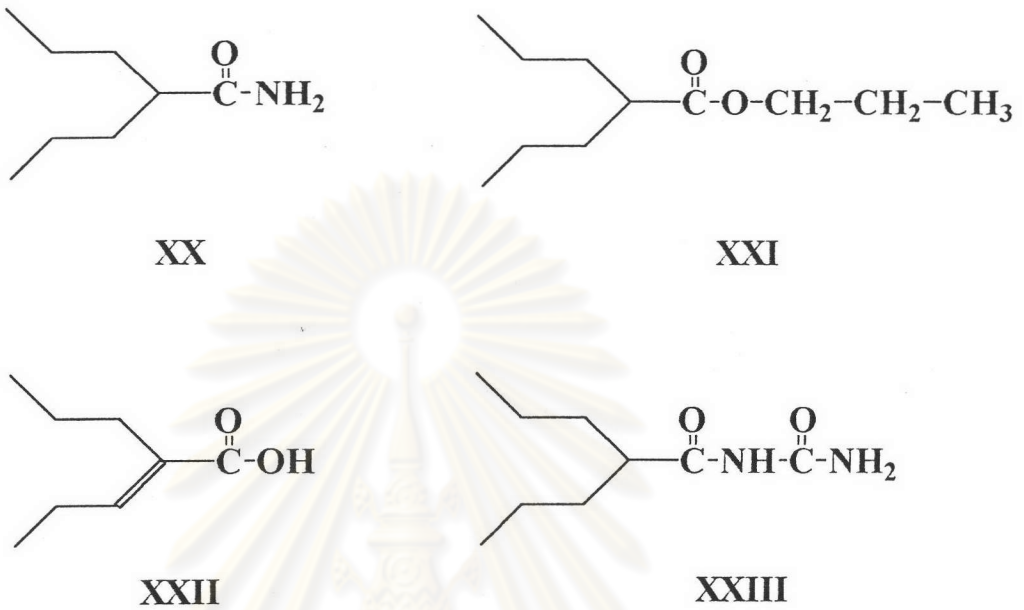


Figure 2 The chemical structures of valproic acid derivatives.

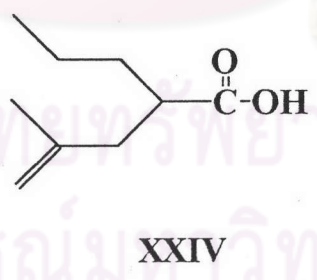


Figure 3. The chemical structure of 4-methyl-2-propyl-4-pentenoic acid.

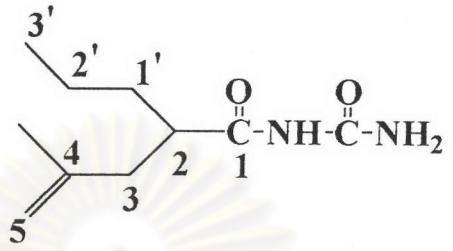
The successful use of phenobarbital (I) in treatment of epilepsy, encouraged chemists to attempt to design active compounds modelled on the partial structure of the barbiturate ring.

2-Phenylbutyrylurea (phenacemide) (XII) may be considered an "open" model of the barbiturate, less on carbon atom. Many compounds of acylureas or monoureides have been synthesized. The two compounds endowed with the greatest activity, experimentally and clinically, are phenacemide (phenylacetylurea, Phenurone®) (XII) and ethylphenacemide (2-phenylbutyryl urea, phenylethylacetylurea, Pheneturide®) (XIII) (Mercier, 1973).

In 1992, Boonardt Saisorn, Chamnan Patarapanich and Wichan Janwitayanuchit synthesized monoureide analogues, N-(2-propylpenta noyl) urea (XXIII) which have the same aliphatic side chain as valproic acid. This compound was evaluated for anticonvulsant activity in mice using the maximal electroshock, Subcutaneous pentylenetetrazole, and bicuculline test. It exhibited a good prospect of being a potent broad spectrum antiepileptic drug with higher margin of safety and lower side effects (Thongchai Sooksawate, 1995).

As mention above, N-(2-propylpentanoyl) urea (XXIII) was decided to be a parent compound to modify the structure to develop improved anticonvulsant. In this research, saturated aliphatic side chain of N-(2-propylpentanoyl) urea was replaced with unsaturated aliphatic side chain of 4-methyl-2-propyl-4-pentenoic acid to obtain the designed

compound, N-(4-methyl-2-propyl-4-pentenoyl) urea (CU-763-11-01, XXV) (see figure 4).



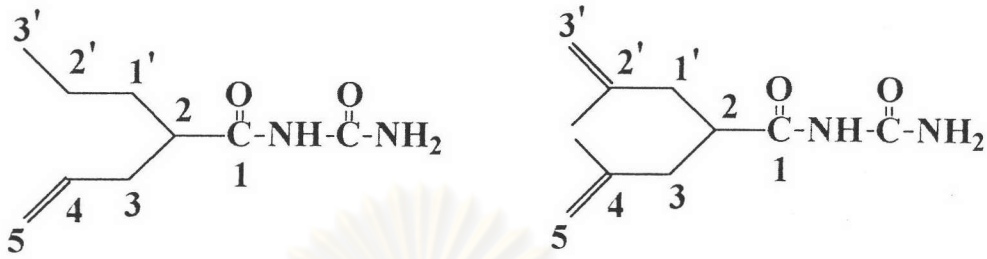
XXV

CU-763-11-01

Figure 4. The chemical structure of N-(4-methyl-2-propyl-4-pentenoyl) urea.

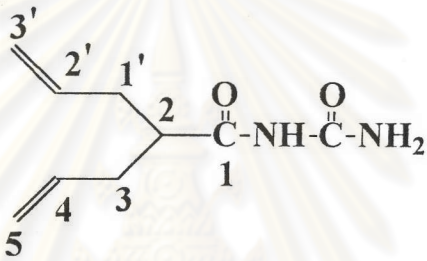
Considering the chemical structure of compound (XXV), it is expected to possess a promissing anticonvalsant activity with a higher margin of safety and lower side effect since it contains pharmacophore, namely acylurea and the partial structure of 4-methyl-2-propyl-4-pentenoic acid.

This research was aimed to synthesize N-(4-methyl-2-propyl-4-pentenoyl) urea including the following three unsaturated N-(2-propylpentanoyl) urea analogues : N-(2-propyl-4-pentenoyl) urea (CU-763-11-02, XXVI), N-(4-methyl-2-(2′-methyl-2′-propenyl)-4-pentenoyl) urea (CU-763-11-03, XXVII), and N-(2-allyl-4-pentenoyl) urea (CU-763-11-04, XXVIII) (see figure 5).



XXVI
CU-763-11-02

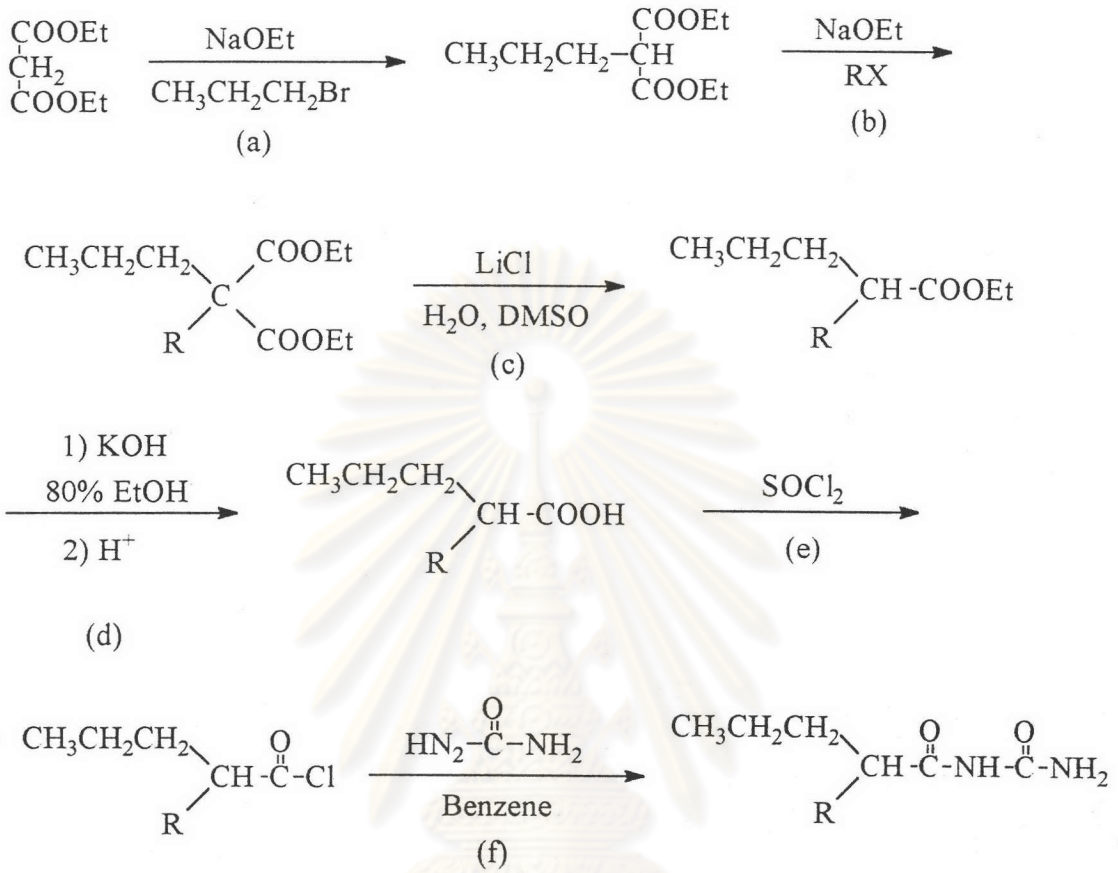
XXVII
CU-763-11-03



XXVIII
CU-763-11-04

Figure 5. The chemical structures of unsaturated N-(2-propyl-pentanoyl) urea analogues.

The synthetic approach of N-(4-methyl-2-propyl-4-pentenoyl) urea and N-(2-propyl-4-pentenoyl) urea is shown in figure 6 and the synthetic approach of N-(2-allyl-4-pentenoyl) urea and N-(4-methyl-2-(2-methyl-2-propenyl)-4-pentenoyl) urea is shown in figure 7.

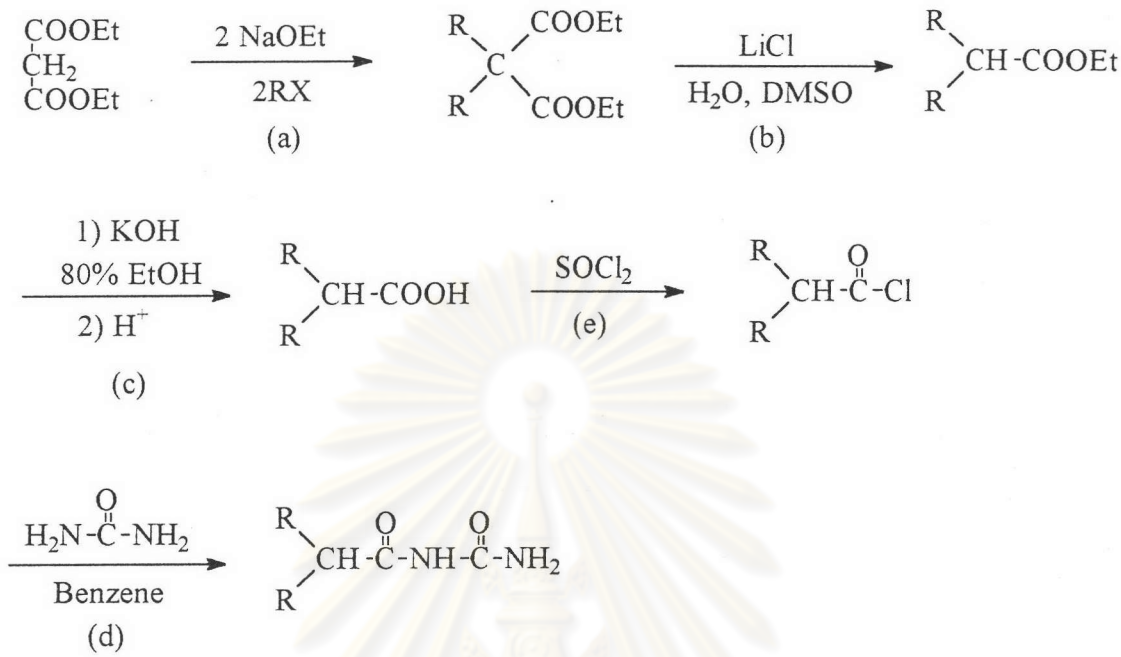


R = $CH_2=\overset{CH_3}{\overset{|}{C}}-CH_2-$ (CU-763-11-01, XXV)

$CH_2=CH-CH_2-$ (CU-763-11-02, XXVI)

(a) ethanol, reflux, 6 hrs; (b) ethanol, reflux, 12 hrs; (c) reflux, 36 hrs; (d) reflux, 2 hrs; (e) 40-50 °C, 3 hrs; (f) reflux, 8 hrs.

Figure 6. The synthetic appoach of N-(4-methyl-2-propyl-4-pentenoyl) urea (CU-763-11-01) and N-(2-propyl-4-pentenoyl) urea (CU-763-11-02).



R = $CH_2=\overset{CH_3}{\overset{|}{C}}-CH_2-$ (CU-763-11-03, XXVII)

$CH_2=CH-CH_2-$ (CU-763-11-04, XXVIII)

(a) ethanol, reflux, 15 hrs; (b) reflux, 36 hrs; (c) reflux, 2 hrs; (d) 40-50 °C, 3 hrs; (e) reflux, 8 hrs.

Figure 7. The synthetic appoach of N-(4-methyl-2-(2′-methyl-2′-propenyl) -4-pentenoyl) urea (CU-763-11-03) and N-(2-allyl-4-pentenoyl) urea (CU-763-11-04).