Barbituric acid or Malonyl urea can be genetically classed as a keto-dicarboxylic acid or 2,4,6-trioxy-pyrimidine. A molecule is represented as follows:

\[
\begin{align*}
4 \text{ CO} & \quad \text{NH} \quad 3 \\
5 \text{ CH}_2 \quad & \text{CO} \quad 2 \\
6 \text{ CO} & \quad \text{NH} \quad 1
\end{align*}
\]

Despite the fact that barbituric acid derivatives do not contain a carboxylic group, they have acidic properties due to the lactam form (-CONH) being in equilibrium with the lactim form (-C(OH):N-), hydrogen of which is readily dissociated, allowing formation of salts with alkalis.

\[
\begin{align*}
\text{CO} & \quad \text{NH} & \quad (\text{OH})-\text{C} & \quad \text{N} \\
\text{CH}_2 & \text{CO} & \text{H-C} \quad \text{C-(OH)} \\
\text{CO} & \quad \text{NH} & \quad (\text{OH})-\text{C} & \quad \text{N}
\end{align*}
\]

The hydrogen of CH$_2$ at position 5 can be readily replaced by different groups as in malonic ester, such as halide, -NO$_2$, alkyl etc. Derivatives of barbituric acid are useful in medicine for a number of purposes.
Barbiturates as Hypnotics and Sedatives

Sleep is a recurring state of inactivity, with a loss of consciousness and a decrease in responsiveness to events in one's environment. The ease with which it can be terminated differentiates it from coma, general anesthesia, alcoholic stupor and seasonal lethargy of certain animals. Sleep is necessary for the repair of the organism and thereby it enables the body to recuperate from the effects of the toils and troubles of the day. Yet it is difficult to understand which part of the body needs such a prolonged recovery period. The autonomic nervous system continues to function in much the same way during sleep as during waking hours, though there is possibly lessened sympathetic and greater parasympathetic activity; the vital centres in the medulla oblongata continue in the main to vary out their normal function. The activity of the various digestive and secretory organs, liver and kidney goes on almost unabated during sleep hours. It is the skeletal musculature which is reduced to comparative quiescence.

It has been demonstrated that during sleep there is slight depression of respiration and of blood pressure, and there are slight changes in the concentration of Potassium and other cations in the blood. During sleep the amplitude and frequency of the
electrical brain waves have been found to undergo characteristic changes and it has been possible to associate particular electro encephalogram patterns with certain stages of sleep.

Though the physiological nature of sleep is not well understood, it is obvious that full physical and mental relaxation are required before sleep is possible. There are many causes, both external and internal which do not allow the person to achieve this relaxation and consequently, sleeplessness is the result. External stimuli such as noise, the unaccustomed motion of a train or airplane, nervous irritation resulting from mental anguish or overwork, pain and maniacal states are among the best known causes of sleeplessness. As it is not always possible to remove the causative condition and to reestablish favourable conditions quickly, drugs capable of inducing sleep have a very important part to play in the treatment of sleeplessness.

Hypnotics (Greek ἱπνός =Sleep) are drugs which have depressant action and are used to induce sleep when natural sleep cannot be obtained. Throughout the middle ages and until the middle of the nineteenth century ethyl alcohol, opium and to some extent cannabis were used to produce euphoric sleep. 
and occasionally therapeutic sleep. Inorganic bromides were introduced as sedatives in later half of the nineteenth century, but when these were used as hypnotics in larger doses they were found to produce bromide intoxication. Chloral hydrate, first prepared by Liebig in 1832, was introduced into medicine by Liebrich in 1869. Chloral hydrate is perhaps the oldest member of hypnotic group of drugs and clinical studies show that it is still one of the cheapest and best. Owing to its irritating effect on stomach and its depressant effect on heart and respiration, after the discovery of barbiturates, chloral hydrate has gone into background. Paraldehyde was introduced into medicine by Cervello in 1882. It is one of the most efficient and least toxic hypnotic but because of its pungent odour and a burning disagreeable taste it is not popular. Bauman and Kast (Z. physiol. Chem., 1888, 14, 52) introduced sulphones as hypnotics in medicine. Before the introduction of barbiturates and other less toxic hypnotics in the first decade of this century, sulphonal \((\text{CH}_3)_2\text{C(SO}_2\text{C}_2\text{H}_5)_2\), trional \(\text{C}_2\text{H}_5\text{C(CH}_3)\text{(SO}_2\text{C}_2\text{H}_5)_2\) and tetronal \((\text{C}_2\text{H}_5)_2\text{C(SO}_2\text{C}_2\text{H}_5)_2\) were most frequently used, but now they have been almost completely discarded. Emil Fischer and Von Mering (Therap. Gegenwart, 1903, 44, 97) varied the
structure of barbituric acid which had been discovered
by Adolf Baeyer and introduced diethyl barbituric acid
under the name Veronal into
medicine. Following this lead
hundreds of barbiturates have
been synthesised and tested for
their hypnotic effect. Despite the fact that barbituric
acid derivatives do not contain a carboxyl group, they
have acidic properties due to the lactam-lactim equili-
brium as mentioned before. As barbiturates form salts
with alkalis, many of them are used as alkali
metal salts.

An entirely new series of
barbiturates has been obtained by the substitution of
sulphur for oxygen of the urea part. These are sulphur
isosteres of barbiturates and are
known as thiobarbiturates.
Thiobarbiturates have very good
anesthetic properties.

The barbiturates comprise an
important and valuable group of central nervous system
depressants. The barbiturates have several advantages
and they lend themselves
to a greater variety of uses than any other group of
central nervous depressants.
1. They are not disagreeable in taste like the otherwise excellent chloral and paraldehyde.

2. Their use is not restricted to hypnosis but can be extended to sedation. On the whole, one fourth or one fifth of the hypnotic dose will produce sedation within one to two hours as against bromides which require a much longer period for the same effect.

3. Some barbiturates especially the thiobarbiturates have anesthetic properties when given intravenously.

4. Some are useful as anticonvulsants.

5. The various classes of barbiturates permit a gradation of sleep production according to the needs of the patients. There are long acting, moderately long acting, short and ultrashort acting barbiturates.

6. The barbiturates are also serviceable in protecting against the toxic effects of local anesthetics.

7. The barbiturates can be administered by several routes, and their parenteral use provides definite advantages in emergencies.

8. The barbiturates given in ordinary hypnotic doses do not show any untoward effect on vital functions of the body.

Some of the disadvantages and counter-indication to the use of barbiturates are as follows:

...
1. The ease of administration leads to self drugging and this results into barbiturate poisoning. Relatively large percentage of suicides has been traced to barbiturate poisoning.

2. Prolonged use of barbiturates may lead to habituation.

3. These drugs sometimes cause allergic reaction.

4. These drugs should not be used in (a) renal impairment since several barbiturates are eliminated through the kidney. (b) liver diseases because a number of them are oxidised and detoxicated in the liver.

The barbiturates can be divided into three groups according to their duration of action, but a certain amount of overlapping occurs.

The table on the next page shows the classification of barbiturates on the basis of duration of hypnotic action.
**Classification of Barbiturates on Basis of Duration of Hypnotic Action.**

<table>
<thead>
<tr>
<th>Barbituric acid.</th>
<th>Synonym</th>
<th>Onset of reaction hours</th>
<th>Average adult hypnotic dose in gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LONG ACTING.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,5'-diethyl</td>
<td>Barbital</td>
<td>0.5-1</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>5-Allyl-5'-isopropyl</td>
<td>Alurate</td>
<td>0.25-0.5</td>
<td>0.065-0.13</td>
</tr>
<tr>
<td>5-ethyl-5'-isopropyl</td>
<td>Iparal</td>
<td>0.5-1</td>
<td>0.12-0.25</td>
</tr>
<tr>
<td>5-ethyl-5'-n-butyl</td>
<td>Neonal</td>
<td>0.5-1</td>
<td>0.05-0.1</td>
</tr>
<tr>
<td>5-ethyl-5'-phenyl</td>
<td>Phenobarbital (Luminal)</td>
<td>0.5-1</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td><strong>MODERATE ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ethyl-5'-isoamyl</td>
<td>Amytal</td>
<td>0.25-0.5</td>
<td>0.1-0.3</td>
</tr>
<tr>
<td>5-ethyl-5'-n-hexyl</td>
<td>Ortal</td>
<td>0.25-0.5</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>(1-methylbutyl)-5'-ethyl</td>
<td>Pentobarbital (Nembutal)</td>
<td>0.25-0.5</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>5-allyl-5'-(1-methylbutyl)</td>
<td>Surital</td>
<td>0.25-0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>5-sec-butyl-5'-(2-bromallyl)</td>
<td>Pernoston</td>
<td>0.25-0.5</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>5-ethyl-5'-cyclohexenyl</td>
<td>Phanodorn</td>
<td>0.25-0.5</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>5-alllyl-5'-isobutyl</td>
<td>Sandoptal</td>
<td>0.25-0.5</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td><strong>SHORT ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,5-dimethyl-5'-cyclohexenyl</td>
<td>Evipal</td>
<td>0.25</td>
<td>0.25-0.4</td>
</tr>
<tr>
<td>5-alllyl-5'-(1-methylbutyl)</td>
<td>Seconal</td>
<td>0.25</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td><strong>ULTRA SHORT ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-thio-5-ethyl-5'-(1-methylbutyl)</td>
<td>Pentothal</td>
<td>0.25</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>2-thio-5-ethyl-5'-isoamyl</td>
<td>Thioethamyl</td>
<td>0.25</td>
<td>Anesthetic</td>
</tr>
</tbody>
</table>
Sedation of any desired degree is obtained within an hour or two, when barbiturates in doses from one third to one fourth those used to induce sleep are administered.

**Barbiturates in Epilepsy:**

Epilepsy denotes a chronic clinical disorder characterised by recurring paroxysmal attacks or fits in which consciousness is lost or impaired in varying degrees with or without a succession of tonic or muscular spasm. Because of bizarre and dramatic character of its symptoms, epilepsy is described in the most ancient medical records. Throughout the middle ages, epilepsy was regarded as a manifestation of the presence of an evil spirit in the afflicted individual.

Individual seizures vary in severity from almost imperceptible momentary lapses of consciousness or mental clouding to violent generalised convulsions lasting for several minutes. Attacks tend to be predominantly motor, sensory or psychic in character, although various combinations of these different types may occur.

In major epilepsy or grand mal there is sudden loss of consciousness accompanied by severe general convulsions. In minor epilepsy or petit mal
which is most frequent in childhood there is a transient loss of consciousness leading to a dreamy state accompanied by very minor or no motor manifestations other than staring, upward rolling of the eyes etc. Localised convulsions which may occur without the loss of consciousness are called Jacksonian seizures or cortical epilepsy.

Though the basic causes of epilepsy are not well understood, a large number of factors are known to contribute to the provocation of seizures in susceptible persons. Certain abnormal physiological conditions, such as an alkaline state of the blood and other body fluids, excessive intake of water without an equivalent increase in the intake of common salt, decreased oxygen supply to the brain and various forms of emotional disturbance have this deleterious effect. The tendency for seizures is decreased by ketogenic diet. Putnam and Merritt (Science, 1937, 85, 525; Arch. Neurol. Psychiat., 1938, 39, 1005; Epilepsia, 1945, 3, 51) have suggested that the abnormalities leading to convulsions may be due to the inactivity of the brain to utilise a metabolite in a normal manner and thereby to maintain normal reactions of these materials.

By means of electro encephalograph Hans Berger in 1931 demonstrated that epileptic
seizures are the outward manifestations of a profound disturbance in the electrical activity within the central nervous system. This electrical disturbance must be due to chemical reaction, the nature of which is unknown. The rate of electrical waves recordable from the brain in grand mal is abnormally fast, in psychic seizures abnormally slow.

Method of Assay of Anticonvulsant Drugs:

An epileptic drug is assayed by techniques involving both electrical and chemical methods. The maximum electro-shock and the metrazol tests together are considered necessary for a reliable preliminary screening. This duplicate testing is necessary because a drug which does not elevate the threshold of one type of convulsions may still be a good anticonvulsant. For electroshock, a direct current stimulus of one tenth ampere for one third second is used on rats. If convulsions caused by metrazol are to be observed in mice, the drug, is administered, and after one hour 100 mg./kg. of metrazol in water solution is injected subcutaneously to start the test. Metrazol induced convulsions have electro encephalogram pattern similar to that of natural epileptic convulsions.

Hippocrates (460-370 B.C.) was the first to recognise that epilepsy was due to some
natural causes. The first truly significant advance in its treatment was made by the English physician Thomas Lay Cock when he introduced bromide therapy. The action of bromides is slow in starting but lasts unusually long in grand mal. For petit mal bromides are useless (Putnam and Merrit, loc. cit.).

In doses sufficient to produce anesthesia practically all hypnotics relieve convulsive attacks. The barbiturates are of great value in the control of convulsions such as occur in tetanus, eclampsia, status epilepticus and cerebral hemorrhage. They are also effective in combating convulsions caused by cocaine, strychnine and picrotoxin and those occurring during general anesthesia. Hauptman (Munch. med. Wochschr., 1912, 59, 1907) introduced ethyl phenyl barbituric acid (Luminal, Phenobarbital) as an anticonvulsant superior to inorganic bromides in the treatment of epilepsy. It is effective in non-hypnotic doses, its action starts within an hour or two after ingestion and its use is not followed by fetid breath, skin rash and sluggishness which frequently accompany bromide medication. It controls effectively severe acute attacks of grand mal as well, but is
useless in Jacksonian seizures. In grand mal the waves are abnormally fast and in petit mal these are alternately fast and slow. Phenobarbital slows down brain waves and therefore has a therapeutic effect on these two conditions. In Jacksonian seizures the waves are unusually slow, and therefore the further slowing down by the drug aggravates this condition. Effective doses of phenobarbital, however, produce some central depression and it is thus inferior in this respect to dilantin.

In 1938 Merrit and Putnam (loc.cit.) introduced 5,5'-diphenyl hydantoin-dilantin— as a very effective anticonvulsant combined with least depressant effect. It is used in the form of sodium salt. Dilantin has been widely used in the control of grand mal and psychomotor seizures and also in petit mal though in the last case the encephalogram is not improved. Untoward effects of dilantin are giddiness, tremours, gastro-intestinal disturbance, dermatitis, soreness of the mouth and the tenderness and hyperplasia of gums.

Mesentoin - 5-phenyl-5'-ethyl-1-methyl hydantoin is also an useful anticonvulsant.
Recently oxamolidenedione derivatives have been found to possess strong anticonvulsant properties. The most active compounds of this group are Tridione, Paradione and Propazone. The first two have been introduced as valuable drugs for the clinical treatment of petit mal. Tridione resembles the barbiturates and bromides in producing sedation at anticonvulsant dosage (Erlenmeyer, Helv. chim. Acta., 1938, 21, 1013; Spielman, J. Am. Chem. Soc., 1944, 66, 1244; Evereth and Richards, J. Pharmacol. Exptl. Therap., 1944, 81, 402; Lennox, J. Am. Med. Assoc., 1945, 129, 1069; Perlstein and Andelman, J. Pediat., 1946, 22, 20).

Barbiturates as Anesthetics:

Anesthetics are drugs which depress vital functions of all types of cells but especially those of nervous tissue. General anesthetics depress the central nervous system to such an extent that all sensitivity to pain is lost. Local anesthetics
produce such immunity to pain when applied to restricted area. Certain anesthetics when injected into the spinal fluid, block impulses transmitted by nerve fibers emanating from the region involved and are used under the name of "spinal anesthesia" for insensibilisation of organs served by the particular nerves.

For many centuries morphine, hyosceine and alcoholic beverages were the main drugs used to ease the pain of surgery. The use of anesthetics for complete and safe abolition of pain in surgical operations is little more than a hundred years old.

Crawford W. Long of Athens, Georgia removed in March 1842 a small tumor from the neck of a patient who was made to inhale ether. The first public demonstration of surgical operation under ether was given by Morton on 16th October 1846. The long known laughing gas, nitrous oxide was used as an anesthetic for dental surgery by Wells and by Morton about the same time though such an use was suggested by Sir Humphrey Davy as early as 1797. Simpson in England used chloroform anesthesia in human beings in 1847. Before the discovery of these anesthesia operations were horrible ordeals and the surgeon attempted to shorten the agony by working with great haste. Thus careful surgery and delicate treatment of tissues were impossible.
Some of the desirable properties of an ideal anesthetic are:

(1) It should have a rapid and pleasant induction without irritation.
(2) It should not have unpleasant odour.
(3) It should have short recovery period free from discomfort and post anesthetic nausea etc.
(4) It should not be explosive.
(5) It should have low toxicity and wide margin of safety.
(6) It should have as few side effects as possible.
(7) It should not be altered in the body but should be excreted unchanged.
(8) It should be sufficiently potent so that it can be administered with a high percentage of oxygen.
(9) It should be volatile enough to be exhaled immediately and excreted when the anesthetic gas mask is removed.
(10) It should be moderately costly.
(11) It should be chemically stable.

Methods of Administration:

Volatile liquid anesthetics can be used by the open method. In the closed system the patient breaths the anesthetic mixture after due purification to remove exhaled carbon dioxide and moisture. Some of the more widely used general anesthetics are described below.
Among the volatile liquid anesthetics the most useful are diethyl ether, divinyl ether (Leake and Chen, Proc. Soc. Exptl. Biol. Med., 1930, 28, 151; Raigh and Major, J. Am. Chem. Soc., 1931, 53, 2662; Gelfan and Bell, J. Pharmacol., 1933, 57, 1), chloroform and ethyl chloride. Chlorine-containing anesthetics cause liver damage. Among the gaseous anesthetics the useful are nitrous oxide, ethylene and cyclopropane (Henderson and Leuckhardt, Anesthesia and Analgesia, 1930, 9, 1).

Preanesthetic Medication:

A number of drugs may be used to prepare a patient for surgical anesthesia with inhalation anesthetics. The purpose of these drugs is to relieve pain, to decrease apprehension especially in highly nervous individuals and to reduce the stage of excitement of the induction period. Even more important is the synergism of certain compounds with inhalation anesthetics which lessens the amount of the latter for completion of surgical anesthesia. Morphine and its derivatives, scopolamine, avertin (tribromo ethanol in amylene hydrate) are used for the purpose. Atropine inhibits secretions and thereby the incidents of post operative pulmonary complications, nausea etc. are lessened by its use.
Barbiturates have a number of uses in anesthesia, including their employment for general anesthesia, basal anesthesia, preanesthetic medication and obstetrical amnesia.

(1) General Anesthesia: For selected surgical operations of brief duration, the ultrashort acting barbiturates especially the thiobarbiturates may be employed for intravenous anesthesia. The main advantages of this application lie in emergency anesthesia, for example under war conditions, where portable or complex equipment is not available. 5-ethyl-5-(1-methyl butyl)-2-thiobarbituric acid -- pentothal and 5-ethyl-5-isomyl-2-thiobarbituric acid -- thioethamyl -- are useful in this way (Volwiler, J. Am. Chem. Soc., 1935, 57, 1961; ibid, 1936, 58, 1355; Miller, Munch, Crossley and Hartung, J. Am. Chem. Soc., 1936, 58, 1090). The anesthesia is rapidly and pleasantly induced and is of short duration and leaves no ill after effect. The disadvantage of barbiturate anesthetics is particularly the impossibility of interrupting the anesthesia at any given point as can be done with volatile anesthetics.

(2) The barbiturates may be employed prior to inhalation anesthesia in doses sufficient to cause basal anesthesia. Basal anesthesia is a lighter degree of anesthesia obtained by giving sufficient preanesthetic medication.
It allows the patient to be brought to the operating room in an unconscious state, yet not sufficiently depressed for surgical procedures. Somnifene (allyl isopropyl barbiturate), Sodium amytal (sodium isoamyethyl barbiturate), Nembutal (ethyl methylbutyl barbiturate), Pernoston (butyl β-bromallyl barbiturate), Rectidon (amyl β-bromallyl barbiturate), Sodium soneryl (butyl ethyl barbiturate), Hebaral (hexyl ethyl barbiturate), Sodium arconal (propyl methyl carbinyl allyl barbiturate), Pentothal (ethyl-(1-methylbutyl)-thiobarbiturate) etc. are used for this purpose.

Some of the advantages of basal narcosis are (1) absence of apprehension in the patient (2) less amount of general anesthesia is required (3) less nausea and vomiting.

(3) Preanesthetic Medication: The barbiturates in combination with atropine or scopolamine are widely used for preanesthetic medication usually in place of morphine.

(4) Obstetrical Amnesia: The barbiturates are employed in obstetrics for rendering the patient tranquil and drowsy so that she will sleep between pains and not
remember the ordeal but nevertheless remain sufficiently conscious to assist in delivery. Nembutal (Na ethyl methyl butyl barbiturate), Sodium amytal (Na isooamyl ethyl barbiturate) and Sodium Soneryl thiopentane (Na butyl ethyl barbiturate) are used for the purpose.

Relation between Structure and Physiological Activity among Barbiturates:

The number of compounds that have been studied is now so large that some general rules can be formulated connecting structure with physiological activity.

1. Both the reactive hydrogens of barbituric acid must be replaced by alkyl or aryl groups in order to have compounds possessing hypnotic properties. Monoalkyl or aryl derivatives are devoid of hypnotic action.

2. Barbituric acid with very small groups in C₅ position is also without activity e.g. dimethyl barbituric acid is inactive even in fairly large doses.

3. An increase in the length of one or both alkyl side chains results in enhanced potency and diminished duration of depression. When the total of the carbon
atoms of the groups on C₅ exceeds seven or eight or
the total molecular weight exceeds 250—the hypnotic
activity decreases. This optimum number viz. eight
carbon atoms must be contributed by two groups
present on C₅. Cyclooctatetraene barbiturate (Jones
eight carbon atoms is devoid of any hypnotic property.

4. When the molecular weight of the substituted barbituric
acid exceeds the optimum value 250, the compound shows
convulsive properties. Ethyl benzyl barbiturate
produces convulsions while dibenzyl barbituric acid is
inactive (Dox & Yoder, J. Am. Chem. Soc., 1922, 44, 1141; see
also Ojiyama et al., J. Pharm. Soc. Japan, no. 533, 1926, 597;
Niitsu, Sei-i-kvai-Med. J., no. 9, 1931, 50, i.e. C.A., 1932,
26, 3846; Dox, J. Am. Chem. Soc., 1922, 44, 1142 etc.).

5. All serious attempts to correlate the results of
substituting various alkyl groups with changes in
activity of the resulting compounds have remained
The following are the general conclusions:

(a) Branched chain aliphatic groups are more active and
less toxic as compared to straight chain ones.

(b) Barbiturates with alkyl radicals are relatively stable
in the body, while those with complex cyclic radicals
are unstable and are readily destroyed in the body.
(e.g. evipal)

(w) Introduction of polar or functional groups into the
alkyl groups such as ether (pl. see next page)
hydroxy, carbonyl, amino or carboxyl groups usually destroys the depressant effect. It may be that these groups lessen the tendency of the alkyl groups to impart lipoid solubility to the molecule (Dox, J. Am. Chem. Soc., 1924, 46, 252; ibid, 1923, 45, 1757; Hill, J. Am. Chem. Soc., 1924, 46, 257). Among the dialkyl barbiturates containing oxygenated functions certain \( \sim \) alkoxy ethyl barbiturates have shown more favourable therapeutic ratio and have shorter duration of anesthesia as compared to amytal.

(d) Tri and tetra alkyl substituted barbituric acids have been studied and are found active (Crossley, Miller and Hartung, J. Org. Chem., 1940, 5, 235-43).

6. If one of the alkyl groups at \( C_5 \) is unsaturated (e.g. propargyl) the resulting barbiturate has anticonvulsant activity at lower doses.

7. \( N \)-alkylation, especially \( N \)-methylation seems to confer anticonvulsant properties on 5,5-disubstituted barbituric acids. Mebaral (\( N \)-methyl phenyl ethyl barbiturate) shows anticonvulsant properties.

8. Substitution of a phenyl group for an ethyl group gives one of the best known hypnotics viz. Luminal which also possesses anticonvulsant properties.
9. Introduction of amino, nitro or hydroxy group in phenyl radical of ethyl phenyl barbiturate causes loss of activity while bromine and chlorine increases toxicity.

10. By the substitution of group containing an asymmetric carbon atom in place of a group devoid of asymmetric carbon, no enhancement in hypnotic properties has been observed.

11. High therapeutic ratio between narcotic and toxic doses have been observed in a series of spirobarbiturates (Cope, Kovacik and Burg, J. Am. Chem. Soc., 1949, 71, 3658).

The above two spirobarbiturates have the most favourable properties. These compounds are an exception to the rule that replacement of both valencies at C₅ by one group gives inert compounds. For example, 5-Benzal barbituric acid and 5-methylene barbituric acids are inactive.

12. Replacement of oxygen of the CO part in urea by sulphur gives rise to sulphur isosteres of barbiturates viz. thiobarbiturates. These are more acidic than the corresponding barbiturates and this property may
perhaps account for the rapid onset of their action. Thiobarbiturates have recently been introduced as intravenous anesthetics.

13. Certain fluorine containing barbiturates have been prepared recently (Huber, Bruce, J. Am. Chem. Soc., 1953, 75, 4668). These are 5-alkyl-5-ω-fluoroalkyl barbiturates and all of them exhibit sedative action and produce true hypnosis.

14. As in all groups of drugs, a combination of physical and chemical properties plays an important role in determining the physiological characters of barbituric acids. Like other depressant agents these compounds must consist of lipotropic alkyl radicals attached to a hydrotropic polar group (the trioxy-pyrimidine part) which is capable of forming associated molecules in polar solvents and which may possess similarity to compounds occurring in the body. Attempts have been made to correlate pH, water solubility, effect on surface tension etc. with the hypnotic effect but the relationship is not simple. Dial which is unsaturated should be easily destroyed in the body and hence should produce hypnosis of shorter duration as compared to Seconal. Actually the reverse is true.
PRESENT WORK.

Kushner, Cassell and Williams (J. Org. Chem., 1951, 16, 1283) have found a number of N-benzyl amides to be effective against electrically induced convulsions and audiogenic metrazol shock in rat. Hibicon- N-benzyl-\(^\beta\)-chloro propionamide ClCH\(_2\)CH\(_2\)CONHCH\(_2\)C\(_6\)H\(_4\) has been found useful in grand mal epilepsy (Kaplan and Maslanka, Diseases of Nervous system, 1952, 13, 88; Hawkes, Arch. Neurol. Psychiat., 1952, 67, 815). Goldman and Williams (J. Org. Chem., 1953, 19, 815) found that benzyl esters of certain 4-carbamyl-1-piperazine carboxylates were active anticonvulsants, as tested by means of audiogenic-metrazol tests in rats. Hibital- benzyl-4-carbamyl-1-piperazine carboxylate C\(_6\)H\(_5\)CH\(_2\)OCON\(\bigcirc\)NCONH\(_2\) was useful in protecting animals against convulsive seizures induced by audiogenic metrazol, electroshock and intravenous metrazol. The above observations indicate the importance of benzyl group in anticonvulsant compounds.

\(N^1\) alkylation of barbiturates make them more useful in epileptic conditions. Mebaral-- 1-methyl-5-ethyl-5'-phenyl barbiturate-- is an useful anticonvulsant. Recently, Miller and Long (J. Am. Chem. Soc., 1951, 73, 4895) have reported that milantin--N-methyl- < phenyl succinimide is effective against both metrazol and
electrically induced convulsions, and is able to control petit mal attacks. Miller et al (J. Am. Chem. Soc., 1953, 75, 5608; 1953, 75, 373) have prepared several N-alkyl derivatives of substituted succinimides.

Papaverine present in opium is one of the most important musculotropic antispasmodics and it contains in its molecule dimethoxy benzyl group. However, benzyl group is not considered very essential for the development of antispasmodic activity (Fodor and Bruckner, Ber., 1938, 71, 541; 1943, 76, 1216; Fodor, Acta. Lit. Sci. Regia. Univ. Hung. Francisco-Josephinae, Sect. Chem. Mineral Phys., 1937, 5, 1-26 i.e. C.A., 1938, 22, 2124).

Several amides of α-amino acids have also shown antispasmodic activity (Billman and Hidy, J. Am. Chem. Soc., 1943, 65, 760; ibid., 1944, 66, 540). N-benzyl nicotinamide and Lyspamin -- nicotinamido-1,2-diphenyl ethane show

\[
\begin{align*}
&\text{N-benzyl nicotinamide} \\
&\text{Lyspamin}
\end{align*}
\]

powerful antispasmodic activity (Suter, Gordonoff, Dubois, Schweiz. med. Wochenschr., 1948, 35, 853).

Very few N¹ benzyl substituted barbiturates are known. Thus Dox and Jones (J. Am. Chem. Soc., 1929, 51, 316) have prepared N-benzyl derivatives of 5,5¹-dialkyl barbiturates by direct substitution on N of 5,5¹-dialkyl barbiturates.
With a view to study their anticonvulsant and anesthetic properties it was considered of interest to synthesise several barbiturates and thiobarbiturates containing substituted benzyl group. The molecule of Veronal was taken as a standard and several barbiturates and thiobarbiturates containing benzyl group on the N atom were synthesised. Following types of compounds have been synthesised and described in section I, part II of the present work.

\[
\begin{align*}
\text{C}_2\text{H}_5 & \quad \text{CO} \quad \text{NH} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \\
\text{N-CH}_2 & \quad \text{x} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \quad \text{NH} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \\
\text{N-CH}_2 & \quad \text{x}
\end{align*}
\]

where \(x = \text{Cl}, \text{Br}, -\text{OCH}_3, -\text{CH}_3\) and -2 CH$_3$

\[
\begin{align*}
\text{C}_2\text{H}_5 & \quad \text{CO} \quad \text{NH} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \\
\text{N-CH} & \quad \text{R} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \quad \text{NH} \\
\text{C}_2\text{H}_5 & \quad \text{CO} \\
\text{N-CH} & \quad \text{R}
\end{align*}
\]

where \(R = -\text{CH}_3, -\text{C}_2\text{H}_5\) and -n C$_3$H$_7$

For comparing their properties with the above types of barbiturates a few barbiturates and thiobarbiturates were synthesised having a substituted benzyl group on the C$_5$ atom of the barbiturate molecule.
Taking benzyl as substituent on C₅ some of the barbiturates have been synthesised. Thus 5-alkyl-5'-benzyl barbiturate was synthesised by John and Hill (Am. Chem. J., 1911, 46, 544), 5-isopropyl-5'-benzyl and 5-cyclohexyl-5'-benzyl barbiturates were synthesised by Bayer patent (German patent, 293163, 1916). Finally series of 5-alkyl-5'-benzyl barbiturates were synthesised by Dox and Yoder (loc. cit.). It has been observed that when the sum of carbon atoms in the groups at position 5 is larger than 7 or 8, the hypnotic activity decreases and sometimes it leads to convulsions (Dox and Yoder, J. Am. Chem. Soc., 1922, 44, 1141; see also C. A., 26, 3848; 29, 8237; 33, 5599). Thus 5-ethyl-5'-benzyl barbiturate is less active and convulsive as compared to ethyl phenyl barbiturate. This may perhaps be due to the sum of the carbon atoms at position 5 exceeding 8 carbon atoms. In the compounds synthesised the second group has been kept as methyl so as to keep the carbon atom total, (not counting the substituent) equal to that of Luminal - phenyl ethyl barbiturate. With this idea the following compounds have been synthesised and described in the part II section II of the work.

\[
\begin{align*}
\text{X} \quad &\begin{array}{c}
\text{CH}_2 \\
\text{CH}_3 \\
\text{CO} \\
\text{NH}
\end{array} & \begin{array}{c}
\text{CO} \\
\text{NH}
\end{array} \\
\text{X} \quad &\begin{array}{c}
\text{CH}_2 \\
\text{CH}_3 \\
\text{CO} \\
\text{NH}
\end{array} & \begin{array}{c}
\text{CO} \\
\text{CS} \\
\text{NH}
\end{array}
\end{align*}
\]

where \(X=\text{Cl}, \text{Br}, -\text{OCH}_3, -\text{CH}_3\) and \(-2\text{CH}_3\)
Following the discovery of the local anesthetic properties of cocaine and the study of its structure, several types of compounds were synthesised. With a view to get a compound having low toxicity and freedom from addiction properties of cocaine, Einhorn and Uhlfelder (Ann., 1909, 371, 131) synthesised rocaine which had the most favourable therapeutic ratio. Following this lead several basic esters were synthesised containing various substituents in benzene nucleus. Rohmann and Scheurle (Arch. Pharm., 1936, 274, 110) found that in a homologous series of esters of the type \( RO\stackrel{\mathcal{C}}{\longrightarrow} COO(CH_2)_n N(C_2H_5)_2 \) the anesthetic potency increases as \( R \) becomes larger.

Alkoxy substituted benzoic esters of the type \( RO_2 CC_6H_4 CH(\mathcal{O}H) CH_2 R^1 R^2 \) have been shown to have local anesthetic properties (British patent, 673413, 1953).

Basic esters of the type \( 4\to ROC_6H_5 CO_2(CH_2)_n R^1 \cdot HCl \) where \( R \) alkyl and \( R^1 \) basic alcohol including heterocyclic alcohol have been shown to possess anesthetic properties (Ger. patent, 824202, 1951). Basic esters of chlorobenzoic and chlorocinnamic acids have been shown to exhibit local anesthetic properties (Andrews, Van Campen, and Schumann, J. Am. Chem. Soc., 1953, 75, 4003).

The above indicates the importance of alkoxy and Cl group in the development of anesthetic properties.
A few phenyl substituted barbituric acids have been studied by Hjort and Dox (J. Pharm., 1929, 35, 155; see also C.A., 31, 5775; 33, 3024; 30, 5992; 22, 1626), but thiobarbiturates containing N1-phenyl group have not been studied. With a view to study thier anesthetic properties several thiobarbiturates containing substituted phenyl group attached to the N atom were prepared. The following compounds have been prepared and described in the part II section I of the present work.

\[
\begin{align*}
\text{CO} & \quad \text{NH} \\
\text{C}_2\text{H}_5 & \quad \text{CS} \\
\text{C}_2\text{H}_5 & \quad \text{N} \quad \text{X}
\end{align*}
\]

where X = -OCH_3 to \(-\text{OC}_6\text{H}_{13}\) in para position and \(X = \text{Cl}, \text{Br}\) in all three positions.